



Call for technical and toxicological data on carrageenan (E 407) for uses in foods for all population groups including infants below 16 weeks of age

EFSA-Q-number:	EFSA-Q-2018-00771
Published:	10/10/2018
Deadline for registering interest:	21/11/2018
Deadline for submission of data:	30/09/2020
New deadline for submission of data:	31/12/2022

Background

According to Regulation (EC) No 1333/2008¹, food additives which were permitted for use in the European Union before 20 January 2009 need to be re-evaluated by the European Food Safety Authority (EFSA). The programme for this re-evaluation is defined by Regulation (EU) No 257/2010².

EFSA has issued a scientific opinion on the safety of carrageenan (E 407) when used as food additive³ in food categories specified in Annexes II and III to Regulation (EC) No 1333/2008, exempting those for infants below 12 weeks of age. The reason was that the risk assessment approach followed at the time by the former EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) in the re-evaluation of food additives did not apply to this age group⁴. The ANS Panel has, therefore, specified in its opinion that the re-evaluation of uses for this particular age group will be performed separately.

¹ Regulation (EC) No 1333/2008 on food additives, OJ L 354, 31.12.2008

<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1333&from=EN>

² Regulation (EU) No 257/2010, setting up a programme for the re-evaluation of approved food additives in accordance with regulation (EC) No 1333/2008, OJ L 80, 26.03.2010.

<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010R0257&from=EN>

Re-evaluation of carrageenan (E 407) and processed Eucheuma seaweed (E 407a) as food additives, EFSA ANS Panel, 2018. <https://doi.org/10.2903/j.efsa.2018.5238>

⁴ Guidance for submission for food additive evaluations. EFSA ANS Panel, 2012. <https://doi.org/10.2903/j.efsa.2012.2760>



On 31 May 2017, EFSA's Scientific Committee (SC) published a guidance document⁵ on the risk assessment of substances present in food intended for infants below 16 weeks of age, enabling the assessment of the safe use of carrageenan (E 407) and of other food additives for the population group below that age.

Following the latest advice from the EFSA's Scientific Committee (SC) published guidance document⁵, the risk assessment to be performed will address the safety of uses of carrageenan (E 407) in foods for infants below 16 weeks of age.

In addition, the ANS Panel identified in the conclusions and recommendations of its published opinion on carrageenan (E 407) data gaps in the risk assessment, relevant for all population groups.

For the sake of efficiency, the European Commission asked EFSA to address the above lack of data (data gaps) during its risk assessment of food additives for uses in food for young infants. Therefore, specific data requirements for all uses of carrageenan (E 407) are included in this call for data.

EFSA will consider the relevance of the information provided for the risk assessment of carrageenan (E 407). The submission of the requested information is without prejudice to the final opinion of the Panel.

According to Article 6(5) of Regulation (EU) No 257/2010 where the requested information has not been submitted to EFSA within the set deadlines, the food additive may be removed from the Union list in accordance with the procedure laid down in Article 10.3 of Regulation (EC) No 1333/2008.

Overall objective

The purpose of this call for data is to offer interested parties (IPs) the opportunity to submit documented information (published, unpublished or newly generated) relevant to the re-evaluation of carrageenan (E 407) to be used in foods for infants below 16 weeks of age, as well as to address the data gaps that have been identified for all population groups in the already published EFSA opinion on this food additive.

Deadlines for submission of data and disclosure of contact details

Interested parties and stakeholders should provide earlier or at the latest by **31/12/2022** the information described below.

Within **6 weeks** from the publication of this call, please communicate in writing by e-mail to: fip@efsa.europa.eu, your availability to submit the requested information by the timeline specified above or any proposal for a new deadline providing justified reasons. Depending on the replies received the final deadline will be communicated to you through e-mail and by updating the current call.

In accordance with Article 6(4) of the Regulation (EU) No 257/2010 the information not submitted within the final deadline will only exceptionally be considered and EFSA can finalise its opinions on the basis of the information already provided.

⁵ Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. EFSA Scientific Committee, 2017.
<https://doi.org/10.2903/j.efsa.2017.4849>



In order to facilitate the collaboration of all interested parties to provide the data needed, we are seeking your consent to disclose the name and address of your organisation/business to the other parties that has expressed an interest to provide the requested information. If you do not wish to make these contact details available, clearly indicate it in your first communication.

Information sought

EFSA invites business operators and other interested parties (governments, interested organizations, universities, research institutions, companies) to submit technical, biological and toxicological information on carrageenan (E 407), as appropriate. This information will be used:

- for the follow-up on issues that have been raised in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of carrageenan (E 407) as a food additive by the former EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food) published in 2018³;
- for the risk assessment of carrageenan (E 407) in food for infants below 16 weeks of age in the food category 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). Data to be submitted should be in accordance with the EFSA Guidance of the Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age⁵.

