

ADOPTED: 6 July 2021 doi: 10.2903/j.efsa.2021.6790

Safety assessment of the substance silver nanoparticles for use in food contact materials

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Abstract

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) assessed the safety of the additive silver nanoparticles intended to be used in plastics. All the silver particles are in the size range of 1–100 nm, with about 15 nm mean diameter and 99% by number of particles below 20 nm. The additive is intended to be used as a surface biocide at up to 0.025% w/w in non-polar plastics for contact with a wide variety of foods, times, temperatures and food contact surface/mass of food ratios. The particulate form is maintained when the additive is incorporated into plastics, albeit with some aggregation/agglomeration observed. The data and information on theoretical considerations, on specific migration and abrasion tests show that, under the intended and tested conditions of uses, the silver nanoparticles stay embedded in the polymer, do not migrate and resist release by abrasion, thus, do not give rise to exposure via food and to toxicological concern. There is migration of silver in soluble ionic form up to 6 μ g/kg food from the surface of the additive particles. This is below the group restriction of 50 μ g silver/kg food proposed by the AFC Panel in 2004 and would lead to a maximum exposure from FCM that would be below the acceptable daily intake (ADI) of 0.9 μ g silver ions/kg body weight (bw) per day established by ECHA. Therefore, the Panel concluded that the substance does not raise safety concern for the consumer if used as an additive at up to 0.025% w/w in polymers, such as polyolefins, polyesters and styrenics, that do not swell in contact with aqueous foods and food simulants. The Panel noted, however, that exposure to silver from other sources of dietary exposure may exceed the ADI set by ECHA.

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Keywords: silver, nano, biocide, food contact materials, plastic, safety assessment

Requestor: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany

Question number: EFSA-Q-2018-00640

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Competing interests: R. Franz declared that Fraunhofer institute at which he was employed provides advisory services to private business operators active in the sector on food contact materials. In line with EFSA's Policy on Independence (http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf) and the Decision of the Executive Director on Competing Interest Management (http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf), a waiver was granted to R. Franz regarding his participation to the EFSA's Working Group on Food Contact Materials (FCM WG) in accordance with Article 21 of the Decision of the Executive Director on Competing Interest Management. Pursuant to Article 21(6) of the above-mentioned Decision, the involvement of R. Franz is authorised as member in the FCM WG, allowing him to take part in the discussions and in the drafting phase of the scientific output, but he is not allowed to be, or act as, a chairman, a vice-chairman or rapporteur of the working group.

Note: The full opinion will be published in accordance with Article 10(6) of Regulation (EC) No 1935/2004 once the decision on confidentiality, in line with Article 20(3) of the Regulation, will be received from the European Commission. The following information have been provided under confidentiality and they are redacted awaiting the decision of the Commission: the method of manufacture (synthesis pathway) and some information on the stability of silver nanoparticles.

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Suggested citation: EFSA CEP Panel (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids), Lambré C, Barat Baviera JM, Bolognesi C, Chesson A, Cocconcelli PS, Crebelli R, Gott DM, Grob K, Lampi E, Mengelers M, Mortensen A, Steffensen IL, Tlustos C, Van Loveren H, Vernis L, Zorn H, Castle L, Di Consiglio E, Franz R, Hellwig N, Merkel S, Milana MR, Barthélémy E and Rivière G, 2021. Scientific Opinion on the safety assessment of the substance silver nanoparticles for use in food contact materials. EFSA Journal 2021;19(8): 6790, 11 pp. https://doi.org/10.2903/j.efsa.2021.6790

ISSN: 1831-4732

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The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.





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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Before a substance is authorised to be used in food contact materials (FCM) and is included in a positive list, EFSA's opinion on its safety is required. This procedure has been established in Articles 8, 9 and 10 of Regulation (EC) No 1935/2004¹ of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food.

According to this procedure, the industry submits applications to the Member States' competent authorities which transmit the applications to the European Food Safety Authority (EFSA) for their evaluation.

In this case, EFSA received an application from the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany, requesting the evaluation of the substance silver nanoparticles. The dossier was submitted by RAS AG.

According to Regulation (EC) No 1935/2004 of the European Parliament and of the Council on materials and articles intended to come into contact with food, EFSA is asked to carry out an assessment of the risks related to the intended use of the substance and to deliver a scientific opinion.

