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Safety evaluation of crosslinked polyacrylic acid polymers (carbomer) as a new food additive

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Abstract

The EFSA Panel on Food Additives and Flavourings (FAF) provides a scientific opinion on the safety of crosslinked polyacrylic acid polymers (carbomer) proposed for use as food additive in solid and liquid food supplements. Carbomer is formed from the monomer, acrylic acid, which is polymerised and crosslinked with allyl pentaerythritol (APE). The polymers are synthesised in ethyl acetate using [REDACTED] as free-radical polymerisation initiator. *In vivo* data showed no evidence for systemic availability or biotransformation of carbomer. Carbomer does not raise a concern regarding genotoxicity. Considering the available data set, the Panel derived an acceptable daily intake (ADI) of 190 mg/kg body weight (bw) per day based on a no observed adverse effect level (NOAEL) of 1,500 mg/kg bw per day from a sub-chronic 13-week study in rat, applying a compound specific uncertainty factor (UF) of 8. At the proposed maximum use levels, the exposure estimates ranged at the mean from 1.1 to 90.2 mg/kg bw per day and at the p95 from 12.5 to 237.4 mg/kg bw per day. At the proposed typical use level, the exposure estimates ranged at the mean from 0.7 to 60.2 mg/kg bw per day and at the p95 from 10.3 to 159.5 mg/kg bw per day. The Panel noted that the maximum proposed use levels would result in exposure estimates close to or above the ADI. The Panel also noted that level of exposure to carbomer from its proposed use is likely to be an overestimation. Taking a conservative approach, the Panel considered that exposure to carbomer would not give rise to a safety concern if the proposed maximum use level for solid food supplements is lowered to the typical use level reported by the applicant.

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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 Flavourings (FAF) was asked to provide a scientific opinion on the safety of crosslinked polyacrylic acid polymers (carbomer) proposed for use as food additive in solid and liquid food supplements, in accordance with Regulation (EC) No 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings.

The present evaluation is based on the data on crosslinked polyacrylic acid polymers (carbomer) in a newly submitted dossier and additional information submitted by the applicant during the assessment process in response to a request by EFSA.

The proposed food additive 'carbomer' is formed from the monomer, acrylic acid, which is polymerised and crosslinked with allyl pentaerythritol (APE). The polymers are synthesised in ethyl acetate using [REDACTED] as free-radical polymerisation initiator.

Two different grades of carbomer can be manufactured by varying the amount of the crosslinker used in the polymerisation reaction (i.e. sold under the trade names Carbopol[®] 974P NF Polymer, defined as 'highly crosslinked', and Carbopol[®] 971P NF Polymer, defined as 'lightly crosslinked') and a third grade of carbomer (Carbopol[®] 71G NF) can be obtained from Carbopol[®] 971P NF Polymer via dry granulation.

The estimated average molecular weight of the three carbomer grades is over 3×10^9 Daltons (Da) but an amount of lower molecular weight fraction (LMWF) is present in the final product [REDACTED]. The carbomer impurities profile was characterised by the applicant showing that they are substances carried over or originated from the starting materials, i.e. residual acrylic acid, residual ethyl acetate, unreacted APE or by-products from the polymerisation initiator. The anticipated dietary exposure estimates to the carbomer impurities using the specifications proposed by the applicant and/or the highest reported analytical levels were calculated by the Panel. For the residual acrylic acid, based on its estimated dietary exposure, the Panel considered that a lowering of the proposed maximum limit for the residual acrylic acid is recommended and it is technologically achievable as indicated by the analytical data provided.

Carbomer showed no evidence for systemic availability or biotransformation in an *in vivo* study in rats dosed by gavage with three ¹⁴C-labelled poly(acrylic acid) of different average molecular weights and degrees of cross-linking.

The toxicology data set comprised studies on sub-chronic toxicity (13-week dietary toxicity study in rats; 13-week dietary toxicity study in dogs) and the basic test battery for *in vitro* genotoxicity.

Overall, the available biological and toxicological data were considered adequate to conclude on the safety of the proposed new food additive.

From the sub-chronic 13-week toxicity study in rats, effects on body weight and body weight gain were observed as well as some minor effects in clinical chemistry parameters. The Panel considered that the decreases in body weight and body weight gain could be reflective of interactions between nutrients and carbomer resulting in nutrient malabsorption, which is considered as an undesirable effect. Therefore, the Panel identified a NOAEL of 1,513 mg/kg bw per day, the mid dose tested. In dogs, the NOAEL identified was of 1,642 mg/kg bw per day, the highest dose tested.

Carbomer does not raise concern with respect to genotoxicity.

Considering the available data set, the Panel derived an ADI of 190 mg/kg bw per day based on a NOAEL of 1,500 mg/kg bw per day from the sub-chronic 13-week toxicity study in rat, applying a compound specific UF of 8.

To assess the dietary exposure to carbomer, the exposure was calculated based on the proposed maximum use levels considering only consumers of food supplements and the proposed typical use level (200,000 mg/kg) in the solid food supplement food category (FC 17.1). At the proposed maximum use levels, the exposure estimates ranged at the mean from 1.1 to 90.2 mg/kg bw per day and at the p95 from 12.5 to 237.4 mg/kg bw per day. At the proposed typical use level for FC 17.1, the exposure estimates ranged at the mean from 0.7 to 60.2 mg/kg bw per day and at the p95 from 10.3 to 159.5 mg/kg bw per day.

The Panel noted that the estimated long-term exposures are very likely conservative, as the uncertainties identified resulted in an overestimation of the exposure to carbomer from its use as a food additive. On the other hand, it was noted that there may be additional exposure to carbomer from other uses e.g. pharmaceuticals.

The Panel noted that the maximum proposed use levels in solid and liquid food supplements would result in exposure estimates close to or above the derived ADI of 190 mg/kg bw per day, with the

highest p95 value being 240 mg/kg bw per day. The uncertainties identified indicated that level of exposure to carbomer from its proposed use as a food additive is likely to be an overestimation. Taking a conservative approach, the Panel concluded that exposure to carbomer would not give rise to a safety concern if the proposed maximum use level for the food supplements supplied in a solid form is lowered to the typical use level reported by the applicant.

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1. Introduction

The present scientific opinion deals with the safety evaluation of crosslinked polyacrylic acid polymers, known under the generic term 'carbomer', proposed as food additive for use in solid and liquid food supplements.

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

1.1.1. Background

The use of food additives is regulated under the European Parliament and Council Regulation (EC) No 1333/2008 on food additives.¹ Only food additives that are included in the Union list, in particular in Annex II to that regulation, may be placed on the market and used in foods under conditions of use specification therein. Moreover, food additives shall comply with the specifications as referred to in Article 14 of that Regulation and laid down in Commission Regulation (EU) No 231/2012².

An application has been introduced for the authorisation of the use of carbomer (cross-linked polyacrylic acid polymers) as a new food additive. Carbomer is intended for use in solid and liquid food supplements (i.e. food categories 17.1 and 17.2 of part E of Annex II to Regulation (EC) No 1333/2008). In solid food supplements it is intended for use at maximum level of 300,000 mg/kg for the controlled extended release of nutrients from the food supplement. In liquid food supplements it is intended for use at the maximum level of 30,000 mg/kg as thickener, emulsifier and stabiliser to develop semisolid and liquid oral formulations with a wide range of flow and rheological properties.

1.1.2. Terms of Reference

The European Commission requests the European Food Safety Authority to perform a risk assessment and to provide a scientific opinion on the safety of the proposed use of carbomer as a food additive in solid and liquid food supplements, in accordance with Regulation (EC) No 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and flavourings.³

1.2. Information on existing evaluations and authorisations

Carbomers, defined as high molecular mass polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols with 56–68% of carboxylic acid groups (for the dried substance), are used in pharmaceutical products and recognised as excipients in the European Pharmacopoeia (European Pharmacopoeia 10.5, 2021).

Carbomer (CAS No 9007-20-9; 9003-01-4; 76050-42-5; 9062-04-8; 9007-16-3; 9007-17-4) is included in the European Commission database for information on cosmetic substances and ingredients (CosIng, online). As a cosmetic ingredient, its functions are reported to be: emulsion stabiliser, gel formation and viscosity control.

