Comparison of the evaluations performed on silver compounds used as biocidal active substances in food contact materials (FCM) by EFSA and ECHA

Joint EFSA – ECHA document February 2020

1. Introduction

EU Commission requested ECHA and EFSA to cooperate in order to ensure consistency between the respective scientific outputs regarding the silver compounds used as (surface) biocidal active substances in food contact materials. In the light of the Memorandum of Understanding between ECHA and EFSA[1] and following the request made by the Commission services to ECHA on 16 November 2018, the two agencies elaborated the present joint document, which provides

i) an overview of the assessments carried out on these substances according to their respective legislative framework (Biocidal Product Regulation (EU) No 528/2012; Regulation (EC) No 1935/2004),

ii) the joint ECHA/EFSA conclusions regarding the alignment of their scientific evaluations, taking account of their respective regulatory framework.

The document also includes a proposal on the way forward.

2. Assessment

2.1. EFSA: Assessments by the Scientific Panel on Additives, Flavourings, processing aids and food Contact (AFC) and by the Scientific Panel on Food Contact Materials, Enzymes and Processing Aids (CEF)

EFSA has evaluated silver sodium hydrogen zirconium phosphate, silver zeolite A, and silver zinc zeolite A in the context of the FCM regulation (Regulation (EC) 1935/2004). The corresponding EFSA opinions are the following:

- Silver Sodium Hydrogen Zirconium Phosphate: opinion of the AFC Panel on a request from the Commission related to a 4th list of substances for food contact materials (2004)[2];
- Silver Zeolite A ((Silver-zinc-sodium-ammonium-alumino-silicate), silver content 2 – 5%): opinion of the AFC Panel on a request from the Commission related to a 7th list of substances for food contact materials (2005)[3] and opinion of the CEF Panel on the re-evaluation of the substance (2011)[4];
- Silver Zinc Zeolite A ((silver-zinc sodium alumino silicate calcium metaphosphate), silver content 1 -1.6 %) and ((silver-zinc sodium magnesium

[1] Memorandum of Understanding between the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA); https://www.efsa.europa.eu/sites/default/files/assets/mouecha.pdf
[2] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2004.65a/epdf
[3] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2005.201a
[4] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.1999/epdf

alumino silicate calcium phosphate), silver content 0.34 - 0.54 %): opinion of the AFC Panel on a request from the Commission related to a 7th list of substances for food contact materials (2005)[3].

The assessments were 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. The 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 (EC, 2001), including the corresponding data requirements.

The methodology is notably based on the evaluation of the exposure through migration, the availability of minimum sets of toxicity data required for safety assessment and information on the microbiological properties.

Exposure is estimated from studies on the potential migration into food or food simulants and considering that a person may consume daily up to 1 kg of food in contact with 6 dm^2 of the relevant FCM. Information on the microbiological properties should enable an evaluation of the safety, efficacy and the microbiological implications of the use of the biocide. 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 limited (<0.05 mg/kg food), reduced (0.05-5 mg/kg food)) or extensive (5-60 mg/kg food) toxicological information. More detailed information on the required data is available in the SCF guidelines (European Commission, 2001)[5].

The dossiers that the applicants submitted for evaluation were in line with the SCF guidelines (European Commission, 2001). Migration data were submitted according to the requested uses and most were measured or estimated to be below or up to 50 µg/kg food. Accordingly, the applicants included “limited” or “reduced” toxicological data sets.

The EFSA opinions have concluded the following:

- absence of genotoxic potential;
- the substances belong to SCF group 3: substances for which an acceptable daily intake (ADI) or a tolerable daily intake (TDI) could not be established, but where the present use could be accepted;
- a group-specific migration limit (SML(T)) of 50 µg/kg food was set as a result of the SCF methodology and of a total lifetime oral intake of about 10 g of silver considered as the human no observed adverse effect level (NOAEL) by the World Health Organisation (WHO, 2004)[6]; the original assessment by WHO was performed in 1993 and “based on epidemiological and pharmacokinetic knowledge”;
- the restriction of 50 µg Ag/kg of food for the substance would limit the intake to less than 13% of the human NOAEL of 10 g of silver (equal to 0.39 mg/person per day);
- in addition to the SML(T) of 50 µg/kg food, restrictions in uses for SZ A were proposed in 2005 as follows: “Maximum content in polymer: 10% (w/w) of silver zeolite A containing ≤ 5% silver - Only for repeated use articles made from polyolefins (up to 40°C for contact times below 1 day) and for poly(alkylene terephthalate) based polymers (up to 99°C for contact times below 2 hours)”[7]. In 2011, the CEF Panel considered that restricting the uses to the compliance with the SML(T) would be self-limiting, i.e. would exclude the use of articles for which the migration would exceed the SML(T). Therefore, the restriction expressed in the 2005 opinion was not reported in the re-evaluation published

[5] https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out82_en.pdf
[6] https://www.who.int/water_sanitation_health/dwq/GDWQ2004web.pdf
[7] In this evaluation, other requested uses, i.e. in polystyrene and poly(vinyl chloride) were excluded due to analytical data showing high migration.

in 2011;
- the SML(T) applies to the sum of any migration of silver ions from plastic FCM SML(T).