2. Data and methodologies

2.1. Data

The applicant has submitted a dossier in support of its application for the authorisation of the substance silver nanoparticles to be used in plastic food contact materials.

Additional information was provided by the applicant during the assessment process in response to the request from EFSA sent on 30 January 2020 (see Documentation provided to EFSA).

Data submitted and used for the evaluation are:

Non-toxicological data

- Data on chemical identity
- Data on characterisation of the particles before and after incorporation in polymer
- Data on physical and chemical properties
- Data on intended use and authorisation
- Data on the manufacturing process of the substance/FCM
- Data on residual content of the substance
- Data on the potential migration of the substance
- Data on possible release due to abrasion

Toxicological data

• None

2.2. Methodologies

The assessment was conducted in line with the principles laid down in Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food. This Regulation underlines that applicants may consult the Guidelines of the Scientific Committee on Food (SCF) for the presentation of an application for safety assessment of a substance to be used in FCM prior to its authorisation (European Commission, 2001), including the corresponding data requirements. The dossier that the applicant submitted for evaluation was in line with the SCF guidelines (European Commission, 2001).

The methodology is based on the characterisation of the substance that is the subject of the request for safety assessment prior to authorisation, its impurities and reaction and degradation products, the evaluation of the exposure to those substances through migration and the definition of minimum sets of toxicity data required for safety assessment.

To establish the safety from ingestion of migrating substances, the toxicological data indicating the potential hazard and the likely human exposure data need to be combined. Exposure is estimated from

¹ Regulation (EC) No 1935/2004 of the European parliament and of the council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004, p. 4– 17.



studies on migration into food or food simulants and considering that a person may consume daily up to 1 kg of food in contact with the relevant FCM.

As a general rule, the greater the exposure through migration, the more toxicological data is required for the safety assessment of a substance. Currently there are three tiers with different thresholds triggering the need for more toxicological information as follows:

- a) In case of high migration (i.e. 5–60 mg/kg food), an extensive data set is needed.
- b) In case of migration between 0.05 and 5 mg/kg food, a reduced data set may suffice.
- c) In case of low migration (i.e. < 0.05 mg/kg food), only a limited data set is needed.

More detailed information on the required data is available in the SCF guidelines (European Commission, 2001).

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA, 2009) and considering the relevant guidance from the EFSA Scientific Committee such as the 'Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health' (EFSA Scientific Committee, 2018).

3. Assessment²

According to the applicant, the additive named silver nanoparticles (also called hereafter 'nanosilver') is supplied formulated as an aqueous dispersion of silver nanoparticles with all the particles in the size range of 1–100 nm. The applicant initially indicated an intention to use the additive as a biocide at up to 0.5% w/w of silver (5,000 mg Ag/kg) added into plastics for the antimicrobial functionalisation of surfaces and polymer matrices. However, further to the request by EFSA for additional data, the applicant restricted its application to a maximum use level of 0.025% w/w (250 mg Ag/kg). The biocidal function described falls under the classification of Product Type 4 (PT4) under the Biocidal Products Regulation (BPR).^{3,4}

The applicant declared that final articles would not be active materials in the sense of the Regulation (EC) No $450/2009^5$ as they would have no effect in the food. The assessment by the Panel of silver nanoparticles in the context of the Regulation (EC) 10/2011 focuses on the safety of consumer exposure and does not address any potential effect on the food microbiota.

The intended applications include both industrial (e.g. food processing), catering and consumer use, with repeated-use and single-use being envisaged. This being the case, articles containing the additive are intended to come into contact with all food types during food production, processing, storage, preparation and serving. The duration of the contact with food is estimated to range from seconds up to months. The temperature of the food contact is said to range from –20 to 200°C and the surface to mass ratio is also in a wide range, from 0.1 to 40 dm²/kg food, depending on the types of article and the related uses.

The applicant initially requested to use the additive both in non-polar plastics ('e.g. polyolefins, polyesters, styrenics') and polar plastics ('e.g. polyamides, polyurethanes, melamine-formaldehyde plastics'). However, further to the request by EFSA for additional data, the applicant restricted its application to non-polar plastics only.