Carbomer (CAS No 9007-20-9) is also pre-registered under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation⁴ and is listed in the inventory of substances likely to meet the Annex III criteria of the same Regulation as suspected hazardous to the aquatic environment and as a suspected skin irritant (ECHA, online a).

With respect to acrylic acid, the constituent monomer of the polymer carbomer, a group specific migration limit (SML) of 6 mg/kg food, expressed as free acrylic acid, is established for acrylic acid along with 13 related substances (e.g. esters of acrylic acid) used as food contact substances by Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.⁵

¹ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008.

² Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) no 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012.

³ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 354, 31.12.2008.

⁴ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006.

⁵ Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011.

2. Data and methodologies

2.1. Data

The applicant submitted a dossier to support the safety evaluation of the present application on crosslinked polyacrylic acid polymers, named as 'carbomer', proposed as a food additive for use in solid and liquid food supplements (Documentation provided to EFSA No. 1). Following a request from EFSA on 05 November 2020, additional data were provided by the applicant on 2 February 2021 (Documentation provided to EFSA No. 2).

2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance of the Scientific Committee on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing Guidance documents from the EFSA Scientific Committee.

The current 'Guidance for submission for food additive evaluation' (EFSA ANS Panel, 2012) has been followed by the FAF Panel for evaluating the present application.

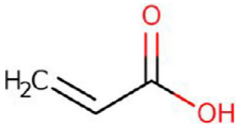
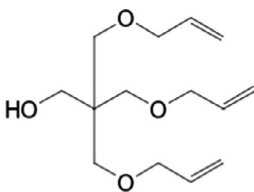
3. Assessment

3.1. Technical data

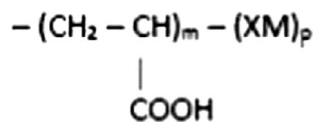
3.1.1. Identity of the proposed food additive

According to the applicant, the proposed food additive consists of crosslinked polyacrylic acid polymers, known as 'carbomer'. These polymers are formed from the monomer, acrylic acid, which is polymerised and crosslinked with allyl pentaerythritol (APE). The polymers are synthesised in ethyl acetate using [REDACTED] as free-radical polymerisation initiator (see Table 1).

Table 1: Monomer, crosslinker and polymerisation initiator of carbomer

Chemical structure	Function and chemical name
	Monomer acrylic acid (2-propenoic acid), CAS: 79-10-7
	Crosslinker allyl pentaerythritol (CAS: 91648-24-7), mixture comprising of: [REDACTED], the structure shown)
[REDACTED]	Polymerisation initiator [REDACTED]

The polymer was characterised by attenuated total reflective infra-red spectroscopy (ATR-IR) and by proton nuclear magnetic resonance spectroscopy ($^1\text{H-NMR}$). The structural unit of carbomer, as provided by the applicant, is the following:



m: number of monomer units; **XM**: crosslinker, **p**: number of crosslinker units, with **m** >> **p**.

Figure 1: Carbomer structural unit

According to the applicant, each carbomer is a network structure of polymer chains interconnected by crosslinks. A representative figure illustrating a carbomer polymer with crosslinks is given in Figure 2.



Figure 2: Representative figure illustrating a carbomer polymer with crosslinks (in blue)

The applicant indicated that three different grades of the carbomer are produced and sold under the trade names Carbopol® 974P NF Polymer, Carbopol® 971P NF Polymer and Carbopol® 71G NF Polymer. Specifically, two grades of carbomer can be manufactured by varying the amount of the crosslinker APE used in the polymerisation reaction (i.e. Carbopol® 974P NF Polymer, defined as 'highly crosslinked', and Carbopol® 971P NF Polymer, defined as 'lightly crosslinked') thus resulting in polymers with different viscosities. A third grade of carbomer (Carbopol® 71G NF Polymer) can be obtained from Carbopol® 971P NF Polymer via dry granulation to give a different particle size. According to the applicant, these different grades are chemically and toxicologically equivalent, all containing at least [redacted] of acrylic acid and less than [redacted] of crosslinker. Upon request for clarification from EFSA, the applicant explained that the amount of crosslinker used in the manufacture of 'lightly crosslinked' 971P NF and 71G NF polymers is ~ [redacted] of the amount used for 'highly crosslinked' Carbopol 974P NF Polymer. For all three polymer grades, the manufacturing molar ratio of crosslinking agent relative to the acrylic acid monomer is [redacted]. The applicant also explained that the degree of crosslinking affects the functional performance of the polymer. The degree of cross-linking affects the viscosity, the dissolution characteristics and the pore size of the polymer. [redacted]

[redacted] (Documentation provided to EFSA No. 1-2).

Based on the information provided by the applicant, the estimated average molecular weight of the three carbomer grades is over 3×10^9 Daltons (Da), but an amount of lower molecular weight oligomer fraction (LMWF) is present in the final product ([redacted])

[redacted]. Analysis using [redacted]

[redacted], showing a series of oligomers increasing in steps of 72 mass units that is consistent with the repeat unit of $-\text{CH}_2-\text{CH}(\text{COOH})-$ depicted in Figure 1. [redacted]

[redacted] (Documentation provided to EFSA No. 1-2).

The impurities profile of carbomer was analysed by gas chromatography-mass spectrometry (GC-MS) for component identification and by gas chromatograph (GC) or high-performance liquid chromatography (HPLC) for quantification. In particular, the applicant differentiated between:

- '*specified impurities*': such as acrylic acid (monomer) and ethyl acetate (solvent). According to the applicant, these impurities are controlled by the manufacturing process and limited by the proposed maximum limits as outlined in Table 2.
- '*unspecified impurities*' derived from the starting materials:
 - residual levels of unreacted cross linker APE. The applicant stated that the reaction conditions employed ensure an almost complete incorporation of the cross linker into the polymer backbone and that the manufacture ratio of APE/acrylic acid monomer is very low [REDACTED]. The [REDACTED] APE components (see structures in Table 1) were reported as being typically [REDACTED] with lower levels of the [REDACTED] APE at typically [REDACTED]. For the three batches of '*lightly crosslinked*' and three batches of '*highly crosslinked*' polymer analysed, the [REDACTED] component was in the range [REDACTED] and the [REDACTED] component was in the range [REDACTED]. No data were provided for the [REDACTED] component (Documentation provided to EFSA No. 2).
 - by-products from the polymerisation initiator [REDACTED]: [REDACTED]. The applicant indicated that [REDACTED] are typically present at levels of [REDACTED]. [REDACTED] and controls on raw materials specifications and the manufacturing processes ensure a high degree of batch-to-batch consistency. [REDACTED] (Documentation provided to EFSA No. 2).

Concerning the polymerisation initiator [REDACTED] itself, the Panel noted that the manufacturing process for carbomer involves heating during the polymerisation step and the drying step. Taking into account the short half-life of the thermally unstable initiator when heated,⁶ the Panel considered there will be no residues of the initiator in the proposed food additive.

Overall, for the '*unspecified impurities*', the applicant stated that these are typically present at levels below [REDACTED] (Documentation provided to EFSA No. 1). The Panel noted that the analytical levels reported for [REDACTED]

[REDACTED], as indicated by the applicant.

The anticipated dietary exposure estimates to the carbomer impurities ('*specified*' and '*unspecified*' impurities and LMWF [REDACTED] using the specifications proposed by the applicant and/or the highest reported analytical levels are reported in Section 3.3.2. (Table 7).

3.1.2. Proposed specifications

Specifications for the new food additive carbomer, as proposed by the applicant, are reported in Table 2.

