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Re-evaluation of alginic acid and its sodium, potassium, ammonium and calcium salts (E 400–E 404) as food additives

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Abstract

The present opinion deals with the re-evaluation of alginic acid and its sodium, potassium, ammonium and calcium salts (E 400–E 404) when used as food additives. Alginic acid and its salts (E 400–E 404) are authorised food additives in the EU in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008. Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010, the Panel concluded that there was no need for a numerical Acceptable Daily Intake (ADI) for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404), and that there was no safety concern at the level of the refined exposure assessment for the reported uses of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) as food additives. The Panel further concluded that exposure of infants and young children to alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) by the use of these food additives should stay below therapeutic dosages for these population groups at which side-effects could occur. Concerning the use of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in 'dietary foods for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and 'in dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2), the Panel further concluded that the available data did not allow an adequate assessment of the safety of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in infants and young children consuming the food belonging to the categories 13.1.5.1 and 13.1.5.2.

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Summary

The present opinion deals with the re-evaluation of alginic acid and its sodium, potassium, ammonium and calcium salts (E 400–E 404) when used as food additives.

Alginic acid and its salts (E 400–E 404) are authorised as a food additive in the European Union (EU) in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives.

In the EU, alginic acid and its salts (E 400–E 404) have been evaluated by the Scientific Committee for Food (SCF) in 1994 (SCF, 1994) who endorsed the evaluation of the Join FAO/WHO expert Committee on Food Additives (JECFA, 1993a): 'Acceptable Daily Intake (ADI) not specified.' In 1998, the SCF issued a report on certain additives for use in foods for infants and young children in good health and in foods for special medical purpose (FSMP) for infant and young children. The Committee concluded that 'the use of sodium alginate is acceptable up to a level of 1 g/L in FSMP used from 4 months of age onwards' (SCF, 1998a,b).

Alginic acid and its salts (E 400–E 404) were evaluated by JECFA in 1993 (JECFA, 1993a). Based on the available data on oral absorption, JECFA did not restrict the daily intake. The Committee therefore allocated a group ADI 'not specified' to alginic acid and derived salts; laxative effects that might occur at a high level of intake are assumed to be of minor toxicological relevance (JECFA, 1993a).

Alginic acid (E 400) is a linear glycuronoglycan polymer consisting mainly of β-(1→4)-linked D-mannuronic and α-(1→4)-linked L-guluronic acid units extracted from natural strains of various species of brown seaweeds (Phaeophyceae). Sodium (E 401), potassium (E 402), ammonium (E 403) and calcium alginates (E 404) are sodium, potassium, ammonium and calcium salts of alginic acid, respectively.

Specifications for these food additives have been defined in Commission Regulation (EU) 231/2012.

The Panel noted that, due to the possible hypersensitivity issues, limits for protein should be reduced as much as possible and included in the EC specifications.

The Panel noted that toxicological studies with an alginate–konjac–xanthan polysaccharide complex, called PGX, were available for its evaluation as novel food by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) did not consider the results of these studies in its re-evaluation of the individual substance alginic acid and its salts (E 400–E 404). It is not possible to conclude to what extent are the reported effects attributable to one of the individual components of the complex. The physicochemical properties of the individual components might also have changed during the manufacturing process of PGX (see Section 1.2).

The *in vitro* degradation by microbiota from human colon and the *in vivo* metabolism of alginic acid and its salts in animals have been investigated. These studies demonstrated that the *in vivo* biological fate of alginic acid and its salts are similar. Alginic acid and its salts would not be absorbed intact regardless of the form administered; they would not be metabolised by enzymes present in the gastrointestinal tract. However, they would be partially fermented during their passage through the large intestine by the action of the intestinal microbiota. The rate of breakdown in the gastrointestinal tract in humans is unknown. However, it is expected that fermentation of alginic acid and its salts would lead to the production of products such as short-chain fatty acids, which were considered of no concern by the Panel.

No adverse effects were observed in short-term and subchronic toxicity studies in rats and in one subchronic study in dogs. In the rat studies, the caecal enlargement described by the authors was considered by the Panel as an adaptive process related to the high doses tested.

Alginic acid and sodium alginate were tested in several *in vitro* assays and in one *in vivo* assay that, despite some limitations, did not reveal any genotoxic effect for alginic acid and sodium alginate. No studies were available for calcium alginate, potassium alginate and ammonium alginate. However, the Panel considered that a read-across approach can be applied to calcium alginate, potassium alginate and ammonium alginate to exclude a potential genotoxicity also for these compounds. The Panel also noted that alginic acid would not be absorbed unchanged and would not be metabolised by enzymes present in the gastrointestinal tract but partially fermented during its passage through the large intestine by the action of the intestinal tract microflora leading to the production of its fermentation products such as short-chain fatty acids (SCFA) which do not raise concerns for genotoxicity (OECD Toolbox 4.0). On this basis, the Panel concluded that there is no concern with respect to the genotoxicity for alginic acid and its salts (E 400–E 404).

According to the results of long-term toxicity studies in mice and rats, the Panel considered that alginic acid and its salts were not of concern with respect to carcinogenicity.

The Panel noted that the data presented in a two-generation study in Sprague–Dawley rats fed diets containing 0% or 5% sodium alginate (equivalent to 0 and 2,500 mg/kg body weight (bw) per day) for a period of 2 years were insufficient for hazard characterisation. However, the Panel noted that in a 90-day study in rats (Documentation provided to EFSA n. 8), no effects were observed on testes and ovary weights and also no histopathological changes were observed in testes, ovaries and uteri. No prenatal developmental toxicity studies were available.

The Panel considered that there was no indication for immunotoxicity or for an allergenic potential of alginic acid and its salts used as food additives.

In human studies, the oral intake of sodium alginate was well tolerated. The Panel also noted that for the medicinal use of a combination of sodium alginate and magnesium alginate in infants and young children with a maximum daily dosage ranging from 417 to 834 mg/kg bw calculated as sodium alginate, constipation, diarrhoea, intestinal obstruction, flatulence, abdominal distension and bezoar are indicated as adverse effects. However, in a multicentre study in infants, no significant differences in the incidences of gastrointestinal adverse events between the groups treated with the combination of sodium alginate and magnesium alginate or with placebo were observed.

Alginic acid and its salts (E 400–E 404) are authorised in a wide range of foods. The Panel did not identify brand loyalty to a specific food category, and therefore, the Panel considered that the non-brand-loyal scenario covering the general population was the more appropriate and realistic scenario for risk characterisation because it is assumed that the population would probably be exposed over the long term to the food additive present at the mean reported use in processed food.

A specific estimated exposure assessment scenario taking into account the food for special medical purpose for infants and young children (Food Category (FC) 13.1.5.1 and FC 13.1.5.2) was also performed to estimate exposure for infants and toddlers and children who may be on a specific diet. Considering that this diet is required due to specific needs, it is assumed that consumers are loyal to the food brand; therefore, the refined brand-loyal estimated exposure scenario was performed using the maximum permitted level for the FSMPs. The Panel noted that no data on use levels were submitted by industry for the food categories 13.1.5.1 and 13.1.5.2, which is in agreement with the absence of data in the Mintel database.

The refined estimates are based on 23 out of 75 food categories in which alginic acid and its salts (E 400–E 404) are authorised. The Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to alginic acid and its salts (E 400–E 404) as a food additive in European countries for the refined scenario if it is considered that the food additive may not be used in food categories for which no usage data have been provided.

The Panel also noted that the refined exposure estimates are based on information provided on the reported level of use of alginates (E 400–E 404). If actual practice changes, this refined estimates may no longer be representative and should be updated.

Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014), and given that:

- from all the data received, data were adequate for a refined exposure assessment for 23 out of 75 food categories;
- based on the reported use levels, a refined exposure (non-brand-loyal scenario) of up to 208 mg/kg bw per day in infants (from 12 weeks up to and including 11 months of age) was estimated;
- alginic acid and its salts were practically undigested, not absorbed intact, but partially fermented by intestinal microbiota in humans;
- adequate toxicity data were available;
- no adverse effects were reported in subchronic studies in rodents at the highest dose tested, of 13,500 mg sodium alginate/kg bw per day in rats;
- there was no concern with respect to the genotoxicity of alginic acid and its salts;
- no carcinogenic effects were reported at the highest dose tested of 37,500 mg sodium alginate/kg bw per day in mice;
- oral intake of 175 mg sodium alginate/kg bw per day for 7 days, followed by 200 mg/kg bw per day for further 16 days was well tolerated in healthy human adults;
- oral treatment of 14 patients on dialysis with approximately 120 mg calcium alginate/kg bw per day over a period of 1 year was well tolerated without side-effects;

- for higher therapeutic daily doses corresponding to 417–834 mg sodium alginate/kg bw in the treatment of infants and young children for gastric reflux, reported side-effects were gastrointestinal disorders including rare formation of intragastric 'mass';
- available data support read-across in safety parameters among alginic acid and its salts (E 400–E 404);

the Panel concluded that there was no need for a numerical ADI for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404), and that there was no safety concern at the level of the refined exposure assessment for the reported uses of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) as food additives. The Panel further concluded that exposure of infants and young children to alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) by the use of these food additives should stay below therapeutic dosages for these population groups at which side-effects could occur.

Infants and young children consuming foods for special medical purposes and special formulae

Concerning the use of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in 'dietary foods for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and 'in dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2), and given that:

- for populations consuming dietary foods for special medical purposes and special formulae, the highest refined exposure estimate (p95) calculated based on MPL were for toddlers (12–35 months) up to 290.4 mg/kg bw per day (brand-loyal scenario);
- infants and young children consuming foods belonging to these food categories may show a higher susceptibility to the gastrointestinal effects of alginic acid and its salts than their healthy counterparts due to their underlying medical condition;
- no adequate specific studies addressing the safety of use of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in this population under certain medical conditions were available;
- no data on use levels were submitted by industry for the food categories 13.1.5.1 and 13.1.5.2, which is in agreement with the absence of data in the Mintel database;

the Panel concluded that the available data did not allow an adequate assessment of the safety of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in infants and young children consuming the food belonging to the categories 13.1.5.1 and 13.1.5.2.

The Panel recommended that the European Commission considers:

- revising the current limits for toxic elements (arsenic, cadmium, lead and mercury) in the EU specifications for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in order to ensure that alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) as food additives will not be a significant source of exposure to those toxic elements in food, in particular for infants and children;
- defining a suitable validated analytical method of appropriate accuracy for the determination of formaldehyde in the specifications for alginic acid and its salts (E 400–E 404).

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1. Introduction

The present opinion deals with the re-evaluation of alginic acid and its sodium, potassium, ammonium and calcium salts (E 400–E 404) when used as food additives.

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

1.1.1. Background

Regulation (EC) No 1333/2008[1] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[2]. This Regulation also foresees that food additives are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by a group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[3] of 2001. The report 'Food additives in Europe 2000'[4] submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.2. Terms of Reference

The Commission asks the EFSA to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.3. Interpretation of terms of reference

This re-evaluation refers exclusively to the uses of alginic acid and its salts (E 400–E 404) as food additives in food, including food supplements, and does not include a safety assessment of other uses of alginic acid and its salts (as described in Section 3.4.2).

1.2. Information on existing evaluations and authorisations

Alginic acid and its salts (E 400–E 404) are authorised as a food additive in the EU in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012[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, pp. 16–33.
[2] Commission Regulation (EU) No. 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No. 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, pp. 19–27.
[3] COM(2001) 542 final.
[4] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord, 2002a,b, 560.
[5] 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, p 1.

In the EU, alginic acid and its salts (E 400–E 404) have been evaluated by the SCF in 1994 (SCF, 1994) who endorsed the evaluation of JECFA (1993a): 'ADI not specified'. The basis was newly presented data together with existing data; however, no toxicological data were specified in the document (SCF, 1994). The SCF stressed that the evaluation only covered the substances when used as food additives. In the SCF Opinion (1994), the ammonium salt of alginic acid was not mentioned. In 1998, the SCF issued a report on certain additives for use in foods for infants and young children in good health and in foods for special medical purpose (FSMP) for infant and young children. The Committee concluded that 'the use of sodium alginate is acceptable up to a level of 1 g/L in FSMP used from 4 months of age onwards' (SCF, 1998a,b).