The substance nanosilver was not evaluated by the SCF and EFSA in the past for its use in food contact materials. However, several silver-containing compounds used mostly as surface biocides have been evaluated by EFSA and are listed in the European Commission provisional list of additives used in Plastics.⁶ A group restriction of 0.05 mg Ag/kg food was proposed by the AFC Panel (EFSA, 2004) to the Commission.

² Technical dossier/Additional data Feb 21/Appendix B_technical dossier/section 1 and 4.

³ Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. OJ L 167, 27.6.2012, p. 1–123. https://eur-lex.europa.eu/legal-content/EN/TXT/ PDF/?uri=CELEX:32012R0528&from=EN

⁴ In 2018, the Swedish Chemicals Agency received an application for approval of silver as a nanomaterial as an active substance. However, it is considered withdrawn by the applicant prior to dossier validation and the European Commission is in the process of adopting a non-approval decision (https://echa.europa.eu/documents/10162/27434452/list_of_notifications_en. pdf/0ad3b68a-1e01-304e-722d-f4a8457842c3).

⁵ Commission Regulation (EC) No 450/2009 of 29 May 2009 on active and intelligent materials and articles intended to come into contact with food. OJ L 135, 30.5.2009, p. 3–11. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX: 32009R0450&from=EN

⁶ https://ec.europa.eu/food/system/files/2016-10/cs_fcm_legis_additives-prov-list.pdf



3.1. Non-toxicological data

3.1.1. Identity of the substance⁷

The synthesis of the nanosilver additive

The particles are

at a particle size below 100 nm

The additive is formulated as two commercial products, as aqueous dispersions containing 10% or 45% w/w silver, both with the two surfactants polyoxyethylene (20) sorbitan monolaurate and polyoxyethylene (25) glycerol trioleate (each at 4% and 18% w/w in the two formulations, respectively). The two formulations data were provided to illustrate that the distribution of particle size in the formulation (the 10% Ag formulation was used) was stable (storage conditions not described).

Concerning the two surfactants, polyoxyethylene (20) sorbitan monolaurate is authorised in plastics and listed in the Union List with the FCM number 568 with no specific restriction (Regulation (EC) 10/2011⁸); polyoxyethylene (25) glycerol trioleate is not listed in the Union List. Being polymer production aids (PPAs), surfactants not listed in the Union List are subject to national legislation and self-assessment,⁹ in line with Article 19 of the Plastics Regulation. The Panel noted that, considering their molecular weight, they are expected to largely stay in the plastic during the processing.

The applicant stated that the purity of the additive depends largely on the purity of

inductively coupled

plasma optical emission spectrometry (ICP-OES) data demonstrate the absence of significant elemental contaminants. The nanosilver in the dispersion was said to have a purity of 99.99%, but no experimental data was provided. The applicant stated that pure metals, such as silver, have a layer of oxides/hydroxides on the surface due to the surrounding atmosphere that contains water and oxygen species. The applicant estimated that the oxygen content is well below 0.01% w/w. Considering the method of production, the Panel had no concerns on the purity of the additive.

The CAS number provided for the additive, CAS No. 7440-22-4, is the one for silver. The additive, and more importantly, its formulations in which the particle size distribution is preserved and aggregation/agglomeration is prevented (see above), has some synonyms, including the material coded NM-300 that corresponds to the commercial product with 10% w/w silver nanoparticles. NM-300 is a nanosilver reference material within the OECD Working Party on Manufactured Nanomaterials (WPMN) international testing program. A second synonym is the material coded BAM-N001 (Certified Reference Material of the Bundesanstalt für Materialforschung und -prüfung, BAM). Consequently, considering the stability with respect to particle size distribution, the Panel took into account the studies on these synonymous materials that were provided by the applicant as full-text literature references.