Table 2: Specifications proposed by the applicant for the new food additive carbomer (Documentation provided to EFSA No. 1)

Common name	Carbomer
Trade names	Carbopol® 974P NF Polymer, Carbopol® 971P NF Polymer, Carbopol® 71G NF Polymer
Definition:	Carbomers are defined as high-molecular mass polymers obtained by polymerisation of acrylic acid and crosslinking with alkenyl ethers of sugars or polyalcohols
CAS nr.	9007-20-9 (primary CAS), 9003-01-4 (secondary CAS)
Carboxylic acid content	56–68% (on dried substance)

⁶ <https://neochemical.ru/File/Akzo%20Data%20110407-Initiators%20for%20High%20Polymers.pdf>

Acrylic acid	Not more than 1,000 mg/kg		
Ethyl acetate	Not more than 0.5%		
Loss on drying	Not more than 2%		
Sulfated ashes	Not more than 2.5%		
Viscosity (mP*s) ^{25°C} (a)	Carbopol® 974P NF	Carbopol® 971P NF	Carbopol® 71G NF
	29.400–39.400	4.000–11.000	
Physical form	Powder	Powder	Granules
Pass through 40 mesh, % 425 µm	–	–	95 min
Pass through 100 mesh, % 150 µm	–	–	10 max

(a): Brookfield RVT, 20 rpm, neutralised to pH 7.3–7.8. 0.5 wt% mucilage, spindle #5 (674P and 71G) or #6 (971P);
–: Not specified.

According to publicly available information, applicable synonyms for Carbopol® 974P NF Polymer and Carbopol® 971P NF Polymer are: carbomer, carboxypolymethylene; for Carbopol® 71G NF Polymer are: carbomer homopolymer type A, carbomer homopolymer (Lubrizol pharmaceuticals, online⁷).

The Panel noted that analytical data performed on five batches, for each grade of carbomer, were provided to demonstrate that carbomer can be consistently manufactured within its proposed specifications. The applicant provided information about the analytical methods employed for each determination (for some of them, the related validation reports were made available).

The applicant indicated that the proposed definition for the food additive is consistent with the European Pharmacopoeia monograph for carbomer. The Panel, however, noted that the European Pharmacopoeia monograph refers to a limit for benzene, a solvent medium which is not used in the manufacturing process of the proposed food additive described in the dossier submitted in support of the current evaluation (ethyl acetate is used instead) and that such definition does not specify the crosslinking agent (allyl pentaerythritol) and the polymerisation initiator [REDACTED]. In addition, the Panel noted that depending on the crosslinker and polymerisation initiator used in the synthesis of carbomer, different impurities may result in the final product. Therefore, the Panel considered that the crosslinker, the polymerisation initiator and the polymerisation solvent used in the manufacturing of carbomer, proposed in the present application, should be specified in the definition. Also, the Panel observed that no specification limit value has been proposed by the applicant for either the starting amount (or proportion) of the crosslinker used in the polymerisation and/or its residual content in the proposed food additive.

The applicant indicated that the total carboxylic acid group content is a key indicator of polymerisation and residual acrylic acid content provides confirmation that the reaction has gone to completion. Accordingly, inclusion of these two key manufacturing parameters for the EU specifications for the food additive was proposed by the applicant (see Table 2). The Panel noted that the reported residual levels of the monomer acrylic acid in five batches of each of the three carbomer grades were all listed as equal to 50 mg/kg. Based on such analytical results on the content of residual acrylic acid in the three grades of the proposed food additive, the Panel considered that lower values than the proposed maximum limit for the specification on residual acrylic acid (not more than 1,000 mg/kg) are technologically achievable.

For the residual polymerisation solvent ethyl acetate, the applicant indicated that it occurs in the final product at levels in the range of 0.2–0.48%, i.e. within the limit proposed for the specification (not more than 0.5%). The reported levels were similar for the three grades of carbomer. The Panel noted that the proposed specification maximum value should be expressed as 'percentage w/w'.

The Panel noted that an average MW value for carbomer is not indicated in the proposed specifications. Following clarifications request, the applicant explained that the carbomer grades cannot be characterised by molecular weight due to their 3D network structure which makes extremely difficult determining the MW distribution in these polymers. Moreover, the techniques commonly employed to determine the MW in polymers, such as GPC, light scattering, ultracentrifugation or osmometry, require the water solubility of the polymer and thus cannot be used being carbomer water insoluble (Documentation provided to EFSA No. 2).

The Panel also noted that in the proposed specifications, a maximum limit for the low MW fraction (LMWF) which may be present in the food additive (see Section 3.1.1) is not included. According to the rationale provided by the applicant, the manufacturing process employed ensures a practically

⁷ <https://www.lubrizol.com/Health/Pharmaceuticals/Excipients/Carbopol-Polymer-Products>

complete (over 99.8%) reaction yield, and thus, significant amount of LMWF would be not expected in the food additive carbomer. The LMWF was measured in three batches of Carbopol[®] 971P NF (*lightly crosslinked*) and three batches of 974P NF Polymer (*highly crosslinked*) [REDACTED]

[REDACTED] These tests established that for the six samples analysed, the [REDACTED] fraction was in the range of [REDACTED] and the [REDACTED] fraction was in the range [REDACTED] of the total carbomer mass (Documentation provided to EFSA No. 2). The Panel considered that a maximum limit for [REDACTED] fraction [REDACTED] [REDACTED] should be introduced in the specifications for the proposed food additive.

The Panel noted that no maximum limits are proposed by the applicant for toxic elements. The applicant stated that metal catalysts and reagents are not used in the employed manufacturing process, and therefore, metal residues are not expected to be present as impurities. The applicant also stated that surfaces of production equipment are constructed of stainless steel and contribution of elemental impurities from this source is unlikely to be significant. Based on historical data developed in 2016, for 321 lots of different carbomer grades, more than 98.7% (317 of 321) of the lots had less than 1 mg/kg each of arsenic, cadmium, cobalt, chromium, copper, mercury, molybdenum, nickel, lead, antimony and vanadium. For the four lots of the 321 that did not meet this value, it was not indicated which of the 11 elements listed was/were higher than 1 mg/kg. The applicant also provided analytical data on elemental impurity analysis using inductively coupled plasma mass spectrometry (ICP-MS), developed and validated by a third-party accredited laboratory. The validation data set included 10 samples representing Carbopol[®]NF grade polymers; each sample was tested in triplicate. The reported analytical data for lead, cadmium and mercury for the 10 samples were all below the respective limits of detection (Documentation provided to EFSA No. 2). Based on the data and information provided on toxic elements, the Panel concurred with the applicant's proposal to not set maximum limits for toxic elements given that the contamination to toxic elements in the proposed food additive is highly unlikely.

3.1.3. Manufacturing process

Monomer, crosslinker, solvent and polymerisation initiator are added to a reactor where they are agitated and heated until completion of reaction. The slurry is transferred to a dryer where it is stripped of solvent at an established temperature and under vacuum. The product is controlled for moisture then milled and de-aerated prior to being packaged for distribution. To manufacture Carbopol[®] 71G NF Polymer, Carbopol[®] 971P NF Polymer is rolled into sheets, broken into particles by grinding and then sieve-screened to obtain appropriately sized particles (Documentation provided to EFSA No. 1).

3.1.4. Particle size and solubility

Particle size

Upon request from EFSA, the applicant provided results of characterisation and particle sizing of six samples of the proposed food additive (three samples of Carbopol[®] 974P NF Polymer and three samples of Carbopol[®] 971P NF Polymer) using electron microscopy in scanning (SEM) and transmission (TEM) modes (Documentation provided to EFSA No. 2). According to the applicant, the morphology of the material is altered by the presence of water and so dispersion and drop-mounts using acetone and hexane was investigated, with hand-shaking and/or ultrasonic agitation. Based on the SEM and TEM results for these drop-mounts, proper dispersion and disaggregation/deagglomeration of the material could not be achieved using acetone or hexane as non-aqueous dispersion media. Therefore, as an alternative approach, dry sample material was deposited directly onto appropriate EM grids. The material was then analysed directly using TEM and was gold coated on the grid prior to SEM analysis. The images (micrographs) showed that the material had the appearance of micron-sized aggregates/agglomerates with nano-scale features. The limitations in the quality of the TEM and SEM images obtained (linked back to the limited sample preparation options available) prevented the quantitative analysis of particle sizes and size distributions of the constituent particles forming the aggregates/agglomerates.