Alginic acid and its salts (E 400–E 404) were evaluated by JECFA in 1993 (JECFA, 1993a). Based on the available data on oral absorption, JECFA did not restrict the daily intake. The Committee pointed out that for non-absorbed compounds an ADI 'not specified' usually had been allocated. The Committee therefore allocated a group ADI 'not specified' to alginic acid and its salts; laxative effects that might occur at a high level of intake are assumed to be of minor toxicological relevance (JECFA, 1993a).

Alginic acid and its salts (E 400–E 404) have also been reviewed by the Nordic Council of Ministers (TemaNord, 2002a,b), who concluded that alginic acid and its salts as defined by the specifications seem to be covered by the JECFA evaluation (JECFA, 1993a).

Alginic acid and its salts (E 400–E 404) belong to the group of food additives that were found in jelly minicups, which were suspended in 2004 by the European Commission from being to be placed on the market and for import (Commission Decision 2004/37/EC; European Commission, 2004), following the measures taken and information provided by the different Member States. Jelly minicups are defined as 'jelly confectionery of a firm consistence, contained in semi-rigid minicups or minicapsules, intended to be ingested in a single bite by exerting pressure on the minicups or minicapsule to project the confectionery into the mouth.'

In 2004, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA (AFC) Panel, 2004) prepared a scientific opinion on a request from the European Commission related to the use of certain food additives derived from seaweed or non-seaweed origin, including alginic acid and its salts (E 400–E 404) in jelly minicups. The AFC Panel concluded that any of these gel-forming additives or of any other type that gave rise to a confectionery product of a similar size, with similar physical and/or physicochemical properties and that could be ingested in the same way as the jelly minicups, would give rise to a risk for choking (European Commission, 2004). The use of these additives in jelly minicups is not authorised in the EU.[6]

In 2006, the EFSA AFC Panel prepared a scientific opinion on the use of formaldehyde as a preservative during the manufacture and preparation of food additives; the Panel estimated that exposure to gelling additives such as alginates containing residual formaldehyde at the levels of 50 mg/kg of additive would be of no safety concern (EFSA, 2006). Maximum limits (not more than 50 mg/kg) are established in the current European Commission Regulation for formaldehyde in several thickening food additives from algae origin including alginic acid and its salts (E 400–E 404) (EU Regulation No 231/2012).

In 2017, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) published a scientific opinion on an alginate–konjac–xanthan polysaccharide complex (PGX) in the framework of Regulation (EC) No 258/97 (EFSA NDA Panel, 2017). PGX is produced by mixing konjac glucomannan, xanthan gum and sodium alginate in a specific ratio, claimed to be proprietary and confidential, and then processing them by a proprietary process involving heat. Based on studies that compared different physicochemical parameters for PGX and the three individual substances, the applicant claimed that PGX is a 'novel complex' rather than a mixture of the three substances. The maximum daily intake of PGX from fortified foods and food supplements recommended by the applicant was 15 g per person. From a 13-week study in Sprague–Dawley rats, which received a diet containing 0%, 1.25%, 2.5% or 5% of PGX, the EFSA NDA Panel derived a no-observed-adverse effect (NOAEL) of 2.5% PGX in the diet equivalent to 1.8 g/kg body weight (bw) per day. This result was based on statistically significant increases in serum activities of alanine transaminase (ALT) and aspartate transaminase (AST) in females in the high-dose group. Considering the highest mean and 95th percentile anticipated daily intake of PGX from fortified foods, the EFSA NDA Panel derived margins of exposure (MoE) of 12 and 6. The MoE derived by the EFSA NDA Panel for PGX consumed as food supplements was 9. The EFSA NDA Panel concluded that the safety of PGX as a novel food for the intended uses and use levels as proposed by the applicant had not been established.

[6] Annex II of Regulation (EC) No. 1333/2008 on food additives for use in foodstuffs.

In 2017, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) adopted a scientific opinion on the safety and efficacy of sodium and potassium alginates for pets, other non food-producing animals and fish (EFSA FEEDAP Panel, 2017). As the technological function of these two additives are determined by the alginate content, sodium and potassium alginate were considered as equivalent. Sodium alginate is intended to be used in feeding stuffs for pets, other non-food-producing animals and fish, with no maximum recommended use level, whereas potassium alginate is intended to be used in feeding stuffs for cats and dogs at levels up to 40,000 mg/kg feed (on dry matter). The FEEDAP Panel concluded that the maximum dose considered safe for cats, dogs, other non-food-producing animals, salmonids and other fish is 40,000 mg alginates (sodium and potassium salts)/kg complete feed, whereas the use of alginates in feeding stuffs for fish is of no concern for the consumer.

2. Data and methodologies

2.1. Data

The Panel was not provided with a newly submitted dossier. EFSA launched public calls for data[7,8,9] and, if relevant, contacted other risk assessment bodies to collect relevant information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to the last Working Group meeting before the adoption of the opinion.[10] Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based, however, not always these were available to the Panel.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database[11]) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online database which was used for checking the labelling of products containing alginic acid and its salts (E 400–E 404) within the EU's food products as GNPD shows the compulsory ingredient information presented in the labelling of products.

2.2. Methodologies

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

The ANS Panel assessed the safety of alginic acid and its salts (E 400–E 404) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the SCF (2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) for studies in rodents or, in the case of other animal species, by JECFA (2000). In these cases, the daily intake is expressed as equivalent. When, in human studies in adults (aged above 18 years), the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day was calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012).

Dietary exposure to alginic acid and its salts (E 400–E 404) from their use as food additives was estimated combining food consumption data available within the EFSA Comprehensive European Food

[7] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of emulsifiers, stabilisers and gelling agents Deadline: 23 May 2010. Available from: http://www.efsa.europa.eu/en/dataclosed/call/ans091123

[8] Call for technical data on certain thickening agents permitted as food additives in the EU - extended deadline: 31 December 2015. Available online: http://www.efsa.europa.eu/it/data/call/141219

[9] Call for food additives usages level and/or concentration data in food and beverages intended to human consumption. Deadline for submission: 31 May 2016. Available online: https://www.efsa.europa.eu/en/data/call/151012

[10] 3-4/5/2017

[11] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Consumption Database with the maximum permissible levels (MPLs) according to Annex II to Regulation (EC) No 1333/2008[12] and/or reported use levels and analytical data submitted to EFSA following a call for data. Different scenarios were used to calculate exposure (see Section 3.4.1). Uncertainties on the exposure assessment were identified and discussed.

In the context of this re-evaluation, the Panel followed the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EC) No 257/2010 (EFSA ANS Panel, 2014).

3. Assessment

3.1. Technical data

3.1.1. Identity of the substances

According to Commission Regulation (EU) No 231/2012,[13] alginic acid (E 400) is identified as a linear glycuronoglycan polymer consisting mainly of β-(1→4)-linked D-mannuronic and α-(1→4)-linked L-guluronic acid units extracted from natural strains of various species of brown seaweeds (Phaeophyceae). Information on the identity of alginic acid and its salts (E 400- E 404) is represented in Table 1.

Table 1: Identity of alginic acid and its salts (E 400–E 404)

	Alginic acid (E 400)	**Sodium alginate (E 401)**	**Potassium alginate (E 402)**	**Ammonium alginate (E 403)**	**Calcium alginate (E 404)**
CAS Registry number	9005-32-7	9005-38-3	9005-36-1	9005-34-9	9005-35-0
EINECS number	232-680-1	–	–	–	–
Molecular formula	$(C_6H_8O_6)_n$	$(C_6H_7NaO_6)_n$	$(C_6H_7KO_6)_n$	$(C_6H_{11}NO_6)_n$	$(C_6H_7Ca_{n}O_6)_n$
Formula weight	176.13 (theoretical) 200 (actual average)	198.11 (theoretical) 222 (actual average)	214.22 (theoretical) 238 (actual average)	193.16 (theoretical) 217 (actual average)	195.16 (theoretical) 219 (actual average)
Synonyms	–	Algin*	–	Analgin*	Calginate*, calcium salt of alginate

CAS: Chemical Abstracts Service; EINECS: European Inventory of Existing Commercial Chemical Substances.
*Taken from SciFinder.

The Panel noted that in the literature term 'Algin' is also used as a general term for all alginates (Voragen et al., 2012; SciFinder, 2013[14]).

Chemically individual alginates can be distinguished using the identification tests for inorganic ions (JECFA, 2006g).

X-ray diffraction studies of mannuronate-rich and guluronate-rich alginates showed that mannuronate residues have a $^4C_1$ conformation, whilst guluronate residues are in the $^1C_4$ conformation (Draget et al., 2005). The structural formulae of the monomers of alginic acid is represented in Figure 1.

[12] Commission 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, p. 16.
[13] 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, pp. 1–295.
[14] SciFinder, 2013.

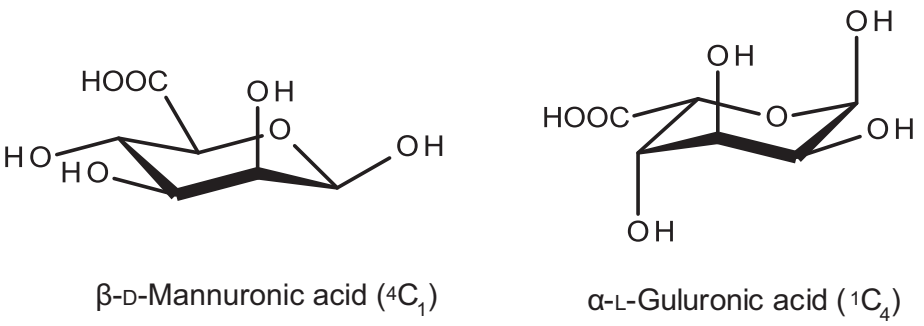

Figure 1: Structural formulae of the monomers of alginic acid in the pyranose ring form

The two uronic acids are not randomly distributed over the polymeric chain (Khotimchenko et al., 2001; Voragen et al., 2012), but the chain consists of homopolymeric and heteropolymeric blocks of mannuronate (M) and guluronate (G). Thus, monomeric M- and G-residues in alginic acid and its salts are joined together in sections consisting of homopolymeric M-blocks (–MMMMM–) and G-blocks (–GGGGG–) or heteropolymeric blocks of alternating M and G (MGMGMG) (Draget et al., 2005; JECFA 2006a; Helgerud et al., 2010). The structure can be represented schematically as: –M–G–M–$(M–M)_n$–M–G–$(M–G)_q$–M–G–$(G–G)_p$–G–M–G–

However, there is some variation in the proportion of uronic acids depending on algae species and the age of the algae. The ratio between mannuronic acid and guluronic acid was determined to be in the range from 0.34 to 1.79 (Khotimchenko et al., 2001). The structural formulae of the polymeric blocks of a glycuronoglycan chain in alginic acid and its salts is represented in Figure 2.