The particle size distribution of the additive (for both formulations, 10% and 45% w/w silver content) was derived from the particle size distribution of the product containing 10% silver nanoparticles (NM-300/NM-300K Representative Manufactured Nanomaterials) that was characterised in the frame of the Joint Research Centre (JRC) programme on nanomaterials (Klein et al., 2011). It was characterised in an inter-laboratory comparative study by using transmission electron microscopy (TEM), scanning electron microscopy (SEM), nanoparticle tracking analysis (NTA), dynamic light scattering (DLS) and zeta-sizer. Based on electron microscopy analysis, the dispersion contained silver particles of about 15 nm mean diameter with 99% by number of particles with a size below 20 nm. A second peak of particles with a narrow diameter distribution of about 5 nm was identified using high resolution TEM. NTA, DLS and zeta-sizer analysis gave higher mean diameters, but were considered to show limited performances and appropriateness. Stability for 12 months was studied by UV–VIS spectrophotometry and graphite furnace atomic absorption spectroscopy (GF-AAS). The silver content and particle size distribution were stable over the 12 months.

⁷ Technical dossier/Additional data Feb 21/Appendix B_technical dossier/section 1 and 2.

⁸ Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02011R0010-20200923&from=EN

⁹ https://ec.europa.eu/food/system/files/2016-10/cs_fcm_plastic-guidance_201110_en.pdf



The particulate form is maintained when the additive is incorporated into plastics, albeit with some aggregation/agglomeration observed. For example, Bott (2017), Bott et al. (2012, 2014) prepared a range of low-density polyethylene (LDPE) samples containing the additive at 0, 50, 150 and 250 mg/kg silver in the plastic. TEM measurements showed that the silver particles were distributed homogeneously in the polymer. The averaged particle sizes were about 20–100 nm for the different samples. The smallest particles imaged were spherical with diameters of about 10 nm. The largest particles or aggregates/agglomerates found were more ellipsoidal with diameters from 100 to 270 nm. Most commonly, spherical particles of about 50 nm in diameter were found in the films.

3.1.2. Physical and chemical properties¹⁰

The densities of the commercial dispersions containing 10% and 45% w/w silver are 1.1 and 2.7 g/cm³, respectively. The nanoparticle dispersions are described by the applicant as being clear, mobile, dark orange and highly viscous, dark brown, respectively.

Concerning solubility, the applicant provided literature on several studies on the release of ionic silver into solution by dispersions of silver nanoparticles. The rate and extent of dissolution depends on the composition of the media and especially on the pH. The release represents an oxidative dissolution of the silver metal, Ag to Ag^+ (i.e. Ag(0) to Ag(I)) that is limited by saturation effects. By way of illustration, Wasmuth et al. (2016) used the test method of transformation/dissolution according to the OECD series on testing and assessment No. 29 'Guidance document on transformation/dissolution of metals and metal compounds in aqueous media' (OECD, 2001). For instance, at pH 8 and 21.5°C for 7 days, dispersions of silver nanoparticles at 1, 10 and 100 mg/L released essentially identical concentrations of ionic silver into solution: 27, 29 and 30 µg/L, respectively.

Silver nanoparticles are thermally stable under the manufacturing conditions of plastics. Considering their nature, silver nanoparticles are not expected to interact with or degrade the plastic to give rise to new organic substances with the potential to migrate from the plastic into food. Therefore, the assessment focused on potential migration of the inorganic additive itself in particulate and in ionic forms.

3.1.3. Specific migration¹¹

Potential migration of the substance at the intended use level of 0.025% w/w was investigated by means of (i) theoretical considerations based on migration modelling, (ii) specific migration from LDPE as a representative of non-polar plastics and (iii) an abrasion test of LDPE.

i) Theoretical considerations

The potential migration of the substance in particulate form was investigated using diffusion models. Under conservative assumptions (e.g. high solubility in food simulants, small particles with low effective molecular masses, high diffusivity plastic such as LDPE), the modelling estimated migration to be very low, below sub-ppt (ng/kg) levels (Bott et al., 2014). Since LDPE is generally recognised as the plastic material with the highest diffusivity for migrants, this conclusion is applicable to any type of other plastics, except for situations where a strong interaction with food/simulant can give rise to polymer swelling, such as between water and some polyamides.