Solubility

According to the information provided by the applicant, the proposed food additive carbomer is described as ultra-high MW cross-linked organic polymers, insoluble in any solvent, including water. These polymers are water-swellaable and form hydrogels in aqueous dispersions at pH ranges encountered in the gastrointestinal (GI) tract. The glass transition temperature (T_g) of Carbopol®-type polymers is 105°C in powder form. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. The polymer chains start gyrating, and the radius of gyration increases progressively as the water content increases. Macroscopically, this phenomenon manifests itself as swelling. Consequently, the material does not dissolve, but it swells greatly, up to 1,000 times the original dry volume depending on the pH and time of contact (Documentation provided to EFSA No. 1). The Panel considered that this behaviour is to be expected in any aqueous medium or in a biological environment and it will result in the loss of any nano-scale features that may be present originally in the dry material. Therefore, the Panel considered that the EFSA Guidance on Nanotechnology (EFSA Scientific Committee, 2018) is not applicable and the risk assessment of the proposed food additive should be done following the Guidance on Food Additive (EFSA ANS Panel, 2012).

The Panel further noted the statement provided by the applicant (Documentation provided to EFSA No. 1) on the description of microplastics used in the context of the ECHA Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC) Opinion on the Annex XV dossier proposing restrictions on intentionally added microplastics in which it is claimed that, according to the applicant, carbomer does not fit the definition of microplastics because they are *'not excreted as solid particles, but rather swell and are transformed into a gel without any defined dimension, and therefore they do not have a physical boundary and will not move as a unit'*.

3.1.5. Methods of analysis in food

The applicant indicated that detection and quantification of carbomer in a formulation is extremely difficult owing to its structure and ultra-high molecular weight (3D polymers with an average MW of 3 billion Da). Despite the fact that these polymers swell under certain conditions, they are not soluble in any solvent and so there are no methods suitable for extraction of the polymer from the formulation as a first step in analysis (Documentation provided to EFSA No. 1).

Carbomer can be characterised spectroscopically, e.g. by IR spectroscopy (Islam et al., 2004), but any triglyceride or fatty acid possibly present in the formulation interferes with the determination. NMR spectroscopy can also be exploited but an extensive sample clean-up, tailored to the specific formulation under test, is needed. Even gravimetric determination could be performed prior separation of carbomer from the complex formulations. The applicant stressed the importance to reduce the complexity of analysed formulation, i.e. removing components interfering with the carbomer measurement, to effectively detect and quantify carbomer in food formulations.

3.1.6. Stability, reaction and fate in food of the proposed food additive

According to the applicant, carbomer stored in sealed containers meet the proposed specifications (see Table 2) for 2 years after the production date. When carbomer is exposed to the air, at room temperature and 50% relative humidity, the moisture pickup is 8% w/w at equilibrium. Tablets formulation containing carbomer (Carbopol® 971P NF Polymer) stored under different temperatures (4, 25, 37, 45 and 55°C) and humidity conditions (11, 51, 91% RH) did not show any increase in weight, with exception for those stored at 37°C/91% RH which gained 40% in weight after 12 months storage (Goskonda et al., 1998).

When heated at 140–170°C, which is above the T_g at ~ 105°C, carbomer undergoes dehydration (elimination of water from 2 nearby acid units to form an anhydride bridge) and ultimately decarboxylation. Decarboxylation occurs much more slowly than dehydration. If the temperature is below the T_g, the rates of dehydration and decarboxylation are extremely slow (Eisenberg and Tokoyama, 1969).

3.2. Proposed uses and use levels

Through the current application, an authorisation of carbomer as a new food additive is sought with regard to the food categories listed in Table 3.

The Panel noted that the applicant submitted proposed maximum use levels of carbomer (in mg/kg) for two food categories according to Annex II of Regulation (EC) No 1333/2008, part D.

Table 3: Proposed uses and use levels of carbomer (Documentation provided to EFSA No. 1)

Food category number	Food category name	Proposed maximum use level (mg/kg)
17.1	Food supplements supplied in a solid form, excluding food supplements for infants and young children	300,000
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children	30,000

The applicant provided a range based upon current use levels of carbomer in similar pharmaceutical products: for FC 17.1, from 50,000 to 300,000 mg/kg and for FC 17.2, from 1,000 to 30,000 mg/kg.

The applicant also mentioned that the normal⁸ use level in FC 17.1 is anticipated to be around 200,000 mg/kg, while the normal use level to FC 17.2 is not provided.

3.3. Exposure data

3.3.1. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011)). The version of the Comprehensive database taken into account in this assessment was published February in 2020.⁹

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons may not be appropriate. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

Considering that the food categories for which an authorisation is sought excludes food supplements for infants and young children,¹⁰ the Panel estimated dietary exposure only for the older age groups. Therefore, food consumption data from children, adolescents, adults and the elderly were used in the exposure assessment. For the present assessment, food consumption data were available from 26 different dietary surveys carried out in 18 European countries (Table 4).

Table 4: Population groups considered for the exposure estimates of carbomer

Population	Age range	Countries with food consumption surveys covering more than 1 day
Children ^(a)	From 36 months up to and including 9 years of age	Belgium, Cyprus, Estonia, Finland, Germany, Italy, Latvia, Netherlands, Portugal, Sweden
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Estonia, Finland, Germany, Italy, Latvia, Netherlands, Portugal, Slovenia, Spain, Sweden
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Croatia, Cyprus, Estonia, Finland, France, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Slovenia
The elderly ^(a)	From 65 years of age and older	Cyprus, Estonia, Finland, France, Greece, Ireland, Italy, Latvia, Netherlands, Portugal, Slovenia, Spain

(a): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in Comprehensive Database (EFSA, 2011).

⁸ The normal use level mentioned by the applicant is then used for the refined exposure assessment scenario as the typical use levels usually considered by EFSA.

⁹ Available online: <http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm>

¹⁰ The term 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013 corresponds to 'toddlers' in the Comprehensive Database (EFSA, 2011). Both terms indicate children aged from 1 to 3 years of age.

Consumption records were codified according to the FoodEx2 classification system (EFSA, 2015). Nomenclature from the FoodEx2 classification system was linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform the exposure assessments. In practice, the FoodEx2 food codes were matched to the FCS food categories.

Food categories considered for the exposure assessment of carbomer

Both forms of food supplements in which the use of carbomer is proposed were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx2 classification system), using the most detailed level possible (up to FoodEx2 Level 7) (EFSA, 2015).

3.3.2. Exposure to carbomer from its proposed use as food additive

Estimate of exposure based on the Food Additives Intake Model (FAIM) template

The applicant has provided an estimate of the exposure to carbomer based on the output obtained using the FAIM model (version 2) (Documentation provided to EFSA No. 1).

The Panel decided not to use the estimate of exposure generated from the FAIM tool used by the applicant in 2020 (dossier submitted in April 2020) because this version of the FAIM tool does not:

- 1) Include the more recent surveys added to the EFSA Comprehensive database
- 2) differentiate between the solid and liquid forms of food supplements within FC 17 (food supplements as defined in Directive 2002/46/EC).
- 3) allow to estimate dietary exposure on a consumer basis; indeed only estimates for the whole population (consumers and no consumers) is possible.

Therefore, the Panel decided to perform a more refined assessment considering consumers only of food supplements. This population (consumers only) is assumed to be exposed to carbomer present at the maximum and at the proposed typical use level submitted by the applicant, on a daily basis via consumption of food supplements.

Refined exposure assessment scenario

The Panel estimated the chronic dietary exposure to carbomer for the following population groups: children, adolescents, adults and the elderly. Dietary exposure to carbomer was calculated by multiplying concentrations of carbomer per food category (Table 3) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are considered as not adequate to assess repeated exposure.

This was carried out for food supplements consumers per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 5). On the basis of these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011). Therefore, in the present assessment, the 95th percentile of exposure was only estimated for children from Belgium, Estonia, Finland, Germany, Latvia, Netherlands and Sweden, for adolescents from Austria, Belgium, Finland, Netherlands, Sweden and Slovenia, for adults from Austria, Belgium, Estonia, Finland, Ireland, Italy, Latvia, Netherlands, Portugal and Slovenia and for the elderly from Estonia, Finland, Ireland, Netherlands and Portugal. Detailed results per population group and survey are presented in Appendix A.