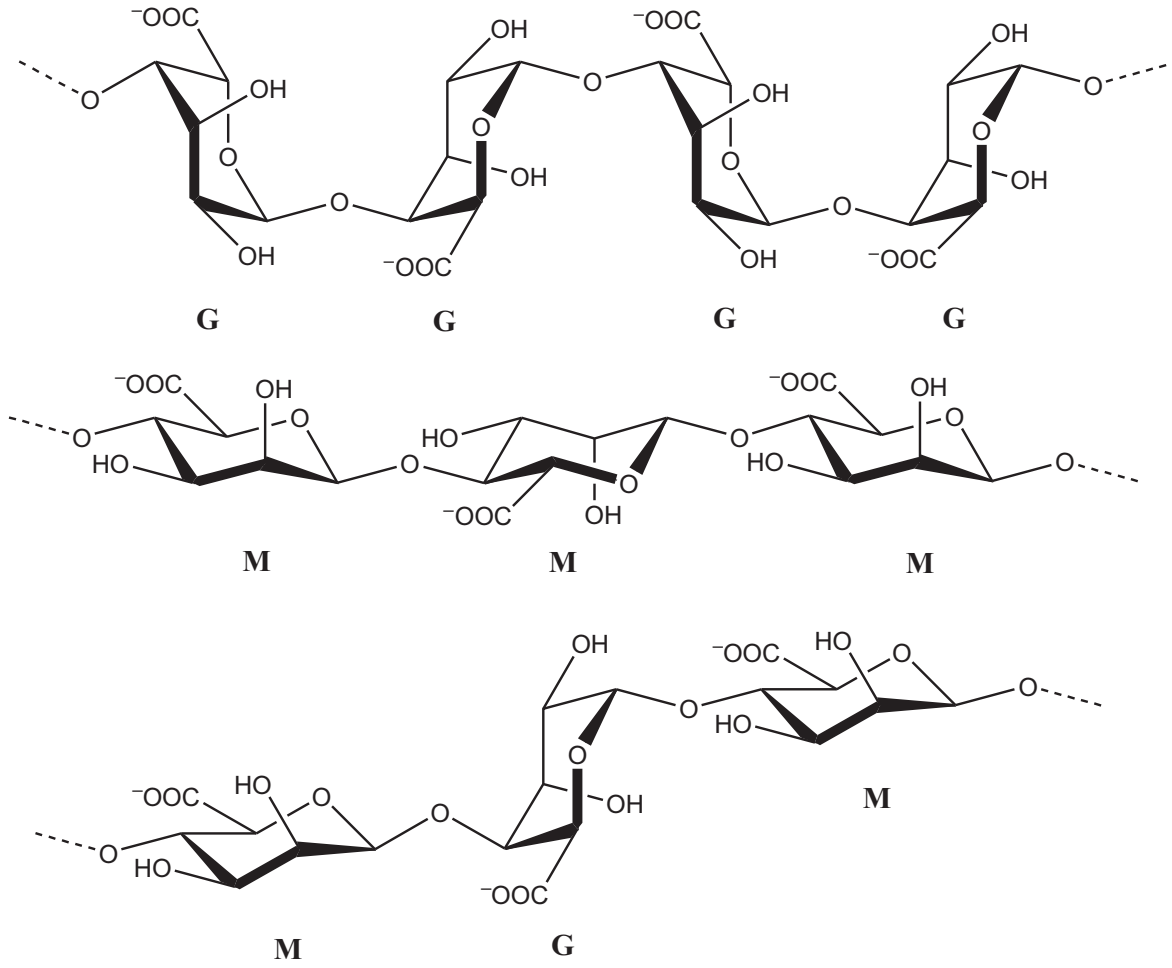

Figure 2: Structural formulae of polymeric blocks of a glycuronoglycan chain consisting of D-mannuronate (M) and L-guluronate (G) units in alginic acid and its salts

According to Regulation (EU) No 231/2012 and JECFA monographs (JECFA, 2006a–e), the typical molecular weight ranges from 10,000–600,000 (typical average).

The physicochemical properties are summarised in Table 2.

Table 2: Physicochemical properties of alginic acid and its salts (E 400–E 404)

Name	Alginic acid (E 400)	Sodium alginate (E 401)	Potassium alginate (E 402)	Ammonium alginate (E 403)	Calcium alginate (E 404)
Physical state colour/ appearance	White to yellowish brown, filamentous, grainy, granular and powdered forms	White to yellowish, fibrous or granular powder	White to yellowish fibrous or granular powder	White to yellowish fibrous or granular powder[1]	White to yellowish, fibrous or granular powder
Odour	Nearly odourless;[1] tasteless[2]	Nearly odourless;[1] tasteless[2]	Nearly odourless[1]		Nearly odourless;[1] slight odour and taste[3]
Solubility	Insoluble in water and organic solvents, slowly soluble in solutions of sodium carbonate, sodium hydroxide and trisodium phosphate;[1,4] precipitates at pH < 3.5[5]	Readily soluble in hot or cold water;[6] forms a viscous colloidal solution in water;[7] insoluble in alcohol, ether and chloroform[5,7]	Readily soluble in hot or cold water;[6] insoluble in organic solvents[5]	Readily soluble in hot or cold water;[6] insoluble in organic solvents[5]	Insoluble in water and acids, soluble in alkaline solution;[3] insoluble in organic solvents[5]

One of the most important properties of alginic acid and its salts solutions is their high viscosity, which is dependent on the degree of polymerisation, temperature, concentration, molecular weight and the presence of polyvalent metal cations. Viscosity of a 1% solution can vary from 4 to 1000 mPa. The viscosity is generally unaffected over the pH range 4–10 (CRC, 1990; Voragen et al., 2012).

The monomers in alginic acid react as a monobasic acid, forming salts with cations. Water-soluble salts of Li, Na, K, Cl, Rb, NH_4 and Mg are known, and these form viscous colloidal solutions that leave transparent films by evaporation, whereas the Cu, Zn, Ag, Ni, Ca, Ba, Hg, Pb or Bi salts are sparingly soluble or insoluble in water (Millis and Reed, 1947). The viscosity also depends on the composition of the aqueous system. The addition of acids and other salts, high levels of sugars, polyols or alcohols, also highly influence the final viscosity of the solutions. The introduction of a small amount of calcium ions to an alginate solution would give a steep rise in solution viscosity due to partial and non-permanent cross-linking (Draget, 2000; Draget et al., 2005; Helgerud et al., 2010).

Alginates at room temperatures form heat-stable gels with acids and with all multivalent cations except magnesium. To react with calcium to form a gel, alginate has to contain a certain proportion of guluronic acid, and the guluronic acid monomers must occur in blocks. The junction zone of the alginate gel network is formed when a G-block in one alginate molecule is physically linked to a G-block in another alginate molecule through chain–Ca^{2+}–chain interactions. This structure is commonly visualised through the 'egg-box model', in which calcium ions fit into the structural void in the alginate chain, like eggs in an egg box.

The M-blocks and the MG-blocks do not participate in the junction zones but form so-called elastic segments in the gel network. An acid alginate gel is formed in a similar way through the involvement of junction zones. G-blocks contribute to the greatest extent to gel formation and gel strength, but M-blocks are also able to support the formation of weak cross-links between chains. Alternating MG-blocks will interfere with the formation of intermolecular cross-linking (Helgerud et al., 2010).

After gelation, the water molecules are entrapped by the alginate gel network but are still free to migrate by diffusion. The gel retains water through hydrogen bonds, but if the gel network contracts, some water will be squeezed out. This effect is called syneresis and is commonly seen in many biopolymer gel systems. For alginate gels, syneresis depends on parameters such as M:G profile, calcium concentration, setting mechanism and molecular weight (Helgerud et al., 2010).

There is a synergy between alginic acid and its salts and pectins, as a mix of the two generally results in a firmer gel compared with the same amounts of each individual biopolymer. In contrast with thermally stable calcium alginate gels, alginate–pectin gels are thermo-reversible (Helgerud et al., 2010).

The dissociation constant pK of monomeric mannuronic acid is 3.38 and of guluronic acid 3.65. Alginic acid with a high proportion of guluronan has a pK of 3.74; when the proportion of mannuronan is high, this value is 3.42 (Draget et al., 2005; Voragen et al., 2012). According to Commission Regulation (EU) No 231/2012, the pH of a 3% suspension in water ranges from 2.0 to 3.5.

According to information provided from one interested party, four commercially available alginate samples were tested using laser diffraction technology to determine particle size distribution. Based on that analysis, the volume mean diameter was between 40 and 400 μm. For the smallest particle size range, 10% particles (in volume) were below 10 μm. Although the method used does not detect particles finer than 0.1 μm, the data show that the majority of particles are of sizes larger than 1 μm and are not in the nanoscale (Documentation provided to EFSA n. 12).

3.1.2. Specifications

The specifications for alginic acid (E 400), sodium alginate (E 401), potassium alginate (E 402), ammonium alginate (E 403) and calcium alginate (E 404) as defined in the Commission Regulation (EU) No 231/2012 and by JECFA (2006a–e) are listed in Tables 3–7.

Table 3: Specifications for alginic acid (E 400) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a–e)

	Commission Regulation (EU) No 231/2012	JECFA (2006a)
Definition	Linear glycuronoglycan consisting mainly of β-(1→4)-linked D-mannuronic and α-(1→4)-linked L-guluronic acid units in pyranose ring form. Hydrophilic colloidal carbohydrate extracted by the use of dilute alkali from natural strains of various species of brown seaweeds (Phaeophyceae)	Alginic acid is a naturally occurring hydrophilic colloidal polysaccharide obtained from the various species of brown seaweed (Phaeophyceae). It is a linear copolymer consisting mainly of residues of β-1,4-linked D-mannuronic acid and α-1,4-linked L-glucuronic[(a)] acid. These monomers are often arranged in homopolymeric blocks separated by regions approximating an alternating sequence of the two acid monomers
Assay	Alginic acid yields, on the anhydrous basis, not less than 20% and not more than 23% of carbon dioxide (CO_2), equivalent to not less than 91% and not more than 104.5% of alginic acid $(C_6H_8O_6)_n$ (calculated on equivalent weight basis of 200)	Yields, on the dried basis not less than 20.0% and not more than 23.0% of carbon dioxide (CO_2), equivalent to not less than 91.0% and not more than 104.5% of alginic acid $(C_6H_8O_6)_n$
Description	Alginic acid occurs in filamentous, grainy, granular and powdered forms. It is a white to yellowish brown and nearly odourless	White to yellowish brown filamentous, grainy, granular or powdered forms
Identification		
Solubility	Insoluble in water and organic solvents, slowly soluble in solutions of sodium carbonate, sodium hydroxide and trisodium phosphate	–
Calcium chloride precipitation test	To a 0.5% solution of the sample in 1 M sodium hydroxide solution, add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes alginic acid from acacia gum, sodium carboxymethyl cellulose, carboxymethyl starch, carrageenan, gelatine, gum ghatti, karaya gum, locust bean gum, methyl cellulose and tragacanth gum	–
Ammonium sulfate precipitation test	To a 0.5% solution of the sample in 1 M sodium hydroxide solution, add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes alginic acid from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, locust bean gum, methyl cellulose and starch	To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes alginic acid from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, carob bean gum, methyl cellulose and starch

	Commission Regulation (EU) No 231/2012	JECFA (2006a)
Colour reaction	Dissolve as completely as possible 0.01 g of the sample by shaking with 0.15 mL of 0.1 N sodium hydroxide and add 1 mL of acid ferric sulfate solution. Within 5 min, a cherry-red colour develops that finally becomes deep purple	–
Test for alginate	–	Passes test Dissolve as completely as possible 0.1 g of sample by shaking with 0.15 mL of 0.1 N sodium hydroxide and add 1 mL of acid ferric sulfate TS. Within 5 min, a cherry-red colour develops that finally becomes deep purple.
pH	Between 2.0 and 3.5 (3% suspension)	2.0–3.5 (0.3 in 10 suspension)
Purity		
Loss on drying	Not more than 15% (105°C, 4 h)	Not more than 15% (105°C, 4 h)
Sulfated ash	Not more than 8% on the anhydrous basis	Not more than 8% on the dried basis
Sodium hydroxide (1 M solution)	Not more than 2% on the anhydrous basis insoluble matter	Not more than 2% on the dried basis Weigh accurately about 1 g of the sample and dissolve in 100 mL of sodium hydroxide TS, centrifuge and decant. Wash the residue five times with water by mixing, centrifuging and decanting. Transfer the residue by means of water to a tared fine glass filter, dry for 1 h at 105°C, cool and weigh. Calculate as percentage of the dry weight
Formaldehyde	Not more than 50 mg/kg	–
Arsenic	Not more than 3 mg/kg	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg	Not more than 5 mg/kg Determine using an atomic absorption technique appropriate to the specified level
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total plate count	Not more than 5,000 colonies per gram	Not more than 5,000 colonies per gram. Initially prepare a 10^{-1} dilution by adding a 50 g sample to 450 mL of Butterfield's phosphate-buffered dilution water and homogenising in a high speed blender
Yeast and moulds	Not more than 500 colonies per gram	Not more than 500 colonies per gram
E. coli	Absent in 5 g	Negative by test
***Salmonella* spp.**	Absent in 10 g	Negative by test

(a): The Panel noted a mistake in the JECFA specifications. The word 'L-glucuronic' should be replaced with 'L-guluronic'.