ii) Specific migration from LDPE

The potential of the additive silver nanoparticles to migrate was investigated experimentally by Bott et al. (2014). Migration studies used LDPE films prepared with different levels of the silver additive incorporated. The food simulants used were 3% acetic acid, 10% and 95% ethanol, each at 60°C for 3, 6, 8 and 10 days of contact by total immersion. Isooctane was also used, under test conditions of immersion for 24 h at 40°C. Detectable migration of total silver (Ag(0) and Ag(+)) as measured by inductively coupled plasma mass spectrometry (ICP-MS) was found in the two aqueous food simulants only. Using a conventional food contact surface area/food mass (SA/M) ratio of 6 dm²/kg simulant, migration of total silver into 10% ethanol was up to 0.7 μ g/kg over the time course studied and into 3% acetic acid the migration was up to 6.0 μ g/kg. Migration into 95% ethanol and isooctane was not detectable at a detection limit of 0.07 μ g/kg for both simulants. Stability tests of silver nanoparticles in the two aqueous food simulants by asymmetric flow field-flow fractionation coupled to a multi-angle

¹⁰ Technical dossier/Additional data Feb 21/Appendix B_technical dossier/section 1 and 3.

¹¹ Technical dossier/Additional data Feb 21/Appendix B_technical dossier/section 1 and 6.



laser light scattering detector (AF4-MALLS) showed rapid oxidative dissolution of the particles and demonstrated that only ionic silver was present in the migration solutions. Thus, silver was only found in those food simulants in which silver nanoparticles are chemically unstable and are oxidatively dissolved into ionic silver species, as demonstrated by spiking experiments.

It was concluded by the authors that there is no migration of particulate silver; rather that there is oxidative dissolution of Ag+ from the silver particles at or very close to the surface of the plastic. An alternative, although not contradictory, mechanism proposed by the applicant for the release of silver is that the outer layer of silver oxide on the particles (see above) serve as a depot which releases small amounts of silver ions.

iii) Abrasion tests

An LDPE film containing the silver nanoparticle additive with a 250 mg silver/kg loading in the plastic was tested for abrasive release of silver (Bott and Franz, 2019) to assess the potential release of particles as a result of abrasion with solid/dry foods. The film was tested as such and after various additional material stresses were applied. (a) Thermal stress: heating at 100°C for 24 h; (b) Thermal stress: freezing to -50°C for 24 h; (c) Solvent stress: swelling by immersion in isooctane at 40°C for 24 h followed by venting for 12 h under a laboratory hood to evaporate any remaining solvent; (d) Mechanical stress: stretching until the film had visible deformation and a slightly rippled surface. Subsequently, the film samples were submitted to the abrasion test using guartz sand and vigorous motion on an orbital shaker for 30 or 60 min. The sand and any resulting abraded polymer/dust was transferred into vials and rinsed with 3% nitric acid by shaking for 15 min to detach/disperse/dissolve released additive particles. After centrifugation, the supernatant was analysed by AF4-MALLS and ICP-MS (monitoring m/z for silver). Based on the ICP-MS analysis for total silver, there was no detectable silver release from the plastic film, as such or after the different material pre-stress procedures used. The limit of detection (LoD) for total silver, using the conventional SA/M ratio of 6 dm²/kg, was 0.1 µg/kg food. The Panel considered that these tests demonstrate that the additive particles stay embedded in the polymers made with the maximum intended use level of 0.025% w/w.

In conclusion, when present at 0.025% w/w in LDPE, the additive resists release by abrasion and did not transfer into a simulant for solid/dry foods. Migration into liquid, especially acidic, food simulants can occur from the surface of the additive particles, from where silver is solubilised and migrates in ionic form. This conclusion is for non-polar polymers, for which the studied LDPE is a reasonable worst case. The conclusion does not extend to polar polymers, such as polyamides, which may be swollen by aqueous simulants. The applicant did not provide data for polar polymers that may be swollen.

3.2. Toxicological data

Based on the above-mentioned data, the additive particles stay embedded in the polymer and do not migrate, thus, do not give rise to exposure via food and to toxicological concern. The Panel noted that silver can be solubilised and migrate in ionic form. Therefore, the Panel considered the exposure to silver ions.