2.2. ECHA: Assessment in the biocides Competent Authority Report (CAR)

Silver zeolite (SZ, CAS 130328-18-6i) silver zinc zeolite (SZZ, CAS 130328-20-0), silver copper zeolite (SCZ, CAS 130328-19-7) and silver sodium hydrogen zirconium phosphate (SSHZP, CAS 265647-11-8) are biocidal active substances evaluated by Kemi, the Swedish evaluating Competent Authority for biocides (eCA) and peer reviewed by the other Member State Competent Authorities with the support of ECHA and the involvement of the applicant. The evaluation phase of the biocidal active substances has been finalised by the eCA while the peer review is still ongoing (i.e. the draft CAR has been discussed at technical level by the Biocidal Product Committee Working Groups; the finalisation of the Biocidal Product Committee Opinion is foreseen by Q2 2020).

The evaluation of the biocidal active substances in the context of the Biocidal Product Regulation (BPR) is based on a dataset covering all toxicological endpoints, which led the eCA to the following outcome on the mammalian toxicology:
- absence of genotoxic potential;
- an ADI of 0.9 µg Ag/kg bw per day, established based on the NOAEL identified in rats in a study by Takizawa (1992) and based on pigmentation of internal organs (liver, kidneys, pancreas, stomach and lymph nodes choroid plexus) at 30 mg SZZ/kg bw per day[8]. The ADI for silver ions was derived from the NOAEL of 9 mg SZZ/kg bw/d, considering the content of Ag in SZZ (0.023), its release rate (0.42) and default assessment factor (100).

Intended uses

Articles are treated with Silver Compound Active Substances (SCAS) with the aim of reducing the risk of bacterial cross-contamination or to inhibit the bacterial growth. Information on the final use of the treated articles are not provided for the purposes of the active substance approval, for which the use of the active substance in a treated article is assessed and not the risks from single treated article. Accordingly, the applicants for the SCAS provided only some examples of the uses of SCAS in Product type 4: food packaging, food containers, kitchen/food utensils, convey belt and flow-through water filters. The eCA therefore selected examples of critical use situations that will probably give rise to the highest exposure to silver ions within a certain use pattern; thus, food contact material and preservation of water filers scenarios have been selected for Product Type 4.

Migration of silver from polymers into food simulants

Applicants provided information on silver ions migrating from LLDPE/LDPE (Linear low-density polyethylene/ Low-density polyethylene) and from different polymers into food simulants for only SSHZP and SZS respectively. The migration data during the first two hours were considered to reflect an acute exposure scenario.

To compensate for the lack of migration studies from different polymers for SSHZP and the complete absence of data for SZ and SCZ, the eCA applied an additional uncertainty factor to the available migration rates.

During the peer review, the Human Health Working Group (HH WG-V-2017) agreed to accept the additional factor to compensate the lack of data, nonetheless the WG "*…indicated the need to produce data on the migration of silver ion from different polymers in food and to avoid the use of additional factors. The submission of specific migration data*

[8] Due to a spelling mistake the following change in the document was made: '30 mg **SSHZP**/kg bw per day' was changed to '30 mg **SZZ**/kg bw per day' (29 June 2021).

should be requested at product authorisation stage. For the purposes of the active substance approval, the WG members agreed to accept the additional factor...[9]".

Exposure

In the absence of specific information on intended uses, the eCA estimated the indirect consumer exposure via food based on the default assumption that 1 kg of food coming into contact with 6 dm^2 of food contact material is consumed per day, as according to Regulation (EU) No 10/2011 and Note for Guidance for Food Contact Materials by EFSA (Updated on 30/07/2008)[10].

Consumer exposure via drinking water was estimated based on the maximum silver release and daily water consumption.

The SCAS were supported in several Product Types (PT 2, 4, 7, and 9), hence the eCA assumed that a consumer can be exposed over a time period to foods which have been in contact with FCM and several different treated articles, which fall under other PTs than PT 4. Accordingly, a cumulative exposure assessment should have been performed. However, it was concluded not manageable to take into account all possible exposure situations, noting the variety of use situations described in the dossiers and the variety of treated items. In order to compensate the impossibility to consider the multiple exposure sources in the exposure assessment, the Technical Meeting IV 2013 agreed to compare the acute exposure scenario with the long-term reference value as a conservative approach.