Table 4: Commission Regulation (EU) No 231/2012 and JECFA (2006b) specifications for sodium alginate (E 401)

	Commission Regulation (EU) No 231/2012	**JECFA (2006b)**
Definition	–	Sodium salt of alginic acid
Assay	Yields, on the anhydrous basis, not less than 18% and not more than 21% of carbon dioxide corresponding to not less than 90.8% and not more than 106.0% of sodium alginate (calculated on equivalent weight basis of 222)	Yields, on the dried basis, not less than 18.0% and not more than 21.0% of carbon dioxide (CO_2), equivalent to not less than 90.8% and not more than 106.0% of sodium alginate $(C_6H_7NaO_6)_n$
Description	Nearly odourless, white to yellowish fibrous or granular powder	White to yellowish brown filamentous, grainy, granular or powdered forms
Identification		
Test for sodium	Passes test	Passes test
Test for alginic acid	Passes test	Passes test
Solubility	–	Dissolves slowly in water, forming a viscous solution; insoluble in ethanol and ether
Precipitate formation with calcium chloride	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes sodium alginate from gum arabic, sodium carboxymethyl cellulose, carrageenan, gelatine, gum ghatti, karaya gum, carob bean gum, methyl cellulose and tragacanth gum
Precipitate formation with ammonium sulfate	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes sodium alginate from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, carob bean gum, methyl cellulose and starch
Purity		
Loss on drying	Not more than 15% (105°C, 4 h)	Not more than 15% (105°C, 4 h)
Water-insoluble matter	Not more than 2% on the anhydrous basis	Not more than 2% on the dried basis
Formaldehyde	Not more than 50 mg/kg	–
Arsenic	Not more than 3 mg/kg	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg	Not more than 5 mg/kg Determine using an atomic absorption technique appropriate to the specified level.
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total plate count	Not more than 5,000 colonies per gram	Not more than 5,000 colonies per gram. Initially prepare a 10^{-1} dilution by adding a 50 g sample to 450 mL of Butterfield's phosphate-buffered dilution water and homogenising in a high speed blender
Yeast and moulds	Not more than 500 colonies per gram	Not more than 500 colonies per gram
E. coli	Absent in 5 g	Negative by test
***Salmonella* spp.**	Absent in 10 g	Negative by test

Table 5: Commission Regulation (EU) No 231/2012 and JECFA (2006c) specifications for potassium alginate (E 402)

	Commission Regulation (EU) No 231/2012	**JECFA (2006c)**
Definition	–	Potassium salt of alginic acid
Assay	Yields, on the anhydrous basis, not less than 16.5% and not more than 19.5% of carbon dioxide corresponding to not less than 89.2% and not more than 105.5% of potassium alginate (calculated on an equivalent weight basis of 238)	Yields, on the dried basis, not less than 16.5% and not more than 19.5% of carbon dioxide (CO_2), equivalent to not less than 89.2% and not more than 105.5% of potassium alginate $(C_6H_7KO_6)_n$
Description	Nearly odourless, white to yellowish fibrous or granular powder	White to yellowish brown filamentous, grainy, granular or powdered forms
Identification		
Test for potassium	Passes test	Passes test
Test for alginic acid	Passes test	Passes test
Solubility	–	Dissolves slowly in water forming a viscous solution; insoluble in ethanol and ether
Precipitate formation with calcium chloride	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes potassium alginate from gum arabic, sodium carboxymethyl cellulose, carrageenan, gelatine, gum ghatti, karaya gum, carob bean gum, methyl cellulose and tragacanth gum
Precipitate formation with ammonium sulfate	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes potassium alginate from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, carob bean gum, methyl cellulose and starch
Purity		
Loss on drying	Not more than 15% (105°C, 4 h)	Not more than 15% (105°C, 4 h)
Water-insoluble matter	Not more than 2% on the anhydrous basis	Not more than 2% on the dried basis
Formaldehyde	Not more than 50 mg/kg	–
Arsenic	Not more than 3 mg/kg	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg	Not more than 5 mg/kg Determine using an atomic absorption technique appropriate to the specified level
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total plate count	Not more than 5,000 colonies per gram	Not more than 5,000 colonies per gram. Initially prepare a 10^{-1} dilution by adding a 50 g sample to 450 mL of Butterfield's phosphate-buffered dilution water and homogenising in a high speed blender
Yeast and moulds	Not more than 500 colonies per gram	Not more than 500 colonies per gram
E. coli	Absent in 5 g	Negative by test
***Salmonella* spp.**	Absent in 10 g	Negative by test

Table 6: Commission Regulation (EU) No 231/2012 and JECFA (2006d) specifications for ammonium alginate (E 403)

	Commission Regulation (EU) No 231/2012	**JECFA (2006d)**
Definition		Ammonium salt of alginic acid.
Assay	Yields, on the anhydrous basis, not less than 18% and not more than 21% of carbon dioxide corresponding to not less than 88.7% and not more than 103.6% ammonium alginate (calculated on an equivalent weight basis of 217)	Yields, on the dried basis, not less than 18.0% and not more than 21.0% of carbon dioxide (CO_2), equivalent to not less than 88.7% and not more than 103.6% of ammonium alginate $C_6H_{11}NO_6)_n$
Description	White to yellowish fibrous or granular powder	White to yellowish brown filamentous, grainy, granular or powdered forms
Identification		
Test for ammonium	Passes test	Passes test
Test for alginic acid	Passes test	Passes test Dissolve as completely as possible 0.1 g of sample by shaking with 0.15 mL of 0.1 N sodium hydroxide and add 1 mL of acid ferric sulfate TS. Within 5 min, a cherry-red colour develops that finally becomes deep purple
Precipitate formation with calcium chloride	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes ammonium alginate from gum arabic, sodium carboxymethyl cellulose, carrageenan, gelatine, gum ghatti, karaya gum, carob bean gum, methyl cellulose and tragacanth gum
Precipitate formation with ammonium sulfate	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes ammonium alginate from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, carob bean gum, methyl cellulose and starch
Solubility	–	Dissolves slowly in water forming a viscous solution; insoluble in ethanol and ether
Purity		
Loss on drying	Not more than 15% (105°C, 4 h)	Not more than 15% (105°C, 4 h)
Sulfated ash	Not more than 7% on the dried basis	Not more than 7% on the dried basis
Water-insoluble matter	Not more than 2% on the anhydrous basis	Not more than 2% on the dried basis
Formaldehyde	Not more than 50 mg/kg	–
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg Determine using an atomic absorption technique appropriate to the specified level
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

	Commission Regulation (EU) No 231/2012	JECFA (2006d)
Total plate count	Not more than 5,000 colonies per gram	Not more than 5,000 colonies per gram. Initially prepare a 10^{-1} dilution by adding a 50 g sample to 450 mL of Butterfield's phosphate-buffered dilution water and homogenising in a high speed blender
Yeast and moulds	Not more than 500 colonies per gram	Not more than 500 colonies per gram
E. coli	Absent in 5 g	Negative by test
***Salmonella* spp.**	Absent in 10 g	Negative by test

Table 7: Commission Regulation (EU) No 231/2012 and JECFA (2006e) specifications for calcium alginate (E 404)

	Commission Regulation (EU) No 231/2012	JECFA (2006e)
Definition		Calcium salt of alginic acid.
Assay	Yields, on the anhydrous basis, not less than 18% and not more than 21% carbon dioxide corresponding to not less than 89.6% and not more than 104.5% of calcium alginate (calculated on an equivalent weight basis of 219)	Not less than 18.0% and not more than 21.0% of carbon dioxide (CO_2), equivalent to not less than 89.6% and not more than 104.5% of calcium alginate $(C_6H_7Ca_{1/2}\ O_6)_n$ on the anhydrous basis
Description	Nearly odourless, white to yellowish fibrous or granular powder	White to yellowish brown filamentous, grainy, granular and powdered forms
Identification		
Test for calcium	Passes test	Passes test
Test for alginic acid	Passes test	Passes test Dissolve as completely as possible 0.1 g of sample by shaking with 0.15 mL of 0.1 N sodium hydroxide and add 1 mL of acid ferric sulfate TS. Within 5 min, a cherry-red colour develops that finally becomes deep purple
Solubility	–	Insoluble in water and ether; slightly soluble in ethanol; slowly soluble in solutions of sodium polyphosphate, sodium carbonate and substances that combine with calcium ions
Precipitate formation with calcium chloride	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes calcium alginate from gum arabic, sodium carboxymethyl cellulose, carrageenan, gelatine, gum ghatti, karaya gum, carob bean gum, methyl cellulose and tragacanth gum
Precipitate formation with ammonium sulfate	–	To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes calcium alginate from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatine, carob bean gum, methyl cellulose and starch
Purity		
Loss on drying	Not more than 15% (105°C, 4 h)	Not more than 15% (105°C, 4 h)

	Commission Regulation (EU) No 231/2012	JECFA (2006e)
Formaldehyde	Not more than 50 mg/kg	–
Arsenic	Not more than 3 mg/kg	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg	Not more than 5 mg/kg Determine using an atomic absorption technique appropriate to the specified level
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total plate count	Not more than 5,000 colonies per gram	Not more than 5,000 colonies per gram Initially prepare a 10^{-1} dilution by adding a 50 g sample to 450 mL of Butterfield's phosphate-buffered dilution water and homogenising in a high speed blender
Yeast and moulds	Not more than 500 colonies per gram	Not more than 500 colonies per gram
E. coli	Absent in 5 g	Negative by test
***Salmonella* spp.**	Absent in 10 g	Negative by test

The JECFA specifications for alginic acid (E 400), sodium (E 401), potassium (E 402), ammonium (E 403) and calcium alginate (E 404) include an assay for the quantification for these additives (JECFA, 2006f). The general method is based on decarboxylation of the alginate by heating with hydrochloric acid and measurement of the formed CO_2.

Furthermore, the JECFA specifications for sodium (E 401), potassium (E 402) and ammonium alginate (E 403) include a method for determination of the water-insoluble matter.

One of the interested party has provided information in the form of aggregated ranges of concentration and other chemistry data based upon analyses of dozens of samples of the material from member companies for: loss on drying (3–15%), sulfated ash (1–6%), pH (2.3–2.8 for alginic acid and 5.5–8 for its salts, sodium hydroxide (1 M solution) insoluble matter (0.0–2.0% for alginic acid), formaldehyde (0–50 mg/kg), arsenic (0.1–2.2 mg/kg), lead (0.1–0.5 mg/kg), mercury (0.01–0.60 mg/kg), total plate count (1–4,000 CFU/g), moulds and yeasts (10–100 CFU/g) and *Salmonella* (negative in 10 g), that have demonstrated that identity and purity of analysed products comply with the EC specifications (Documentation provided to EFSA n. 10).

Concerning formaldehyde, an interested party (Documentation provided to EFSA n. 11) is of the opinion that the standard methods of analysis for formaldehyde (i.e. Association of Analytical Communities, formerly Association of Official Agricultural Chemists (AOAC) Official Method 931.08, Formaldehyde in Food) were found to give erroneous and high results. A single laboratory-validated colourimetric method that does not use acid hydrolysis (Farrell, 2007; Documentation provided to EFSA n. 11) has been developed for measuring residual formaldehyde in alginate products. The estimated limit of detection (LOD) and limit of quantification (LOQ) for the method were 0.7 mg/kg and 2.3 mg/kg, respectively, and the obtained recovery was 95%. The determined levels in four alginate products tested were close to the LOQ for the method and according to the authors, this indicates that the chemical and heat treatments involved in the manufacturing process are efficient at removing formaldehyde from the product. The Panel noted that the sensitivity of the colourimetric methods is lower than that of more sophisticated techniques.

The safety of use of formaldehyde as a processing aid during the storage and manufacturing of thickening agents from algae origin was evaluated by the EFSA (2006) and it was concluded that exposure to gelling additives such as alginic acid and its salts containing residual formaldehyde at the levels of 50 mg/kg of additive would be of no safety concern. The Panel noted that maximum limits (not more than 50 mg/kg) are established in the current EC Regulation for formaldehyde in alginic acid (E 400) and its salts (E 401–E 404) (EU No 231/2012). According to information gathered by the Panel, it is not clear if formaldehyde continues to be used for those needs by some manufacturers, whilst other manufacturers report not using it anymore (EFSA 2006; Documentation provided to EFSA n. 11).

Formaldehyde has also been shown to be a natural component of most marine algae including brown seaweeds. The levels detected in seaweeds used for alginate extraction were 14 mg/kg for *Laminaria digitata*, 17 mg/kg for *Fucus serratus* and 23 mg/kg for *Ascophyllum nodosum* (Yang et al., 1998). Most

of this formaldehyde is expected to be eliminated by drying during the manufacturing process of alginic acid and its salts.

The Panel considered that it could be appropriate to define in the specifications for alginic acid and its salts (E 400–E 404) a suitable validated analytical method of appropriate accuracy for the determination of formaldehyde.