A. Information regarding the follow up of the conclusions and the recommendations for carrageenan (E 407) (EFSA ANS Panel, 2018)³

With reference to the conclusions and recommendations in the Scientific Opinion on the re-evaluation of carrageenan (E 407) as food additive by the former EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food) published in 2018³ information is sought on:

1. Technical data

- The characterisation of all the different commercial preparations marketed as food additive E 407, from at least five independently produced batches of each preparation, in relation to:
 - the characterisation of carrageenan (the weight ratio of the κ -, ι - and λ - carrageenan);
 - the full molecular weight distribution. In addition, the weight- and number-average molecular weight range as calculated for each of the batches of carrageenan (E 407) should be provided;
- an interlaboratory validated analytical method to detect low molecular weight carrageenan in commercial preparations of carrageenan (E 407) at the limit specified in the Commission Regulation (EU) No 231/2012 (5% for the fraction below 50 kDa);
- the stability of carrageenan (E 407) in food, addressing the usual variation of parameters (temperature, pH) relevant for the authorised food uses. In particular, information on possible degradation products under acidic conditions in relevant food products is needed; detailed analytical data on the stability of these food additives in different food matrices including those with low pH (e.g. FC 12.3), and taking into account the influence of heat during food processing and storage (e.g. in FC 2.3, 4.2.2, 4.2.4.1, 11.2) covering food for infants and young children (FC 13.1);



- current levels of lead, mercury, cadmium and arsenic in commercial samples of the food additive;
- the lowest technologically achievable level for lead, mercury, cadmium and arsenic in order to adequately define their maximum limits in the specifications.

EFSA seeks specific information on the methods of analysis used to generate the technical data requested above. These include but are not limited to e.g. the principle of the method, the scope of the method (i.e. the range of sample types that the method is used for), the concentration units used to express the analytical result(s), validation of the method (in particular limit of detection (LOD) and limit of quantification(LOQ)).

2. Biological and Toxicological data

Biological and toxicological data, primarily obtained with the different carrageenan preparations marketed as the food additive (E 407), and complying with existing specifications (as set in Regulation (EU) 231/2012) are sought. The test preparations should be characterized with respect to the weight ratio of the κ -, ι - and λ - carrageenan and the full molecular weight distribution. It has been noted that the characterization of the test material in most of the toxicological studies reviewed by the ANS Panel³ in the re-evaluation of the food additive (E 407) was limited.

These data should address the following uncertainties in the biological and toxicological data, as identified by the ANS Panel (EFSA, 2018)³:

- the lack of reliable comparative toxicokinetic and toxicological studies between the different types of carrageenan and their corresponding low molecular weight fractions;
- the theoretical possibility that limited degradation could occur under conditions representative of the *in vivo* situation;
- that no firm conclusion on the other types of carrageenan could be drawn from the observation of occult blood in faeces of rhesus monkeys dosed with a commercial carrageenan (κ/λ -carrageenan types at a ratio of 70:30 from *Chondrus crispus*);
- the lack of adequate toxicological studies performed with low weight- average molecular weight carrageenan (around 200 kDa), apart from one 90-day study (with an average molecular weight carrageenan in the range of 196–257 kDa, not specified if it was a number average or a weight-average);
- the testing of carrageenan preparations for chronic toxicity and reproductive and developmental toxicity. Tests were performed almost exclusively with κ/λ -carrageenan; almost no data on ι -carrageenan were available;
- the inadequate data on the possible relevance of carrageenan exposure for existing inflammatory bowel diseases in humans;



- the unclear relevance for humans of observations in animal studies pointing to the induction of glucose intolerance and glucosuria by carrageenan;
- the possible role of sulfate and the interactions of the various forms of carrageenans with the gut microflora in some of the reported inflammatory effects of carrageenans.

3. Literature searches

Literature searches should be conducted relevant for the safety evaluation of carrageenan (E 407) for all uses in foods for all population groups from 06/03/2018⁶ up to the date of the data submission, as described in the Guidance for submission for food additive evaluations (see its section 5.3)⁴.

B. Information required for the risk assessment of carrageenan (E 407), for uses in foods for infants below 16 weeks of age

1. Technical data

For the uses of carrageenan (E 407), in foods for infants below 16 weeks (EC 13.1.5.1) EFSA seeks:

- information on the levels of use of carrageenan (E 407), alone or in combination with other thickening agents (indication of food additive name(s) and level(s) of use) in the special formulae used for infants below 16 weeks of age under special medical conditions (if not covered by the data request under A.1.);
- information on the fate and the reaction products of carrageenan (E 407) in special formulae used for infants below 16 weeks of age under special medical conditions (if not covered by the data request under A.1.);
- information on particular specification requirements for identity and the purity of carrageenan (E 407) (see A.1) for special formulae used for infants below 16 weeks of age under special medical conditions (including information with respect to the weight ratio of the κ -, ι - and λ -carrageenan and the full molecular weight distribution and the content of lead, mercury, cadmium and arsenic).