The Panel noted the group restriction of 50 μ g silver/kg food proposed by the EFSA AFC Panel in the past (EFSA, 2004). This group restriction was based on the toxicological dataset provided and taking into consideration that a 'total lifetime oral intake of about 10 g of silver was considered as the human no observed adverse effect level (NOAEL)' by the World Health Organization (WHO, 2004).¹² The original assessment by WHO was performed in 1993, based on 'epidemiological and pharmacokinetic knowledge' considering argyria sign of silver overload and with scientific references ranging from 1935 to 1989 (WHO, 2003). Using the default FCM exposure scenario (European Commission, 2001), the restriction of 50 μ g Ag/kg of food limits the intake from food contact plastics to less than 13% of the human NOAEL of 10 g of silver (equal to 0.39 mg/person per day).

The Panel is aware that, in their evaluation of active substances in the context of the Biocidal Product Regulation (BPR), the Human Health Working Group of the Biocidal Product Committee of ECHA has derived an ADI for silver of 0.9 μ g Ag ions/kg bw per day from a 105 weeks oral combined chronic/carcinogenicity study with silver zinc zeolite in Fisher 344 rats (1992) and based on pigmentation of internal organs (liver, kidneys, pancreas, stomach and lymph nodes choroid plexus)

¹² WHO considered that available data were inadequate to permit derivation of health-based guideline value.



observed in the next higher dose (ECHA-EFSA, 2020).¹³ This assessment provides an ADI that is based on more recent studies than the human NOAEL reported by the WHO that was considered until now by EFSA in their opinions, and it can be used to assess the risk of specific migration under the FCM regulation. Therefore, the ADI set in the context of the BPR should be considered to revisit the proposed group restriction applied to the migration of silver ions.

3.3. Discussion

The ADI set by ECHA of 0.9 μ g Ag/kg bw per day corresponds to 54 μ g/kg food if assuming the default FCM exposure scenario and an adult body weight of 60 kg. The Panel considered that the highest measured migration of silver ions from LDPE made with the maximum use level of 250 mg Ag/kg plastic (0.025% w/w) into 3% acetic acid was 6 μ g/kg and could result in an exposure of adults of about 10% of the ADI set by ECHA. For toddlers, when considering the P95 consumption of fruit and vegetable juices (that may be acidic) of 43 g/kg bw per day (EFSA CEF Panel, 2016), the migration of 6 μ g/kg food could result in an exposure of about 29% of the ADI set by ECHA. For infants, the scenario of using 3% acetic acid as simulant was considered inappropriate and 10% ethanol was used instead. With the migration of 0.7 μ g/kg in 10% ethanol and the consumption of 150 g liquid formula/kg bw per day (EFSA CEF Panel, 2016), the migration could result in an exposure of about 12% of the ADI.

The CEP Panel noted, however, that other sources of dietary exposure to silver have been identified, notably in the second French total diet study (ANSES, 2011), which estimated exposures exceeding the ADI set by ECHA. For instance, the mean exposures of the French adult and children (3–17 years) population to silver were estimated at 1.3 and 1.6 μ g/kg bw per day, respectively. For infants and toddlers, the ADI may also be exceeded (ANSES, 2016).

4. Conclusions

Based on the above-mentioned data, the Panel concluded that under the intended and tested conditions of uses, the particles of the additive silver nanoparticles stay embedded in the polymer, do not migrate and resist release by abrasion, thus, do not give rise to exposure via food and to toxicological concern. There is a low level of migration of silver in soluble ionic form (up to 6 μ g/kg food) from the surface of the additive particles. This is below the group restriction of 50 μ g silver/kg food proposed by the AFC Panel (EFSA, 2004) and would lead to a maximum exposure from FCM that would be below the ADI of 0.9 μ g/kg bw per day established by ECHA.

The Panel concluded that the use of the substance as an additive at up to 0.025% w/w in polymers such as polyolefins, polyesters and styrenics that do not swell in contact with aqueous food and food simulants does not raise safety concern for the consumer.

The Panel noted however that exposure to silver from other sources of dietary exposure may exceed the ADI set by ECHA.

Documentation provided to EFSA

- 1) Initial dossier. August 2018. Submitted by RAS AG.
- 2) Additional data. February 2021. Submitted by RAS AG.

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¹³ The publication of the final Risk Assessment Committee report is pending.



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Abbreviations



SA/M	surface area per food mass
SCF	Scientific Committee on Food
SEM	scanning electron microscopy
SML	specific migration limit
TEM	transmission electron microscopy
UV-VIS	ultraviolet-visible
w/w	weight by weight