In addition, the interested party has provided information on ranges of protein content (N × 6.25%) for alginic acid E 400 of 0.5–1.25% and its salts: E 401 of 0.5–1.2%, E 402 of 0.0–1.16, E 403 0.6–3.2% and E 404 of 0.00–1.16% (Documentation provided to EFSA n. 10). The Panel noted that limits for protein should be included in the EU specifications. According to the interested party (Documentation provided to EFSA n. 10), any enzymatic activity within the live seaweed is either destroyed in the process of the seaweed being dried and/or denatured during the manufacturing process, in which the seaweed is subjected to high heat and both acidic and alkaline conditions.

Because of the polysaccharidic nature of these compounds, they can be a substrate of microbiological contamination during storage. The latter has been demonstrated recently by the mycotoxin contaminations of gums (Zhang et al., 2014). The Panel noted that the differences in the microbiological criteria for alginic acid and its salts between the specifications given by the EU Regulation and those given by JECFA are not decisive.

Pesticides are not used, nor needed in the production of seaweeds and according to industry (Documentation provided to EFSA n. 10); available analytical data show no presence of pesticides.

The European Pharmacopeia, 9th Edition (2016) includes specifications for alginic acid and sodium alginate.

The Panel noted that, according to the EU specifications for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) impurities of the toxic elements arsenic, cadmium, lead and mercury are accepted up to concentrations of 3, 1, 5 (2 for E 403) and 1 mg/kg, respectively. Contamination at such levels could have a significant impact on the exposure to these elements, for which the exposures already are close to the health-based guidance values or benchmark doses (lower confidence limits) established by EFSA (EFSA CONTAM Panel, 2009a,b, 2010, 2012a,b,c, 2014).

3.1.3. Manufacturing process

The following manufacturing processes have been identified:

Alginic acid and its salts are structural components of the cell walls of brown seaweed in which they make up to 40% of the total dry matter (Voragen et al., 2012). The bulk of world-wide alginate production is provided by the two species *Macrocystis pyrifera* andnn *Ascophyllum nodosum*; however, some other alga genera (*Laminaria* spp., *Fucus* spp.) contain alginic acid and its salts as well (CRC, 1990; Khotimchenko et al., 2001).

One of the interested parties has provided outlines of the production process of alginic acid from seaweed and sodium, potassium, ammonium and calcium alginates from alginic acid in the form of flow charts summarised in the Figure 3. This process diagram depicts precipitation with water and acid, but, according to the interested party, precipitation may also be performed with calcium (Ca^{2+}) or alcohol (Documentation provided to EFSA n. 10).

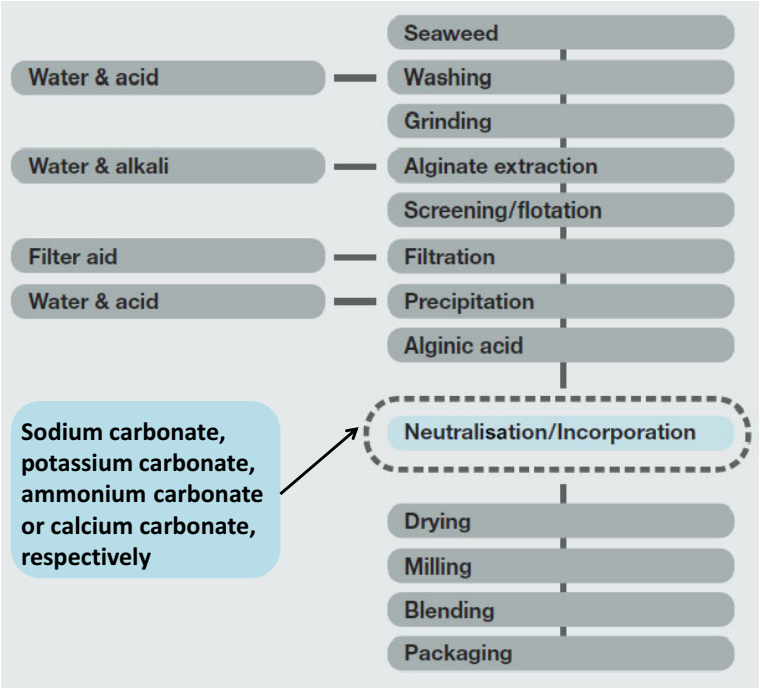

Figure 3: Outlines of a production process of alginic acid (E 400) and sodium (E 401), potassium (E 402), ammonium (E 403) and calcium alginate (E 404)

According to the literature data, the production of alginic acid and its salts is based on a series of ion-exchange processes. The water-insoluble calcium alginate in the raw material is first converted to the soluble sodium salt by extraction with sodium carbonate solution. After dilution with water, a solid phase consisting predominantly of cellulose is removed by flotation, sieving and filtration. From the dissolved sodium alginate, alginic acid is obtained either by precipitation with acid, or by precipitation with calcium chloride as calcium alginate and subsequent conversion to insoluble alginic acid by washing with acid. The product is bleached with hypochlorite, washed and dried. Washed and dried alginic acid can be used as such; however, it is usually treated with sodium carbonate or other bases to produce alginate salts (Voragen et al., 2012).

Sometimes the seaweed is soaked in a formaldehyde solution before it is extracted with alkali. The formaldehyde helps to bind the coloured compounds to the cellulose in the cell walls, so much of the colour is left behind in the seaweed residue when the alkaline extract is filtered (McHugh, 2003). The limit for residual formaldehyde of 50 mg/kg is set in the EC specifications for alginic acid and alginic acid and its salts (see Section 3.1.2).

A similar production method is described by Draget (2000). In the first step, the algal tissue is treated with mineral acid, and in the second step, the alginic acid is brought into solution by neutralisation with sodium carbonate or sodium hydroxide. After separation processes such as sifting, flotation, centrifugation and filtration, the dissolved sodium alginate is precipitated either by alcohol, by calcium chloride or by mineral acid, converted to the sodium salt if needed and finally dried and milled (Draget, 2000).

3.1.4. Methods of analysis in food

The following official methods have been identified:

Different standardised methods for the qualitative detection of alginic acid and its salts in foods are reported in the literature. The extraction methods are based on the solubility behaviour (soluble in alkaline aqueous solutions, insoluble in organic solvents) of alginic acid and its salts.

For the qualitative test of alginic acid and its salts in chocolate products, the AOAC Official Method 959.06 is reported by the Association of Analytical Communities (AOAC, 2003). Alginic acid and its salts are extracted from the test sample by repeated dissolution with alkali and precipitation with alcohol. Alginic acid and its salts are detected by a colour reaction by addition of a ferric hydroxides–sulfuric acid reagent.

The AOAC Official Method 963.25 describes the colourimetric analysis of alginic acid and its salts in food dressings (mayonnaise, salad dressing and French dressing) (AOAC, 2000). Alginic acid and its salts are isolated by repeated extraction steps using an acetone–alcohol mixture and dioxane, in all steps the alginic acid and its salts remain in the precipitate. After dissolution with alkali, alginates are detected using the ferric hydroxide–sulfuric acid reagent.

In addition, methods for the analysis of uronic residues after hydrolysis of the polysaccharide are reported (Voragen et al., 2012). Mannuronic and guluronic acid can be analysed by gas chromatography or high-pressure liquid chromatography (HPLC). This method allows the analysis of the uronic acid composition of alginic acid and its salts and, after partial hydrolysis, the proportions of mannuronan and guluronan blocks.

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

Dry powder of sodium alginate may have a shelf life of several months when stored dry, cool and without sunlight exposure (Draget, 2000; Draget et al., 2005). In contrast, dry alginic acid has a very limited stability at room temperature, due to intramolecular acid catalysis. The glycosidic linkages of alginic acid and its salts can be cleaved by both acid and alkaline hydrolysis and by oxidation with free radicals. However, these reactions are not likely to occur at room temperature and pH values around neutrality. Impurities like phenolic compounds extracted together with the alginate may increase the degradation of alginic acid and its salts (Draget, 2000; Draget et al., 2005). At high acidic conditions and high temperatures, alginic acid and its salts can be decarboxylated. Halogens, polyphenols, ascorbic acid and thiols are able to depolymerise alginic acid and its salts. Degradation by bacterial enzymes (alginate depolymerases) has also been described (Voragen et al., 2012).

Fruits naturally rich in pectin, such as apples, form gels when a sodium alginate solution is added after cooking. In contrast to thermally stable calcium alginate gels, alginate–pectin gels are thermoreversible. The alginate–pectin synergy is one of very few interactions for alginate with other hydrocolloids and, so far, the only one of commercial value (Helgerud et al., 2010).

3.2. Authorised uses and use levels

Maximum levels of alginic acid and its salts (E 400–E 404) have been defined in Annex II to Regulation (EC) No 1333/2008[15] on food additives, as amended. These levels are defined by the Panel as 'maximum permitted levels' (MPLs) in this document.

Currently, alginic acid (E 400), sodium alginate (E 401), potassium alginate (E 402), ammonium alginate (E 403) and calcium alginate (E 404) are authorised food additives in the EU at *quantum satis* (QS) in almost all foodstuffs (in 69 food categories (FCs) apart from peeled, cut and shredded fruit and vegetables (FC 4.1.2, E 401, 2,400 mg/kg), jam, jellies and marmalades and sweetened chestnut puree (FC 4.2.5.2, 10,000 mg/kg), other similar fruit or vegetable spreads (FC 4.2.5.3, 10,000 mg/kg), processed cereal-based foods and baby foods for infants and young children (FC 13.1.3, E 400, E 401, E 402, E 404, 500 mg/kg), and dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1 E 401, 1,000 mg/kg), dietary foods for babies and young children for special medical purposes (FC 13.1.5.2, E 401 1,000 mg/kg, E 400, E 402, E 404 500 mg/kg). Alginic acid and its salts (E 400–E 404) are included in the Group I of food additives authorised at QS.

Table 8 summarises food categories that are permitted to contain alginic acid and its salts (E 400–E 404) and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

[15] 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, p. 16–33.

Table 8: MPLs of alginic acid and its salts (E 400–E 404) in foods according to the Annex II to Regulation (EC) No 1333/2008

Food Category number	Food category name	E-number/ Group	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
1.3	Unflavoured fermented milk products, heat-treated after fermentation	Group I		*Quantum satis*
1.4	Flavoured fermented milk products including heat-treated products	Group I		*Quantum satis*
1.6.1	Unflavoured pasteurised cream (excluding reduced fat creams)	E 401 E 402		*Quantum satis*
1.6.3	Other creams	Group I		*Quantum satis*
1.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	*Quantum satis*
1.7.5	Processed cheese	Group I		*Quantum satis*
1.7.6	Cheese products (excluding products falling in category 16)	Group I		*Quantum satis*
1.8	Dairy analogues, including beverage whiteners	Group I		*Quantum satis*
2.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		*Quantum satis*
2.3	Vegetable oil pan spray	Group I		*Quantum satis*
3	Edible ices	Group I		*Quantum satis*
4.1.2	Peeled, cut and shredded fruit and vegetables	E 401	Only prepacked refrigerated unprocessed fruit and vegetables ready for consumption, to be sold to the final consumer/may only be used in combination with E 302 as glazing agents and with a maximum level of 800 mg/kg of E 302 in the final food	2400
4.2.1	Dried fruit and vegetables	Group I		*Quantum satis*
4.2.2	Fruit and vegetables in vinegar, oil, or brine	Group I		*Quantum satis*
4.2.4.1	Fruit and vegetable preparations excluding compote	Group I		*Quantum satis*
4.2.5.2	Jam, jellies and marmalades and sweetened chestnut puree as defined by Directive 2001/113/EC	E 400–E 404	Maximum individually or in combination with E 400–E 404, E 406, E 407, E 410, E 412, E 415 and E 418	10000
4.2.5.3	Other similar fruit or vegetable spreads	E 400–E 404	Maximum individually or in combination with E 400–E 404, E 406, E 407, E 410, E 412, E 415 and E 418	10,000
4.2.5.4	Nut butters and nut spreads	Group I		*Quantum satis*
4.2.6	Processed potato products	Group I		*Quantum satis*
5.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	Group I	Only energy reduced or with no added sugar	*Quantum satis*