Exposure assessment to carbomer was carried out by the FAF Panel based on use levels submitted by the applicant: (1) proposed maximum levels; and (2) proposed typical level for the FC 17.1.

Table 5: Summary of dietary exposure to carbomer from its proposed maximum and typical use levels as a food additive in four population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Proposed maximum use level exposure assessment scenario				
• Mean	8.7–90.2	5.3–67.7	3.5–37.9	1.1–64.8
• 95th percentile	22.2–156.8	12.5–237.4	18.4–199.5	15.4–73.9
Proposed typical use level exposure assessment scenario^(a)				
• Mean	6.0–60.2	3.7–45.4	2.3–25.3	0.7–43.2
• 95th percentile	15.4–106.8	8.8–159.5	12.8–135.7	10.3–49.3

(a): The applicant provided a typical use level only for the FC 17.1.

At the proposed maximum use levels, the mean exposure to carbomer from its use as a food additive ranged from 1.1 mg/kg bw per day in the elderly to 90.2 mg/kg bw per day in children. The 95th percentile of exposure to carbomer ranged from 12.5 mg/kg bw per day in adolescents to 237.4 mg/kg bw per day in adolescents.

At the proposed typical use levels, the mean exposure to carbomer from its use as a food additive ranged from 0.7 mg/kg bw per day in the elderly to 60.2 mg/kg bw per day in children. The 95th percentile of exposure to carbomer ranged from 10.3 mg/kg bw per day in the elderly to 159.5 mg/kg bw per day in adolescents.

Between the two food categories considered, the main one contributing to the total mean exposure estimates (Appendix B) was food supplements supplied in a solid form, excluding food supplements for infants and young children (FC 17.1) for all population groups (89–100.0% for the proposed maximum levels and 84–100.0% for the proposed typical levels).

The estimate of exposure generated from the FAIM tool used by the applicant in 2020 (Documentation provided to EFSA No. 1) is lower than the current one calculated by the FAF Panel: at the mean, it ranged from 0.0 mg/kg bw per day in all age groups to 19.4 mg/kg bw per day in the elderly; at the 95th percentile, it ranged from 0.0 mg/kg bw per day in all age groups to 29.9 mg/kg bw per day also in the elderly. Differences between the applicant's and the Panel's estimates are due to the fact that the estimate of exposure generated from FAIM tool could only be performed for the whole population, while the refined exposure assessment, performed by the Panel, considered only consumers of food supplements. In addition, the refined exposure assessment, performed by the Panel, included more recent surveys than the FAIM tool estimate which resulted in a wider range.

3.3.3. Uncertainty analysis

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 6.

Table 6: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction^(a)
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/-
Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Concentration data: – levels considered applicable for all items within the entire food category	+
Food supplements consumers only exposure assessment scenario: – exposure calculations based on the maximum proposed use levels – exposure calculations based on the typical proposed use levels for FC 17.1 and maximum proposed use levels for FC 17.2	+ +/-

(a): +, uncertainty with potential to cause over-estimation of exposure; -, uncertainty with potential to cause underestimation of exposure.

Carbomer is proposed for use in the two food categories of food supplements. All foods belonging to these food categories were assumed to contain carbomer at the maximum proposed use level of 300,000 mg/kg for solid food supplements and of 30,000 mg/kg for liquid food supplements in the proposed maximum use levels exposure assessment scenario. The applicant indicated that the normal use levels in the solid food supplement food category (FC 17.1) are anticipated to be around 200,000 mg/kg. This proposed level was considered in the typical use levels exposure assessment scenario. Both exposure assessment scenarios are considering the population of consumers only of food supplements.

Given these observations, the Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to carbomer from its use as a food additive.

3.3.4. Anticipated dietary exposure to impurities

The applicant provided analytical levels on the content of the 'specified impurities', i.e. residual acrylic acid and ethyl acetate, of the LMWF [REDACTED] and of the 'unspecified impurities' (unreacted crosslinker ([REDACTED] APE), by-products from the polymerisation initiator ([REDACTED] and [REDACTED])). For the 'specified' impurities, the applicant proposed specification maximum values, i.e. 'not more than 1,000 mg/kg' for residual acrylic acid and 'not more than 0.5%' for residual ethyl acetate (see Table 2). The potential exposure to such compounds from the use of the proposed food additive can be calculated by assuming contamination of the food additive may be up to the specifications limit values (and/or the highest reported analytical levels) and then by calculation pro-rata to the estimates of anticipated dietary exposure to the proposed food additive itself (the highest 95th percentile, see Table 5). The outcome of such an exercise is illustrated in the following Table 7.

Table 7: Anticipated dietary exposure to the carbomer impurities using the limits from the proposed specifications and/or the highest reported analytical levels submitted by the applicant (Documentation provided to EFSA No. 1 and 2)

Impurity	Specification proposed by the applicant	Exposure to the impurity* (mg/kg bw per day)
	Highest reported analytical level	
Acrylic acid	Not more than 1,000 mg/kg	0.24
	[REDACTED]	0.01
Ethyl acetate	Not more than 0.5%	1.19
	[REDACTED]	1.14
[REDACTED]	–	–
[REDACTED]	[REDACTED]	0.01
[REDACTED]	–	–
[REDACTED]	[REDACTED]	< 0.01
Unreacted crosslinker ([REDACTED] APE)	–	–
	[REDACTED]	0.12
LMWF [REDACTED]	–	–
	[REDACTED]	1.42

*: Calculation pro-rata to the highest P95 value of the exposure estimates for the proposed food additive at the proposed maximum use levels, i.e. 237 mg/kg bw per day (see Table 5).

3.4. Biological and toxicological data

The biological data provided by the applicant to describe the gastrointestinal distribution of the proposed food additive carbomer were obtained from studies performed with ¹⁴C-labelled poly(acrylic acid)s synthesised as described by Riley et al., 2001b. The Panel considered the test substance representative of the carbomer proposed for use as food additive within the present application.

The repeated dose toxicity studies and the genotoxicity studies provided by the applicant were performed with the test substances named Carbopol® 974P and Carbopol® 974P NF Polymer, respectively, conforming to the proposed specifications.

The toxicological studies submitted in support of the application were performed in compliance with GLP.

3.4.1. Absorption, distribution, metabolism and excretion

The gastrointestinal distribution profiles for three ^{14}C -labelled poly(acrylic acid)s synthesised from ^{14}C -acrylic acid (Riley et al., 2001b) of different average molecular weights and degrees of cross-linking have been investigated *in vivo* in rat (Riley et al., 2001a). Male fasted Wistar rats were dosed by gavage with 0.25 g of the respective test material (3% w/w in water, pH 4.3). Animals had free access to water until they were sacrificed at predefined times (0.25, 1, 2, 4 and 6 h) after dosing, and the entire gastrointestinal tract was removed and sectioned to determine the distribution of the radio-labelled polymer ($n = 3$ rats per time point and polymer). Samples of blood, kidney, liver, faeces and urine were also collected. The results for polymer distribution within the rat intestine at various time points (15 min to 6 h) were presented in detail. The radio-labelled polymers were shown to move through the stomach within 4 h (low molecular weight, low viscosity polymer clearly faster than the high- and ultra-high molecular weight polymers). The transit of all three polymer forms through the first two sections of the small intestine was rapid, yet the polymers accumulated at the ileo-caecal junction; then after 6 h, the majority of all polymers were in the caecum, with some in the colon. In one case, high molecular weight polymer was detected in the faeces. The total amount of polymer detectable in the gastrointestinal tract at each time point was close to 100% whereas radioactivity was very low or undetectable in liver, kidney, blood or urine samples.

Overall, the results revealed similar gastrointestinal profiles of the three polymers tested despite the huge differences in molecular weight with no evidence for systemic availability or biotransformation of the polymers. Very small amount of radioactivity was detected at 2 h in liver and kidney; this most likely due to a minor, not characterised, low MW fraction of impurities related to acrylic acid.