Risk characterisation

The eCA followed the approach agreed by the Technical Meeting and performed the risk assessment comparing the exposure estimation with the human health reference value (ADI) and concluded that none of the SCAS may be approved due to risk to consumer via use of solid treated articles used as food contact materials and drinking water. In addition, for SCZ and SSHPZ the non-approval proposal was based also on not sufficiently demonstrated efficacy.

2.3. Main differences in the assessments

ECHA and EFSA acknowledge the following main differences in their assessment:

- Scope of the assessment
- Toxicological assessment based on a different dataset
- Exposure assessment

Scope of the assessments

In accordance with the respective regulations, the scope of the assessments is different, and this drives the methodologies.

The eCA concluded on the risk by comparing the exposure estimation with the human health reference value (ADI). EFSA concluded on the safe uses (expressed as SML and/or restrictions in uses to which final articles have to comply with) based on the requested uses, the provided dataset and the comparison with the WHO NOAEL.

[9] FINAL minutes – WGV2017_TOX_6-5, 6-6, 6-7 Draft CAR on AgZeolite, AgCuZeolite, AgNaHZrPO4 PTs 2, 4, 7, 9

[10] EFSA Guidance document on the submission on the of a dossier on a substance to be used in food contact materials for evaluation by EFSA by the Panel on additives, Flavouring, Processing aids and materials in contact with Food (AFC). https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2008.21r

Toxicological assessment based on a different dataset

In line with their respective legislations and guidance on data requirements, EFSA and ECHA made use of different datasets in their evaluations.

The toxicological data set, provided to the eCA for biocides, included a chronic study. This enabled the eCA to perform a comprehensive assessment that led to the setting of an ADI.

With regards to the hazard assessment, EFSA was provided with a limited/reduced dataset that supported concluding on the lack of genotoxicity potential for which biocides peer review reached the same conclusion. EFSA also considered the human NOAEL derived by WHO.

Exposure assessment

As reported in chapter 2.2, faced with the practical impossibility to perform a sufficiently representative cumulative exposure assessment, the eCA estimated an acute exposure and did not consider repeated uses. When estimating the occurrence, EFSA considered the migrations levels from single and/or repeated uses in relation to the tiered approach.

To compensate for insufficient information on migration, the eCA added an extra factor to the available migration rates. EFSA did not follow a similar approach because either data were available, or the specific migration could be estimated.

When estimating the exposure, the eCA and EFSA have used the same assumption that 1 kg of food coming into contact with 6 dm^2 of food contact material is consumed per day.

The EFSA opinions considered for food consumption the adult population whereas the eCA considered also vulnerable groups, i.e. children, toddlers and infants that eat/drink proportionally more than adults on a kg body weight basis.

3. Conclusions

As requested by the Commission, ECHA and EFSA have intensified their cooperation concerning the review of PT04 silver compounds which are being used in food contact materials.

The conclusions and considerations in this document present the shared view of ECHA and EFSA.

In line with their respective legislations and guidance on data requirements, EFSA and ECHA performed two evaluations with different objectives and methodologies noting that the scenario to estimate the exposure on a daily basis is harmonised.

ECHA and EFSA conclude that the EFSA opinions in the context of the FCM regulation and the assessment made by the eCA in the context of the BPR are consistent, within their respective regulatory framework.

Way forward

The biocides assessment provides an ADI that is based on more recent studies than the human NOAEL reported by the WHO that was considered by EFSA in their opinions of 2004, 2005 and 2011, and that can be used to assess the risk of specific migration under the FCM regulation[11]. Therefore, the ADI set in the context of the BPR should be taken into account to revisit the existing total specific migration limit (SML(T)) applied to the migration of silver ions possibly with an allocation factor and the consideration of populations other than adults.

The collaboration between EFSA and ECHA interface started in 2014 and is developing to support the Commission in articulating the different regulatory framework with regards to the risk assessment and through this exercise, EFSA and ECHA gained a better understanding of commonalities and differences in their scope and methodologies. This will facilitate further cooperation.

[11] The ADI set by ECHA of 0.9 µg Ag/kg bw per day corresponds to 54 µg/kg food (considering the default person body weight of 60 kg). Considering other sources of exposure, a default allocation factor to plastic FCM of 10 or 20% of the 54 µg/kg food may be appropriate and this would correspond to 5 or 10 µg/kg food, respectively, and hence to a lower SML(T) than the current 50 µg/kg food.