Food Category number	Food category name	E-number/ Group	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
5.2	Other confectionery including breath-freshening microsweets	Group I	The substances listed under numbers E 400, E 401, E 402, E 403, E 404, E 406, E 407, 407a, E 410, E 412, E 413, E 414, E 415, E 417, E 418, E 425 and E 440 may not be used in jelly minicups, defined, for the purpose of this Regulation, as jelly confectionery of a firm consistence, contained in semi-rigid minicups or minicapsules, intended to be ingested in a single bite by exerting pressure on the minicups or minicapsule to project the confectionery into the mouth	*Quantum satis*
5.3	Chewing gum	Group I		*Quantum satis*
5.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		*Quantum satis*
6.2.2	Starches	Group I		*Quantum satis*
6.3	Breakfast cereals	Group I		*Quantum satis*
6.4.2	Dry pasta	Group I	Only gluten-free pasta and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	*Quantum satis*
6.4.4	Potato gnocchi	Group I	Except fresh refrigerated potato gnocchi	*Quantum satis*
6.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		*Quantum satis*
6.5	Noodles	Group I		*Quantum satis*
6.6	Batters	Group I		*Quantum satis*
6.7	Pre-cooked or processed cereals	Group I		*Quantum satis*
7.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	*Quantum satis*
7.2	Fine bakery wares	Group I		*Quantum satis*
8.2	Meat preparations as defined by Regulation (EC) No 853/2004	E 401 E 402 E 403 E 404	Except *bifteki*, *soutzoukaki*, *kebab gyros* and *souvlaki*/only preparations in which ingredients have been injected; meat preparations composed of meat parts that have been handled differently: minced, sliced or processed and that are combined together	*Quantum satis*
8.3.1	Non-heat-treated meat products	Group I		*Quantum satis*
8.3.2	Heat-treated meat products	Group I	Except *foie gras*, *foie gras entier*, *blocs de foie gras*, *Libamáj*, *libamáj egészben*, *libamáj tömbben*	*Quantum satis*
8.3.3	Casings and coatings and decorations for meat	Group I		*Quantum satis*

Food Category number	Food category name	E-number/ Group	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
9.2	Processed fish and fishery products including molluscs and crustaceans	Group I		*Quantum satis*
9.3	Fish roe	Group I	Only processed fish roe	*Quantum satis*
10.2	Processed eggs and egg products	Group I		*Quantum satis*
11.2	Other sugars and syrups	Group I		*Quantum satis*
12.1.2	Salt substitutes	Group I		*Quantum satis*
12.2.2	Seasonings and condiments	Group I		*Quantum satis*
12.3	Vinegars	Group I		*Quantum satis*
12.4	Mustard	Group I		*Quantum satis*
12.5	Soups and broths	Group I		*Quantum satis*
12.6	Sauces	Group I		*Quantum satis*
12.7	Salads and savoury-based sandwich spreads	Group I		*Quantum satis*
12.8	Yeast and yeast products	Group I		*Quantum satis*
12.9	Protein products, excluding products covered in category 1.8	Group I		*Quantum satis*
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	E 400 E 401 E 402 E 404	Only in desserts and puddings/E 400, E 401, E 402 and E 404 are authorised individually or in combination	500
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 401	From 4 months onwards in special food products with adapted composition, required for metabolic disorders and for general tube-feeding	1,000
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 401	From 4 months onwards in special food products with adapted composition, required for metabolic disorders and for general tube-feeding	1,000
		E 400 E 402 E 404	Only in desserts and puddings	500
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		*Quantum satis*
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Group I		*Quantum satis*
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	*Quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	*Quantum satis*

Food Category number	Food category name	E-number/ Group	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	*Quantum satis*
14.1.4	Flavoured drinks	Group I		*Quantum satis*
14.1.5.2	Other	Group I	Excluding unflavoured leaf tea; including flavoured instant coffee	*Quantum satis*
14.2.3	Cider and perry	Group I		*Quantum satis*
14.2.4	Fruit wine and made wine	Group I		*Quantum satis*
14.2.5	Mead	Group I		*Quantum satis*
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Group I	Except whisky or whiskey	*Quantum satis*
14.2.7.1	Aromatised wines	Group I		*Quantum satis*
14.2.7.2	Aromatised wine-based drinks	Group I		*Quantum satis*
14.2.7.3	Aromatised wine-product cocktails	Group I		*Quantum satis*
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol	Group I		*Quantum satis*
15.1	Potato-, cereal-, flour- or starch-based snacks	Group I		*Quantum satis*
15.2	Processed nuts	Group I		*Quantum satis*
16	Desserts excluding products covered in category 1, 3 and 4	Group I		*Quantum satis*
17.1[(a)]	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	Group I		*Quantum satis*
17.2[(a)]	Food supplements supplied in a liquid form	Group I		*Quantum satis*
17.3[(a)]	Food supplements supplied in a syrup-type or chewable form	Group I		*Quantum satis*
18	Processed foods not covered by categories 1–17, excluding foods for infants and young children	Group I		*Quantum satis*

MPL: maximum permitted level.
(a): FCS 17 refers to food supplements as defined in Directive 2002/46/EC of the European Parliament and of the Council excluding food supplements for infants and young children.

According to Annex III, Part 1 of Regulation (EC) No 1333/2008, alginic acid and its salts (E 400–E 404) are authorised as carriers in all food additives at QS.

In addition, according to Annex III, Part 3 of Regulation (EC) No 1333/2008, alginic acid and its salts (E 400–E 404) are also authorised as food additives, in food enzymes at QS. E 400, E 401, E 402 and E 404 can be also used as carriers in food enzymes.

Furthermore, according to Annex III, Part 5, Section A, of Regulation (EC) No 1333/2008, alginic acid and its salts (E 400–E 404) are also authorised as food additives, including carriers, in all nutrients at QS.

According to Annex III, Part 5, Section B, E 401, E 402 and E 404 can be added in nutrients intended to be used in foodstuffs for infants and young children under FCS 13.1, under the condition that for E 401 and E 404 the maximum level in foods mentioned in FCS 13.1.3 Processed cereal-based foods and baby foods for infants and young children is not exceeded, and for E 402 the maximum level in foods mentioned in FCS 13.1. is not exceeded.

3.3. Exposure data

3.3.1. Reported use levels

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to QS.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a public call[16] for usage level data on alginic acid and its salts (E 400–E 404). In response, very limited information (n = 3) was provided by Mars Chocolate UK (Documentation provided to EFSA n. 7). In addition, Marinalg International also provided some information on the present use (Documentation provided to EFSA n. 2).

Furthermore, in October 2015, a public call[17] for food additive usage level and/or concentration data in food and beverages intended for human consumption, including alginic acid and its salts (E 400–E 404), was launched, with a deadline of May 2016. In response to this public call, updated information on the actual use levels of alginic acid and its salts (E 400–E 404) in foods was made available to the EFSA by industry.

3.3.1.1. Summarised data on reported use levels in foods provided by industry

Industry provided the EFSA with data on use levels (n = 269) of alginic acid and its salts (E 400–E 404) in foods for 27 out of the 75 food categories in which alginic acid and its salts (E 400–E 404) are authorised.

Updated information on the actual use levels of alginic acid and its salts (E 400–E 404) in foods was made available to the EFSA by Marinalg International (Documentation provided to EFSA n. 15), the European Dairy Association (EDA; Documentation provided to EFSA n. 14), Food Drink Europe (FDE; Documentation provided to EFSA n. 13), EUROGUM A/S (Documentation provided to EFSA n. 16), Asociacion Espanola de Exportadores e Industriales de Aceitunas de Mesa (ASEMESA; Documentation provided to EFSA n. 17), AVIKO (Documentation provided to EFSA n. 19), International Chewing Gum Association (ICGA; Documentation provided to EFSA n. 18) and Specialised Nutrition Europe (SNE; Documentation provided to EFSA n. 20).

The Panel noted that 13 usage levels on processed cheese (FC 1.7.5), fruit and vegetable preparations (FC 4.2.4.1), chewing gums (FC 5.3), decorations, coatings and fillings (FC 5.4), sauces (FC 12.6), flavoured drinks (FC 14.14), desserts (FC 16), dietary foods for special medical purposes (FC 13.2), dietary food for weight control diets (FC 13.3) referred to a niche product(s). As other usage levels were available for all food categories, the Panel decided to exclude them from further analysis in the refined exposure scenarios, except for chewing gums, as for this category no other data was reported.

The Panel noted that Eurogums A/S is not a food industry that uses additives in its food products but is a food additive producer. Usage levels reported by food additive producers are not considered at the same level as those provided by food industry. Food additive producers might recommend usage levels to the food industry but the final levels might, ultimately, be different. Therefore, unless food additive producers confirm that the recommended levels are used by the food industry, they are not considered in the refined exposure scenarios. Data from food additive producers will only be used in the *maximum level exposure assessment* scenario in cases of QS authorisation when no data are available from food industry. In this way, the most complete exposure estimates are calculated.

The number of usage data provided by industry for each of the alginic acid and its salts (E 400–E 404) and the number of food categories for which usage data were provided out of the total authorised food categories are presented in Table 9.

[16] http://www.efsa.europa.eu/en/dataclosed/call/ans100609
[17] https://www.efsa.europa.eu/en/data/call/151012

Table 9: Number of usage data provided by industry for alginic acid and its salts and the number of food categories for which usage data were provided out of the total authorised food categories

	E-number				
	E 400	**E 401**	**E 402**	**E 403**	**E 404**
Usage level data (n)	1	254	0	0	14
Number of FCs where usage level data reported	1	26	0	0	6
Number of authorised FCs	71	75	73	70	72

Appendix A provides data on the use levels of alginic acid and its salts (E 400–E 404) in foods as reported by industry.

3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPD is an online database that monitors new introductions of packaged goods in the market worldwide. It contains information of over 2 million food and beverage products of which more than 900,000 are or have been available on the European food market. Mintel started covering the EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel's GNPD.[18]

For the purpose of this scientific opinion, the Mintel GNPD[19] was used to check the labelling of food and beverage products including food supplements containing alginic acid and its salts (E 400–404) within the EU's food products as the Mintel GNPD shows the compulsory ingredient information presented in the labelling of products.

Appendix B presents the percentage of the food and beverage products including food supplements labelled with alginic acid and its salts (E 400–E 404) between 2011 and September 2016, out of the total number of food products per food subcategories according to the Mintel's GNPD food classification.

According to the Mintel's GNPD, in the given period, alginic acid (E 400) was labelled on 134 products that were mainly meat snacks, yoghurts and various cakes, pastries, sweet goods and desserts.

In addition, sodium alginate (E 401) was labelled on 4,866 products, mainly dairy-based frozen products, other various cakes, pastries, sweet goods and desserts and pickled condiments.

Furthermore, potassium alginate (E 402) was labelled on 41 products, mainly on margarines.

No products were found under the given conditions in the Mintel database for ammonium alginate (E 403).

For calcium alginate (E 404), 173 products were labelled, mainly cakes, pastries, sweet goods and desserts, meat products and substitutes.

Altogether 5,230 products (1.11%) from the total 463,167 were labelled with any of the alginic acid and its salts (E 400–E 404).

This includes 13 products in the category for butter (FC 02.2.1), and one in beer (FC 14.2.1) in which categories alginic acid and its salts are not authorised.

3.3.3. Food consumption data used for exposure assessment

3.3.3.1. 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, 2011a). New consumption surveys added in the Comprehensive database were also taken into account in this assessment.[11]

The food consumption data gathered by EFSA were collected by different methodologies and so direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced due

[18] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[19] http://www.gnpd.com/sinatra/home/ accessed on 23/11/2016 (up to the 26/9/2017).

to possible subjects' underreporting and/or misreporting the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

Food consumption data from the following population groups: infants, toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 10).

Table 10: Population groups considered for the exposure estimates of alginic acid and its salts (E 400–E 404)

Population	Age range	Countries with food consumption surveys covering more than one day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children[(a)]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly[(a)]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Sweden, UK

(a): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the Food Classification System (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories.

3.3.3.2. Food categories selected for the exposure assessment of alginic acid and its salts (E 400–E 404)

The food categories in which the use of alginic acid and its salts (E 400–E 404) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories or their restrictions/exceptions are not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the present estimate. This omission may result in an underestimation of the exposure. The food categories that were not taken into account are described below (in ascending order of the FCs codes):

- 1.7.6 Cheese products (excluding products falling in category 16); however, these products were reclassified under 01.7.5 Processed cheese
- 2.3 Vegetable oil pan spray
- 6.6 Batters
- 6.7 Pre-cooked or processed cereals
- 8.3.3 Casings and coatings and decorations for meat
- 12.1.2 Salt substitutes
- 14.2.4 Fruit wine and made wine
- 14.2.5 Mead
- 14.2.7.2 Aromatised wine-based drinks
- 14.2.7.3 Aromatised wine-product cocktails.