⁶ date of last literature search reported in the EFSA ANS opinion



2. Toxicological data⁷

Within the frame of the EFSA Guidance of the Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age⁵ and taking into account the uncertainties expressed in the EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food) published in 2018³, the following information on the toxicological properties of carrageenan (E 407) is required:

- a repeated dose toxicity study with direct oral administration of carrageenan (E 407) (fully characterized as described in sections A1 and A2, representative for the food additive preparations used in FC 13.1.5.1) to neonatal animals. Data to be reported should include gross and histopathological examination of the gastrointestinal tract, influence on the microbiota and a possible modification of the bioavailability of nutrients (vitamins and minerals, such as calcium, iron and zinc). The study shall be performed in piglets unless justification for the relevance of a study in another neonatal animal is given;
- clinical data focusing on gastrointestinal effects to assess the safety of carrageenan (E 407) when used in foods for infants below 16 weeks of age (FC 13.1.5.1);
- post-marketing surveillance reports on undesired and adverse reactions (including e.g. flatulence, gastrointestinal discomfort, changes of stool- frequencies and -consistency, diarrhoea and allergic reactions), indicating the ages and other relevant data of the exposed infants and young children and the use level of carrageenan (E 407) in the marketed products;
- published and unpublished case reports (e.g. available nutriviigilance data) on undesired and adverse effects, including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions, associated with the oral administration of carrageenan (E 407) to infants and young children.

3. Literature searches

Literature searches should be conducted relevant for the safety evaluation carrageenan (E 407) when used in foods for infants below 16 weeks of age up to the date of the data submission, as described in the Guidance for submission for food additive evaluations (section 5.3)⁴.

⁷ existing data should be resubmitted and information should be included to ensure that the test preparation fulfil the present requirements and are representative for the commercial preparations used in special infant formula (FC 13.1.5.1).



Confidentiality

According to article 8 of Regulation (EU) No 257/2010 setting up a re-evaluation programme of approved food additives, confidential treatment may be given to information the disclosure of which might significantly harm the competitive position of business operators or other interested parties.

Therefore, the business operators and/or the interested parties should indicate which information wish to be treated as confidential and provide verifiable justification supporting this request. Note that the information described in article 8(2) of the Regulation (EU) No 257/2010 cannot be confidential.

In application of Article 8(4) of Regulation (EU) 257/2010, following a proposal from EFSA, the Commission will decide after consulting the interested business operator and/or the other interested parties, which information may remain confidential.

Submission of information

Interested business operators and/or interested parties should submit the information to EFSA in electronic form (e.g. CD-rom, DVD, etc.) with a

- cover letter that should contain:
 - Reference to the specific call and the specific EFSA question number indicated (EFSA-Q-2018-00771);
 - Reference to the substance concerned and its E number;
 - The contact details⁸ (name of contact person, name of company/organisation, e-mail address and telephone number) of the person responsible for the data submission and, if applicable, the list of interested business operators and/or interested parties represented and their contact details;
- statement of the submitter that they hold all the necessary rights to grant EFSA permission to use and, where appropriate, to disclose the submitted information, data, document, paper or study for the purposes better defined in this call. In case the submitter does not enjoy the necessary rights for these data or studies, they should share the contact details of the respective owner(s) of data and/or of the relevant intellectual property right, so that EFSA may seek their approval directly;
- separate folders with the confidential and with the non-confidential parts.

Possibility for EFSA to use the data for the safety assessment of the same or other substance under the same or other legal or regulatory frameworks.

In case future mutual interests arise in exchanging any relevant information (i.e. technical or toxicological data) with the Joint WHO – FAO Expert Committee on Food Additives (JECFA) for the re-evaluation of food additives, we would appreciate your written consent for data sharing between EFSA and JECFA on this additive.

Note that EFSA may use or re-use relevant information or data (i.e. technical, toxicological data) for the evaluation of the same or another substance under the same or a different legal or regulatory framework from the one mentioned above.

⁸ The interested parties shall notify EFSA of any change in the contact details by sending an e-mail to the FIP mailbox (fip@efsa.europa.eu).



Correspondence

Please send all electronic correspondence, including enquiries to:

fip@efsa.europa.eu

Submissions should be sent to the following address:

European Food Safety Authority
FIP Unit
Via Carlo Magno 1/a
I-43126 Parma
Italy

Following the emergency restrictions on movement imposed by EU governments due to the COVID-19 outbreak, a Decision by EFSA's Executive Director has been recently signed concerning the electronic submission of applications for regulated products during COVID-19 outbreak.

With this decision, exceptionally and during the emergency period due to the Corona virus outbreak - EFSA will allow companies and institutions (applicants, the European Commission, EU Member States) to share documentation with the Authority through their chosen internet-based software. This Decision applies to the submission of technical dossiers, update of technical dossiers and responses to requests for missing or additional information during the life-cycle of the application (see related news⁹) These measures will remain in place until further notice.

⁹ <https://www.efsa.europa.eu/en/news/e-submission-regulated-product-applications-through-internet-based-software>



Annex I

Naming convention to be used for submission of information

Please create a folder with subfolders for each section applicable, as indicated below, and name files using the E number_section identification numbers_study name abbreviation of your choice, and indicating confidentiality:

Section 1. Technical data
Section 2. Biological and Toxicological data
Section 3. Literature searches