3.4.2. Acute toxicity

No data on acute toxicity of carbomer were submitted by the applicant.

3.4.3. Sub-chronic toxicity

Rat

In a 30-day dose range-finding study, male and female Sprague-Dawley (CrI:CD[®]BR) rats were treated with Carbopol[®] 974 (assumed purity of 100%) via the diet (Documentation provided to EFSA No. 3). The rats were randomly assigned to five dosing groups (10 rats/group and sex) with concentrations levels of 0, 6,250, 12,500, 25,000 and 50,000 mg/kg diet (equal to 0, 581, 1,127, 2,303 and 4,654 mg/kg bw per day in males and 0, 614, 1,229, 2,448 and 4,991 mg/kg bw per day in females). No mortalities or treatment-related findings in clinical observations, body weights, food consumption and ophthalmology were reported. Some not dose-related statistically significant changes were observed in females in haematology (slight increases in platelet counts and decreases in leucocyte and lymphocyte counts) and in serum biochemistry (slight decrease in total protein concentration in high-dose females) which were not considered toxicologically relevant. Changes in absolute and relative organ weights (decrease in heart, adrenal, brain with stem and increase in kidney weight) were reported only for single dose groups in females (not dose-related) or males (high dose) in the absence of gross pathology or histopathology findings in these organs. In the liver of female rats, a dose-related increase in the severity of chronic active inflammation was observed (minimal/slight/moderate: 9/1/0, 2/8/0 and 1/6/3 in control, 25,000 and 50,000 mg/kg groups, respectively). The authors considered that due to the spontaneous nature of this lesion and in the absence of other related relevant toxicological findings, these observations did not provide strong evidence for liver toxicity of the test substance. The Panel agreed with this conclusion.

In a 13-week dietary toxicity study, male and female Sprague-Dawley (CrI:CD[®]BR) rats were treated with Carbopol[®] 974 (assumed purity of 100%) (Documentation provided to EFSA No. 4). The rats were randomly assigned to four dosing groups (10 rats/group and sex) with concentrations levels of 0, 12,500, 25,000 and 50,000 mg/kg diet (equal to 0, 744, 1,513 and 3,147 mg/kg bw per day in males and 0, 835, 1,681 and 3,416 mg/kg bw per day in females). No mortalities or treatment-related findings in clinical observations, food consumption and ophthalmology were reported. Decreases in body weight gains (weeks 1–13) of the animals in the high-dose group were reported for males (18%) and females (24%). Statistically significant decreases in body weights were only reported for high-dose males (9–11%). Decreases in erythrocyte counts along with increases in mean cell volume and mean cell haemoglobin were minor (decreases in the two latter effects in low-dose females were considered incidental) and well within the historical control ranges. In addition, changes in total protein albumin,

globulin, chloride, blood urea nitrogen (BUN) and inorganic phosphorus (P) concentrations were observed in high-dose males (BUN also in the mid dose and P also in the mid and low dose) and were considered potentially treatment-related. In high-dose females, there were decreases in calcium, potassium and chloride concentrations as well as a slight increase in aspartate aminotransferase activity (but not in alanine aminotransferase). The above effects were minor and may be due to malabsorption of essential nutrients. No relevant changes were reported for urinalysis values. In high-dose males, the relative adrenal weight was increased; in high-dose females the relative brain with stem weight was increased. No toxicologically relevant gross pathology or histopathology findings were reported.

Overall, the indication for liver toxicity reported in the 30-day dose-range finding study was not confirmed in the sub-chronic study. Despite the fact that no clear signs of toxicity were observed at any of the dose levels tested in the 13-week study, the Panel considered that the decreases in body weight and body weight gain along with changes in clinical chemistry in the high-dose groups would be reflective of nutrient malabsorption following interactions of nutrients in the GI tract with carbomer, which is considered as an undesirable effect. Therefore, the Panel identified a NOAEL of 1,513 mg/kg bw per day.

Dog

In a study, Beagle dogs were treated with Carbopol[®] 974 (assumed purity of 100%) in the diet for at least 13 weeks (Documentation provided to EFSA No. 5). Three groups of dogs each consisting of four males and four females received a diet containing the test substance at levels of 0, 12,500, 25,000 and 50,000 mg/kg diet (equal to 0, 420, 802 and 1,657 mg/kg per day in males and 0, 394, 784 and 1,642 mg/kg per day in females). Clinical examinations were performed daily on all dogs and body weights and food consumption were recorded weekly. Ophthalmic examinations were performed on all animals prior to treatment and at the end of treatment. Clinical pathology parameters (haematology and serum chemistry) were analysed during week 13. Necropsies were performed on all animals and selected organs were weighed. Selected tissues from all animals were examined microscopically. There were no test substance-related clinical observations. Mean body weight, body weight changes and food consumption were similar in treated and control animals. The ophthalmic examination noted no visible lesions in control or treated animals. There were also no treatment-related effects on haematology or serum chemistry parameters and no gross pathology or microscopic findings.

Overall, this study provides no indication of any toxic effects in dogs treated with Carbopol[®] 974 at doses up to 50,000 mg/kg diet (1,657 and 1,642 mg/kg bw per day, for males and females, respectively) for 13 weeks. The Panel agreed with this conclusion and identified a NOAEL of 1,642 mg/kg bw per day.

3.4.4. Genotoxicity

3.4.4.1. Genotoxicity of carbomer

The applicant submitted data from two *in vitro* genotoxicity tests in accordance with the recommendations of the EFSA Scientific Committee on genotoxicity testing (EFSA Scientific Committee, 2011) and the Tier 1 requirements for genotoxicity testing foreseen by the applicable 'Guidance for submission for food additive evaluation' (EFSA ANS Panel, 2012).

The basic test battery performed consisted of:

- A bacterial reverse mutation assay (OECD TG 471).
- An *in vitro* mammalian cell micronucleus test (OECD TG 487).

Bacterial reverse mutation assay

Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA were treated with suspensions of the test substance Carbopol[®] 974P NF Polymer using both the Ames plate incorporation (experiment 1) and pre-incubation (experiment 2) methods at up to 5,000 µg/plate, in triplicate, both with and without the addition of a rat liver homogenate metabolising system (S9-mix), in compliance with OECD TG 471 (Documentation provided to EFSA No. 6). The vehicle (acetonitrile) control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with and without metabolic activation, demonstrating the sensitivity of the assay and the efficacy of the S9-mix. There was no visible reduction in the growth of the bacterial background

lawn at any dose level, in both the experiments, either in the presence or absence of metabolic activation (S9-mix). A test substance precipitate was noted at and above 1,500 µg/plate in both the presence and absence of metabolic activation (S9-mix) in experiments 1 and 2; however, this observation did not prevent the scoring of revertant colonies. There were no biologically relevant increases in the frequency of revertant colonies in any experimental condition. Two statistically significant values were noted in experiment 1 (TA98 at 5 and 1,500 µg/plate in the absence of metabolic activation); however, these responses were not concentration-related and were within the historical control range for the strain, therefore were considered of no biological relevance.

***In vitro* micronucleus test in human lymphocytes**

The clastogenic and aneugenic potential of the test substance was tested in an *in vitro* micronucleus test in human lymphocytes, in compliance with the OECD TG 487 (Documentation provided to EFSA No. 7). Duplicate cultures of human lymphocytes, treated with the test substance Carbopol® 974P NF Polymer, were evaluated for micronuclei in binucleate cells at three dose levels, together with vehicle and positive controls. Three exposure conditions in a single experiment were used for the study: a 4-h exposure in the presence and absence of a standard metabolising system (S9-mix) and a 24-h exposure in the absence of metabolic activation. At the end of the exposure period, the cell cultures were washed and then incubated for a further 24 h in the presence of cytochalasin B. The dose levels used in the main experiment were selected by a preliminary toxicity test. The maximum concentration was limited by the formation of precipitate. The maximum concentration tested in all the experimental conditions was 2 µg/mL. The vehicle controls (dimethyl sulfoxide) had frequencies of cells with micronuclei within the range expected for normal human lymphocytes. The positive control induced statistically significant increases in the frequency of cells with micronuclei, demonstrating the sensitivity of the assay and the efficacy of the S9-mix. The test substance did not induce any statistically significant increases in the frequency of cells with micronuclei. No cytotoxicity was observed.