For the following food categories, the restrictions/exceptions that apply to the use of alginic acid and its salts (E 400–E 404) could not be taken into account, and therefore the whole food category was considered in the exposure assessment. This may result in an overestimation of the exposure:

- 1.6 Cream and Cream powder (authorised only in 1.6.1 and 1.6.3 but the whole food category is taken into account in the assessment).
- 5.1 Cocoa and Chocolate products as covered by Directive 2000/36/EC, only energy reduced or with no added sugar.
- 8.2 Meat preparations as defined by Regulation (EC) No 853/2004, except *bifteki*, *soutzoukaki*, *kebab gyros* and *souvlaki*/only preparations in which ingredients have been injected; meat preparations composed of meat parts that have been handled differently: minced, sliced or processed and that are combined together.
- 8.3.2 Heat-treated meat products, except *foie gras*, *foie gras entier*, *blocs de foie gras*, *Libamáj*, *libamáj egészben* and *libamáj tömbben*.
- 4.1.2 Peeled, cut and shredded fruit and vegetables, only prepacked refrigerated unprocessed fruit and vegetables ready for consumption, to be sold to the final consumer (only in MPL scenario).

For category 1.3: unflavoured fermented milk products, heat-treated after fermentation; and category 1.2: unflavoured fermented milk products, including natural unflavoured buttermilk (excluding sterilised buttermilk) non-heat treated after fermentation; differentiating the products in the Comprehensive database is not possible, therefore both of these were considered together in the estimation.

Alginic acid and its salts (E 400–E 404) are also authorised in FC 18 (Processed foods not covered by categories 1–17, excluding foods for infants and young children). Considering that FC 18 is extremely unspecific foods (e.g. composite foods, processed foods, prepared or composite dishes) belonging to this food category were reclassified under food categories in accordance with their main component and included as such in the exposure assessment.

Food items under food categories 13.2, 13.3 and 13.4 consumed by population groups – children, adolescents, adults and the elderly – may be very diverse and, in addition, there is very limited information on their consumption. Therefore, eating occasions belonging to the food categories 13.2, 13.3 and 13.4 were reclassified under food categories in accordance to their main component.

The use levels available for food categories 13.2 and 13.3 were not considered for the exposure assessment.

Overall, six food categories were included in the exposure assessment without considering the restrictions/exceptions as set in Annex II to Regulation (EC) No 1333/2008. Ten food categories were not taken into account in the exposure assessment because they or their specific restrictions/exceptions are not referenced in the EFSA Comprehensive Database. For the refined scenario, 51 added food categories were not taken into account because no concentration data were provided for these food categories to EFSA. For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied. Overall, for the regulatory maximum level exposure scenario, 30 food categories were included, whilst for the refined scenarios, 23 food categories were included in the present exposure assessment to alginic acid and its salts (E 400–E 404) (Appendix C).

3.4. Exposure estimates

3.4.1. Exposure to alginic acid and its salts (E 400–E 404) from their use as food additives

The Panel estimated chronic dietary exposure for the following population groups: infants; toddlers, children, adolescents, adults and the elderly.

A combined dietary exposure estimate was calculated for the alginic acid and its salts (E 400–E 404) by selecting within each food category, the highest use level among the use levels reported for each of the different concerned types.

Dietary exposure to alginic acid and its salts (E 400–E 404) was calculated by multiplying alginic acid and its salts (E 400–E 404) concentrations for each food category (Appendix C) with their respective consumption amount per kilogram of 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 all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 10). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey for the total population and per population group. The 95th percentile of exposure was only calculated for population groups with sufficiently large sample size to allow this calculation (EFSA, 2011a). Therefore, in the present assessment, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not estimated.

Exposure assessment to alginic acid and its salts was carried out by the ANS Panel based on: (1) MPLs as set down in the EU legislation or the maximum levels as provided by industry for categories in which alginic acid and its salts are authorised as QS (defined as the *regulatory maximum level exposure assessment scenario*); and (2) the reported use levels data (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

These scenarios do not consider the consumption of food supplements (FC 17.1, 17.2 and FC 17.3) or FSMP. Estimation of exposure from the consumption of food supplements was not carried out as no usage level data were provided for these categories. Exposure scenario with the inclusion of food categories on FSMPs for infants and toddlers (FC 13.1.5.1 and FC 13.1.5.2) was carried out separately.

A possible additional exposure from the use of alginic acid and its salts (E 400–E 404) as carriers in all food additives, as food additives in food enzymes, as food additives including carriers in all nutrients, including in foodstuffs for infants and young children in accordance with Annex III to Regulation (EC) No 1333/2008 (Part 1, 3, 5) was not considered in any of the exposure assessment scenarios due to the absence of information on concentration levels.

In addition, formaldehyde exposure was calculated for the non-brand-loyal scenario and the FSMP scenario.

3.4.1.1. Regulatory maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008 and listed in Table 8, or based on the maximum reported use levels provided by industry, excluding exposure via FSMP, as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014) for categories in which alginic acid and its salts are authorised as QS. The maximum reported use levels used for the food categories for which use levels were submitted, are listed in Appendix C.

The Panel considered the exposure estimates derived following this scenario as the most conservative as it is assumed that the consumer will be exposed to alginic acid and its salts (E 400–E 404) in food at MPL or maximum reported use levels continuously (over a lifetime), assuming that alginic acid and its salts are only used in the food categories for which data were submitted by the food industry.

3.4.1.2. Refined exposure assessment scenario

The refined exposure assessment scenario is based on use levels reported by industry. This exposure scenario can consider only food categories for which the above data were available to the Panel.

Appendix C summarises the concentration levels of alginic acid and its salts (E 400–E 404) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on different model populations excluding exposure via FSMPs:

- The brand-loyal consumer scenario: it was assumed that a consumer is exposed long term to alginic acid and its salts (E 400–E 404) present at the maximum reported use for one food category. This exposure estimate is calculated as follows:
  - Combining food consumption with the maximum of the reported use levels for the main contributing food category at the individual level.
  - Using the mean of the typical reported use levels for the remaining food categories.
- The non-brand-loyal consumer scenario: it was assumed that a consumer is exposed long term to alginic acid and its salts (E 400–E 404) present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels.

Another specific refined scenario for exposure assessment from FSMPs consumed by infants and young children was carried out separately.

3.4.1.3. Specific exposure assessment scenarios

- **FSMP consumers only scenario**
  - As alginic acid and its salts are also authorised in the food categories 13.1.5.1 (E 401) and 13.1.5.2 (E 400, E 401, E 402 and E 404) with MPL, a specific exposure assessment scenario taking into account these two food categories was performed to estimate the exposure of infants and toddlers who may eat and drink FSMP.
  - The consumption of FSMP is not reported in the EFSA Comprehensive database. To consider the potential exposure to food additives via the consumption of these foods, the Panel assumed that the amount of FSMP consumed by infants and toddlers resembles that of comparable foods consumed by infants and toddlers from the general population. So, the consumption of FSMP categorised as food category 13.1.5 is assumed to be equal to that of formulae and food products categorised under food categories 13.1.1, 13.1.2, 13.1.3 and 13.1.4.
  - Consumers only of foods for special medical purposes were assumed to be exposed to alginic acid and its salts (E 400–E 404) present at the maximum permitted level on a daily basis via consumption of food categories 13.1.5.1 and 13.1.5.2. For the remaining food categories, the mean of the typical reported use levels was used.

This scenario does not consider the consumption of food supplements. Appendix C summarises the concentration levels of alginic acid and its salts (E 400–E 404) used in this specific exposure assessment scenario.

3.4.1.4. Dietary exposure to alginic acid and its salts (E 400–E 404)

Table 11 summarises the estimated exposure to alginic acid and its salts (E 400–E 404) from their use as food additives in six population groups (Table 10) according to the different exposure scenario's. Detailed results per population group and survey are presented in Appendix D.

Table 11: Summary of anticipated exposure to alginic acid and its salts (E 400–E 404) from their use as food additives in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Maximum level exposure assessment scenario												
Mean	39.7	108.0	110.1	300.3	81.5	210.9	41.5	100.4	36.6	72.0	35.1	68.5
95th percentile	124.1	305.6	193.7	355.0	152.4	388.6	80.4	176.9	68.7	143.3	66.1	120.6
Refined estimated exposure assessment scenarios												
Brand-loyal scenario												
Mean	11.1	68.2	45.3	192.0	42.3	121.6	23.3	57.3	16.1	42.6	14.0	39.0
95th percentile	59.5	276.7	104.1	242.4	86.9	227.6	47.6	116.0	35.7	124.2	31.2	101.3
Non-Brand Loyal												
Mean	5.3	50.6	21.6	99.5	19.7	68.1	12.2	31.9	7.5	22.6	6.2	21.0
95th percentile	32.9	207.5	53.0	142.3	41.6	120.6	23.3	55.8	16.8	41.7	13.6	35.7

In the *maximum level exposure assessment scenario*, mean exposure from alginic acid and its salts (E 400–E 404) from their use as food additives ranged from 35.1 mg/kg bw per day in the elderly to 300.3 mg/kg bw per day in toddlers. The 95th percentile of exposure from alginic acid and its salts (E 400–E 404) ranged from 66.1 mg/kg bw per day in elderly to 388.6 mg/kg bw per day in children.

In the *refined estimated exposure scenarios*, in the *brand-loyal scenario*, mean exposure from alginic acid and its salts (E 400–E 404) from their use as food additives ranged from 11.1 mg/kg bw per day in infants to 192.0 mg/kg bw per day in toddlers. The high 95th percentile exposure from alginic acid and its salts (E 400–E 404) ranged from 31.2 mg/kg bw per day in elderly to 276.7 mg/kg bw per day in infants.

In the *non-brand-loyal scenario*, mean exposure from alginic acid and its salts (E 400–E 404) from their use as food additives ranged from 5.3 mg/kg bw per day in infants to 99.5 mg/kg bw per day in toddlers. The 95th percentile of exposure from alginic acid and its salts (E 400–E 404) ranged from 13.6 mg/kg bw per day in elderly to 207.5 mg/kg bw per day in infants.

For all scenarios and all age groups, the main contributors were processed fruits and vegetables and meat products.

For the *maximum level exposure assessment scenario*, unprocessed fruits and vegetables was also one of the main contributing categories in every age group. As no usage level was available for this category, it does not appear in the refined scenarios, and results in a possible overestimation in the maximum level exposure assessment scenario, as the given restrictions cannot be taken into consideration for it.

For infants and toddlers, unflavoured milk products were also considered an important contributing category in the non-brand-loyal scenario, as well as desserts in the brand-loyal scenario for toddlers.

For children, adolescents and adults, in all scenarios, fine bakery wares also included in the main contributing food categories, as well as for elderly in the non-brand-loyal scenario.

The main food categories contributing to the exposure to alginic acid and its salts (E 400–E 404) are presented in Appendix E.

In the *specific scenario for FSMPs* for infants and toddlers, the mean exposure ranged from 31.0 mg/kg bw per day to 100.8 mg/kg bw per day for infants and from 20.1 to 114.0 mg/kg bw per day for toddlers. For the same age groups, the 95th percentile exposure ranged from 69.0 mg/kg bw per day to 195.4 mg/kg bw per day for infants and 62.6 mg/kg bw per day to 290.4 mg/kg bw per day for toddlers.

3.4.1.5. Exposure to formaldehyde from the use in alginic acid and its salts (E 400–E 404)

According to the EU purity criteria, the content of formaldehyde is limited to a maximum of 50 mg/kg in alginic acid and its salts. Information from industry suggested that residual levels of formaldehyde in alginate products are around 2–3 mg/kg (Documentation provided to EFSA n. 11).

Based on these two values, the Panel calculated the exposure to formaldehyde from the uses of alginic acid and its salts as food additives in different foodstuffs for the refined exposure scenario and for the FSMP scenario. The highest p95th exposure across all populations was 14.5 μg/kg bw per day for toddlers in the FSMP scenario using the EU purity criteria level down to 0.9 μg/kg bw per day using the information from industry.