Overall, the test substance was negative in a bacterial reverse mutation assay performed in *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and in *Escherichia coli* strain WP2uvrA and in an *in vitro* micronucleus test in human lymphocytes. Therefore, the test substance does not raise a concern regarding genotoxicity.

3.4.4.2. Genotoxicity of carbomer impurities

In addition to the evaluation of the potential genotoxicity of the proposed food additive carbomer, the Panel also considered relevant information on the impurities that may be present in the food additive (Documentation provided to EFSA No. 2). The applicant provided information regarding the genotoxic potential of the following substances present as impurities in the final product: acrylic acid, ethyl acetate, [REDACTED] and allyl pentaerythritol.

Considering the available experimental data, the absence of relevant structural alerts for DNA reactivity and the low anticipated exposure levels to these impurities (see Table 7), the Panel concluded that the starting materials and the other impurities present in polymers proposed as food additive do not raise concern for genotoxicity.

3.4.5. Reproductive and developmental toxicity

In line with the current Guidance (EFSA ANS Panel, 2012), the data from the repeated dose oral sub-chronic toxicity studies in rats and dogs and from toxicokinetic did not trigger a requirement for additional testing for reproductive and developmental toxicity.

4. Discussion

In the present opinion, the Panel evaluated the safety of crosslinked polyacrylic acid polymers, known under the generic term 'carbomer', proposed for use as food additive in solid and liquid food supplements at the maximum use level of 30,000–300,000 mg/kg. The food categories for which an authorisation is sought with the current application are 17.1 and 17.2 of part E of Annex II to Regulation (EC) No 1333/2008. The proposed food additive is formed from the monomer, acrylic acid, which is polymerised and crosslinked with APE. The polymers are synthesised in ethyl acetate using [REDACTED] as free-radical polymerisation initiator. According to the applicant, two grades of carbomer can be manufactured by varying the amount of the crosslinker (APE) used in the

polymerisation reaction (i.e. sold under the trade names Carbopol® 974P NF Polymer, defined as 'highly crosslinked', and Carbopol® 971P NF Polymer, defined as 'lightly crosslinked') thus resulting in polymers with different viscosities. A third grade of carbomer (Carbopol® 71G NF Polymer) can be obtained from Carbopol® 971P NF Polymer via dry granulation to give a different particle size.

The applicant proposed a definition consistent with the European Pharmacopeia monograph for carbomer which, however, refers to the possible residual presence of a solvent medium (benzene) which is different from the one described in the current application (ethyl acetate) and does not specify either the crosslinking agent (APE) or the polymerisation initiator () which are used for manufacturing carbomer as described in the present application. Nevertheless, the Panel pointed out that depending on the crosslinker and polymerisation initiator used in the synthesis of carbomer, different impurities may result in the final product. Therefore, the Panel considered that the crosslinker, the polymerisation initiator and the polymerisation solvent used in the manufacturing of carbomer proposed as food additive should be specified in the definition since these have been part of the safety assessment.

The applicant provided analytical data on the content of the 'specified impurities', i.e. residual acrylic acid and ethyl acetate, of the low MW fraction (LMWF) and of the 'unspecified impurities', i.e. unreacted crosslinker (APE), by-products from the polymerisation initiator (and), which can result in the proposed food additive.

For the 'specified impurities', the applicant proposed specification maximum values, i.e. 'not more than 1,000 mg/kg' for residual acrylic acid and 'not more than 0.5%' for residual ethyl acetate (see Table 2). The anticipated dietary exposure estimates to the carbomer impurities using the specifications proposed by the applicant and/or the highest reported analytical levels are described in Section 3.3.2 (see Table 7).

For acrylic acid, the group SML is of 6 mg/kg, expressed as free acrylic acid, for acrylic acid along with 13 related substances (e.g. esters of acrylic acid) used as food contact substances (Commission Regulation (EU) No 10/2011), based on a temporary TDI (tTDI) of 0.1 mg/kg bw per day (SCF, 1991). The estimated anticipated dietary exposure to acrylic acid at the proposed maximum use levels considering the specification value proposed by the applicant (1,000 mg/kg) would exceed the tTDI of 0.1 mg/kg bw per day (0.24 mg/kg bw per day, see Table 7) which may indicate a safety concern. Therefore, the Panel recommends that the European Commission considers lowering the proposed maximum limit for the residual acrylic acid. This is technologically achievable as indicated by the analytical data provided which were significantly lower than 1,000 mg/kg (i.e. 50 mg/kg with anticipated estimates < 0.02 mg/kg bw per day, see Table 7).

For ethyl acetate, an ADI of 25 mg/kg bw per day has been established by JECFA (JECFA, 1997). The specification proposed by the applicant for this residual solvent is 0.5% and this would not give rise to an anticipated level of exposure that would be of concern (1.19 mg/kg bw per day, see Table 7).

Concerning the LMWF , this will comprise mainly of oligomers. As noted by the EFSA CEF Panel '*Oligomers/polymers with a molecular weight above 1,000 Da are unlikely to be absorbed by the gastrointestinal tract and so they are not considered to present a toxicological hazard, unless they are hydrolysed or induce a local effect on the gastrointestinal tract. Most substances below 600 Da are absorbed and the rate and extent of absorption is determined by factors other than simply the size and shape of the molecule. A cut-off value for the LMWF at 1,000 Da is recommended, as it covers any shape of molecules influencing the likelihood of absorption*' (EFSA CEF Panel, 2016). The LMWF is covered by the toxicological data set provided for the proposed food additive itself (Section 3.4) and the inclusion of a specification value on the LMWF is recommended by the Panel in order to ensure that any material of commerce in future (i.e. the additive) can be sufficiently represented by the test substances evaluated in this application.

For the unreacted cross-linking agent allyl pentaerythritol (APE), the Panel noted that a registration dossier was submitted to ECHA in which a repeated dose toxicity study summary was available and a NOAEL of 750 mg/kg bw per day (the highest tested dose) was identified by the registrant (ECHA, online b). If such NOAEL is considered, according to the resulting MOE/MOS (> 6,000), no concern would be identified for this substance.

For , an ADI of 0.5 mg/kg bw per day has been established by JECFA (JECFA, 1999). At the estimated anticipated dietary exposure level (0.01 mg/kg bw per day, see Table 7), no concern would be identified for . Considering that in a previous scientific opinion on the evaluation of as a flavouring substance, the EFSA AFC Panel considered that can be expected as the hydrolysis product of (EFSA, 2008), the

same ADI may be used as a reference point also for [REDACTED]. At the estimated exposure level (< 0.01 mg/kg bw per day, see Table 7), no concern would be identified for [REDACTED].

Carbomer is water insoluble and water-swellaable and forms hydrogels in aqueous dispersions. The polymers swell up to 1,000 times their original volume in water to form a gel when exposed to pH ranges encountered in the GI tract.

Data from one *in vivo* study in rats dosed by gavage with three ^{14}C -labelled poly(acrylic acids) of different average molecular weights and degrees of cross-linking showed no evidence for systemic availability or biotransformation of the three polymers tested which cover large differences in molecular weight of carbomer (all above average MW of 140,000). Very small amounts of radioactivity were detected at 2 h in liver and kidney which was interpreted by the Panel as likely due to the absorption of impurities with low MW related to acrylic acid.

The toxicology data set comprised studies on sub-chronic toxicity (13-week dietary toxicity study in rats; 13-week dietary toxicity study in dogs) and the basic test battery for *in vitro* genotoxicity.

Because of the lack of systemic availability, the Panel considered that the biological and toxicological data submitted in accordance with the Tier 1 requirements of the 'Guidance for submission for food additive evaluations' (EFSA ANS Panel, 2012) were adequate to conclude on the safety of the proposed new food additive.

Overall, carbomer was negative in the basic test battery of *in vitro* genotoxicity assays consisting of a bacterial reverse mutation assay (OECD TG 471) and an *in vitro* mammalian cell micronucleus test (OECD TG 487). The Panel, therefore, considered that carbomer does not raise a concern with respect to genotoxicity.

From the sub-chronic 13-week study in rats, effects on body weight and body weight gain were observed as well as some minor effects in clinical chemistry parameters. The Panel considered that the decreases in body weight and body weight gain could be reflective of interactions between nutrients and carbomer resulting in nutrient malabsorption, which is considered as an undesirable effect. Therefore, the Panel identified a NOAEL of 1,513 mg/kg bw per day. In dogs, the NOAEL identified was of 1,642 mg/kg bw per day, the highest dose tested.

Considering the available data set, the Panel derived an ADI of 190 mg/kg bw per day based on a NOAEL of 1,500 mg/kg bw per day from the sub-chronic 13-week toxicity study in rat. On the basis of the data available, the Panel did not consider justified the use of the default UF of 100, resulting from the combination of a factor of 10 for the toxicokinetic and toxicodynamic differences between individuals (intra species) and of an additional factor of 10 for the toxicokinetic and toxicodynamic differences between species (interspecies). Indeed, because of the lack of systemic availability or biotransformation of the proposed new food additive, the Panel considered that the toxicokinetic components of the two subfactors, accounting for the intra- and interspecies variability, would not contribute to the overall UF to be applied for the derivation of the ADI (toxicokinetic subfactors equal to 1). The compound specific UF for carbomer can then be calculated to be ~ 8 , to take into account possible interspecies (remaining UF = 2.5) and intraspecies (remaining UF = 3.16) differences in the consequences of carbomer-induced nutrient malabsorption. Moreover, in deriving the ADI from the available data, the Panel did not deem necessary to apply an additional time-correction factor of 2 for extrapolation from sub-chronic to chronic exposure. Therefore, the Panel considered the refined UF of 8 as sufficiently conservative considering that the substance is not systemically available and the effects observed in the rat were probably secondary to the high dose tested (nutrient malabsorption), rather than to toxicity.

The Panel performed an exposure assessment to carbomer from its proposed maximum use levels considering only consumers of food supplements. The food categories for which an authorisation is sought exclude food supplements for infants and young children.¹⁰ Therefore, the Panel estimated dietary exposure only for the older age groups: children, adolescents, adults and the elderly.

At the proposed maximum use levels, the mean dietary exposure to carbomer ranged from 1.1 mg/kg bw per day in the elderly to 90.2 mg/kg bw per day in children. The 95th percentile of exposure to carbomer ranged from 12.5 mg/kg bw per day in adolescents, to 237.4 mg/kg bw per day in adolescents.

The Panel also noted that the applicant indicated that the typical use level in the solid food supplement food category (FC 17.1) is anticipated to be around 200,000 mg/kg rather than the maximum level of 300,000 mg/kg used in the exposure calculations.

Considering this proposed typical use level for FC 17.1, the mean dietary exposure to carbomer ranged from 0.7 mg/kg bw per day in the elderly to 60.2 mg/kg bw per day in children and at the 95th percentile, exposure to carbomer ranged from 10.3 mg/kg bw per day in the elderly, to 159.5 mg/kg bw per day in adolescents.

Between the two food categories considered, the main one contributing to the total mean exposure estimates was food supplements supplied in a solid form, excluding food supplements for infants and young children (FC 17.1) for all population groups (89–100% for the proposed maximum use levels and 84–100% for the proposed typical use levels). The Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to carbomer from its use as a food additive. On the other hand, it is noted there may be additional exposure to carbomer from other uses, for example pharmaceuticals.

5. Conclusions

Based on the available toxicological data, the Panel derived an ADI of 190 mg/kg bw per day for carbomer. The maximum proposed use levels in solid and liquid food supplements would result in exposure estimates close to or above the ADI with the highest p95 value being 240 mg/kg bw per day.

The uncertainties identified indicated that level of exposure to carbomer from its proposed use as a food additive is likely to be an overestimation. Taking a conservative approach, the Panel concluded that exposure to carbomer would not give rise to a safety concern if the proposed maximum use levels for the food supplements supplied in a solid form are lowered to the typical use level reported by the applicant.

6. Recommendations

The Panel recommends the European Commission to consider:

- specifying in the definition the polymerisation solvent, the crosslinker and the polymerisation initiator used in the manufacturing of carbomer proposed for use as food additive.
- lowering the proposed maximum limit for acrylic acid, as supported by the analytical data provided by the applicant and the consideration by the Panel.
- including a maximum limit for the low MW fraction (██████████ fraction) in order to ensure that any material of commerce in future to be used as food additive can be sufficiently represented by the test substances evaluated in this application.

7. Documentation as provided to EFSA

- 1) Dossier 'Technical dossier for the application by Lubrizol Advanced Materials, Inc. to authorise crosslinked polyacrylic acid polymers ("carbomer") as food additive'. July 2020. Submitted by Lubrizol Advanced Materials, Inc.
- 2) Additional information submitted on 2nd February 2021. Submitted by Lubrizol Advanced Materials, Inc. in response to a request from EFSA.
- 3) Hazleton Washington, Inc. Study No. HWA 2323-135, 1992. 30-Day Range-Finding Oral Toxicity Study in Rats. Unpublished report. Submitted by Lubrizol Advanced Materials, Inc.
- 4) Hazleton Washington, Inc. Study No. HWA 2323-136, 1992. 13-Week Toxicity Study with Carbopol® 974P in rats. Unpublished report. Submitted by Lubrizol Advanced Materials, Inc.
- 5) Hazleton Washington, Inc. Study No. HWA 2323-138, 1992. 13-Week Toxicity Study with Carbopol® 974P in dogs. Unpublished report. Submitted by Lubrizol Advanced Materials, Inc.
- 6) Covance CRS Research Ltd. Study No. WV83WY, 2019. Reverse Mutation Assay "Ames Test" using *Salmonella typhimurium* and *Escherichia coli*. Unpublished report. Submitted by Lubrizol Advanced Materials, Inc.
- 7) Covance CRS Research Ltd. Study No. WQ73JN, 2019. Micronucleus Test in Human Lymphocytes *in vitro*. Unpublished report. Submitted by Lubrizol Advanced Materials, Inc.

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Abbreviations

ADI	Acceptable Daily intake
APE	allyl pentaerythritol
ATR-IR	attenuated total reflective infra-red spectroscopy
BUN	blood urea nitrogen
Da	Dalton
EM	Electron microscopy
FAF	EFSA Panel in Food Additives and Flavourings
FAIM	Food Additives Intake Model
FC	Food category

FCS	Food categorisation system
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
GI	gastrointestinal
GLP	good laboratory practice
GPC	gel permeation chromatography
GPC-MS	gel permeation chromatography-mass spectrometry
¹ H-NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
ICP-MS	inductively coupled plasma mass spectrometry
IR	Infra-red
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMWF	low molecular weight fraction
MOE	margin of exposure
MOS	margin of safety
MS	mass spectrometry
MW	molecular weight
NMR	nuclear magnetic resonance spectroscopy
NOAEL	no observed adverse effect level
P	inorganic phosphorus
RAC	ECHA Committee for Risk Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SEAC	Committee for Socio-economic Analysis
SEM	Scanning electron microscopy
SML	Specific migration limit
TDI	Tolerable Daily Intake
tTDI	temporary Tolerable Daily Intake
TEM	Transmission electron microscopy
Tg	glass transition temperature
UF	Uncertainty Factor

Appendix A – Summary of total estimated exposure of carbomer from their proposed use as food additives for the maximum and the typical level exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix A can be found in the online version of this output ('Supporting information' section): <https://doi.org/10.2903/j.efsa.2021.6693>

Appendix B – Main food categories contributing to exposure to carbomer using the maximum proposed use level and the proposed typical level exposure (> 5% to the total mean exposure)

Appendix B can be found in the online version of this output ('Supporting information' section): <https://doi.org/10.2903/j.efsa.2021.6693>