The Panel evaluated the risks associated with methanol and its subsequent metabolism to formaldehyde in the opinion on aspartame (EFSA ANS Panel, 2013). Because the increase of formaldehyde above the baseline level due to 4 mg formaldehyde/kg bw per day was a small fraction of the natural occurring variation, the Panel concluded that this level of formaldehyde did not constitute a significant additional risk. The Panel noted that the exposure at the limit of specifications for formaldehyde in alginates was 14.5 μg/kg bw per day which is around 300 times lower than the amount arising from aspartame.

Therefore, the Panel concurred with the previous EFSA AFC opinion (EFSA, 2006) that exposure to residual formaldehyde from alginic acid and its salts at the EU purity criteria level of 50 mg/kg, would not be of safety concern.

3.4.1.6. Uncertainty analysis

Uncertainties in the exposure assessment of alginic acid and its salts (E 400–E 404) have been discussed above. 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 12.

Table 12: 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	+/–
Use of data from food consumption survey of a few days to estimate long-term (chronic) exposure for high percentiles (95th percentile)	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Concentration data: – levels considered applicable for all items within the entire food category, – not fully representative of foods on the EU market	 + +/–
The 23 food categories which were taken into account in the refined exposure assessment scenarios out of all authorised food categories (N = 75), corresponded to 16–45% of the amount (g of foods by body weight) of food consumption documented in the EFSA Comprehensive Database	–
Food categories selected for the exposure assessment: exclusion of food categories due to missing FoodEx linkage (n = 10/75 food categories excluded)	–
Food categories selected for the exposure assessment: inclusion of food categories without considering the restriction/exception (n = 6 MPL scenario/n = 5 refined scenarios out of 75 food categories)	+
Food categories included in the exposure assessment: data not available for certain food categories which were excluded from the exposure estimates (n = 52 not taken into account for the refined scenarios out of 75 food categories)	–
Authorisation according to Annex III to Regulation (EC) No 1333/2008 not considered	–
Regulatory maximum level exposure assessment scenario: – exposure calculations based on the maximum reported use levels (reported use from food industries/food additive producer) or MPLs – assumption the food additive is not used in the food categories in which it is authorised at QS and for which no use levels were submitted	 + –
Refined exposure assessment scenarios: – exposure calculations based on the maximum or mean levels (reported use from industries) – assumption the food additive is not used in the food categories for which no use levels were submitted	 +/– –

MPL: maximum permissible level.
(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Alginic acid and its salts (E 400–E 404) are authorised as a Group I food additive and also have specific authorised uses, in total 75 food categories (Table 8), from which 23 were taken into account in the refined exposure scenarios. Data on usage levels in foodstuffs in other categories were not reported by the food industry, or have been excluded due to a missing connection with the Comprehensive Database. However, the Panel noted that information from the Mintel GNPD (Appendix B) indicated that some of the remaining 52 food categories were labelled with alginic acid and its salts (bread and rolls, pasta, salads and savoury-based sandwiches, breakfast cereals, etc.).

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the real exposure to alginic acid and its salts (E 400–E 404) as food additives in European countries for the regulatory maximum level exposure scenario and for the refined scenario if it is considered that the food additive may not be used in food categories for which no usage data have been provided.

For the exposure scenarios, uncertainties would lead to an underestimation of exposure to alginic acid and its salts (E 400–E 404), if it is considered that the food additive may be present in foods as carry-over (Annex III to Regulation No 1333/2008).

3.4.2. Exposure via other uses

Exposures to alginic acid and its salts due to the following uses were not considered in this opinion.

3.4.2.1. Alginic acid and its salts as ingredients in slimming products and other foods

Uses of alginic acid and its salts in dietary supplements to moderate appetite and energy intake and for supportive treatment of obesity have been reported (Hoad et al., 2004; Dettmar et al., 2011). In these products, alginic acid and its salts are regarded as possible satiating materials, particularly in obese subjects (Pelkman et al., 2007; Georg Jensen et al., 2012). According to Hoad et al. (2004), alginic acid and its salts consumed as a component of a diet showed intragastrically gelling and lump formation in MRI scans under the physiological pH conditions.

Brownlee et al. (2005) reviewed the fibre-like activities of alginic acid and its salts, particularly their effects on intestinal absorption and the colon, and also their potential use as a dietary supplement for the maintenance of normal health, or the alleviation of certain cardiovascular or gastrointestinal diseases.

3.4.2.2. Pharmaceutical use

Information on pharmaceutical uses was obtained by searches of the literature, the websites of national competent authorities for medicinal products and publicly available SmPC (summary of product characteristics) on the nationally available authorised products indicated to EFSA by the European Medicines Agency (EMA) communication (Documentation provided to EFSA, n. 9).

Alginic acid and its salts are used as active ingredients or excipients in pharmaceutical products (e.g. Martindale, 2014).

As active ingredients alginic acid, magnesium alginate and sodium alginate are given, sometimes formulated in combination with carbonates and other antacids (aluminium hydroxide), in the management of gastroesophageal reflux disease (GERD). Alginic acid or its salts react with gastric acid to form a viscous gel acting as mechanical barrier to reduce reflux of gastric content (Mandel et al., 2000; Kapadia and Mane, 2007; Martindale, 2014; Reimer et al., 2016).

In medicinal products, the adult single dosages for sodium alginate is 500–1000 mg, given up to four times daily[20] and for alginic acid it is 300 mg, given up to six times daily.[21]

Alginic acids and its salts are used as excipients such as suspending and thickening agents, stabilisers for oil-in-water emulsions and as binding and disintegrating agents (Martindale, 2014).

3.5. Biological and toxicological data

3.5.1. Absorption, distribution, metabolism and excretion

There is evidence that certain high-molecular-weight dietary polysaccharides could be partially broken down in the large intestine of humans. In addition to intermediate metabolites such as lactate, acrylate or fumarate, the main end products of this colonic anaerobic digestive process are short-chain fatty acids (SCFA), such as acetic, propionic and butyric acids, that are absorbed from the colon (Cummings and Englyst, 1987).

3.5.1.1. *In vitro* studies

Some *in vitro* data on microbial fermentation of alginate were available.

In total, 178 strains from 11 *Bacteroides* species found in the human colon were assessed for their ability to ferment mucins and plant polysaccharides including gums (Salyers et al., 1977a). Many of the *Bacteroides* strains tested were able to ferment different plant polysaccharides, including amylose, dextran, pectin and gums. The ability to use mucins and plant polysaccharides varied considerably among the *Bacteroides* species tested. Sodium alginate (origin, Kelco Co.) was shown to be only fermented by *Bacteroides ovatus* strains.

In total, 154 strains from 22 species of *Bifidobacterium*, *Peptostreptococcus*, *Lactobacillus*, *Ruminococcus*, *Coprococcus*, *Eubacterium* and *Fusobacterium*, which are present in high concentrations in the human colon, were assessed for their ability to ferment 21 different complex carbohydrates. Among these, sodium alginate (origin, Kelco Co.) was not fermented by any strain of the investigated species (Salyers et al., 1977b).

3.5.1.2. *In vivo* studies

Humphreys and Triffitt (1968) investigated the absorption and excretion of ^{14}C-alginic acid in rats in groups of two. Radiolabelled alginic acid was produced from cultures of the brown seaweed (*Laminaria*

[20] Gaviscon peppermint liquid: https://www.medicines.org.uk/emc/medicine/16651
[21] Rennie extra: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1478842841316.pdf

digitata) in oxygenated seawater with ^{14}C-labelled sodium bicarbonate for up to 42 h. Alginic acid was then extracted from labelled seaweed and hydrolysed by hydrochloric acid for 5 (Test material 1) and 18 h (Test material 2). The ^{14}C-labelled alginates were fed as 10% (equivalent to 12,000 mg/kg bw per day) of the diet to 10-week-old rats (no further details available). After feeding, cumulative faeces and urine were collected in a metabolism cage for 17 h. Thereafter, the rats were killed and blood was sampled from the abdominal aorta. The intestinal content was washed out and combined with the faeces. Radioactivity was measured by the scintillation method in alginic acid, faeces, urine and blood. In a second independent trial, the cumulative radioactivity in exhaled air was determined for 17 h after feeding, as well as radioactivity in blood samples (see Trial 1) but not in faeces and urine. In both trials, no other tissues were analysed other than blood samples. All experiments were performed with both extracted alginic acids (Test material 1 and 2). At 17 h after the oral treatment with ^{14}C-labelled alginates, most of the applied radioactivity was detected in faeces (85.6–91.4% of the radioactive dose) and only traces were found in urine (0.11–0.16%), exhaled air (0.21–0.42%) and plasma 0.02–0.07%). However, 8% or 14% of applied radioactivity was not recovered.

According to the authors, this result could be explained by an incomplete intake of the diet containing the labelled alginate or by radioactivity remaining in the carcass, which was not analysed. The Panel noted that the nature of the radioactivity measured in the biological samples was not specified. This study would demonstrate the low absorption of ^{14}C-labelled alginates after oral administration in rats and the major faecal elimination of the derived radioactivity.

The faecal excretion of unchanged alginates was investigated by Nakamura et al. (1988). Groups of three male Wistar rats were given a single oral dose of 90 mg/kg bw of unlabelled alginic acid, sodium alginate, potassium alginate or calcium alginate as aqueous solution or suspension. Faeces were collected for 3 days and analysed by HPLC methods for their content of alginates. The administered alginates remained in the stomach for 2 h and then moved to the small intestine after 4 h and to the large intestine after 8 h. Within 3 days after gavage, 73–79% of the applied dose was excreted via the faeces. The results were similar for the four test compounds, despite their chemical nature as acid or salts. When measured in plasma, there were no significant differences in the plasma concentration of Na, K or Ca caused by the administration of corresponding alginates. According to the authors, although the possibility of the fermentation of alginates could not be ruled out completely, most of the orally administered alginates would be excreted unchanged into the faeces of rat.

Overall, the *in vitro* degradation by microbiota from human colon and the *in vivo* metabolism of alginic acid and its salts in animals have been investigated. These studies demonstrated that the *in vivo* biological fates of alginic acid and its salts are similar. Alginic acid and its salts would not be absorbed intact regardless of the form administered; they would not be metabolised by enzymes present in the gastrointestinal tract. However, they would be partially fermented during their passage through the large intestine by the action of the intestinal microbiota. The rate of breakdown in the gastrointestinal tract in humans is unknown. However, it is expected that the limited extent of hydrolysis of alginic acid and its salts would lead to the production of their fermentation products such as SCFA. Based on the available knowledge on the role of SCFA as end products of the fermentation of dietary fibres by the anaerobic intestinal microbiota (Topping and Clifton, 2001; Den Besten et al., 2013), the Panel considered that their formation as fermentation products from alginic acid and its salts does not raise a safety concern.

3.5.2. Acute toxicity

In the only oral acute toxicity study available, Sprague–Dawley rats (five males and five females) were exposed by gavage to sodium alginate at a dose level of 5,000 mg/kg bw. No clinical signs occurred during the 14-day post-exposure observation period. No effects were noted at necropsy. The oral LD_{50} is > 5,000 mg/kg bw (Woodard Research Corp., 1972; Documentation provided to EFSA n. 4).

The Panel considered that available data suggest a low acute oral toxicity of alginic acid and its salts.

3.5.3. Short-term and subchronic toxicity

The short-term and subchronic oral toxicity studies in different species described below were not performed according to current guidelines.

3.5.3.1. Short-term toxicity studies

In a study with alginic acid, groups of five rats (no data about sex and strain) were fed a diet containing 0%, 5%, 10% or 20% of the test material (equivalent to 0, 6,000, 12,000, 24,000 mg/kg

bw per day) for 2 months. An additional control group received 20% Cellu Flour (dietary fibre) in the diet. A dose level of ≤ 10% in the diet had no effects on food consumption or body weight gain, but slight laxative effects were detected at 10%. Decreased food consumption and reduced body weight gain were observed at the high-dose level, also in comparison with the Cellu Flour control. In this study only limited parameters were investigated (Thienes et al., 1957).

In a study with rats, all animals (n = 4–5 per group; strain and sex not stated) obtained a diet containing up to 5% equivalent to (6,000 mg/kg bw per day) calcium or potassium alginate (2%, 4%, 5% equivalent to 2,400, 4,800 and 6,000 mg/kg bw per day) for 2 weeks (Thienes et al., 1957). In comparison with controls, potassium alginate but not calcium alginate induced a slight laxative effect (moisture of faeces and faeces weight increased) at the 5% level. Other parameters were not investigated.

Groups of four male and four female CD rats were fed for 12 days a control diet or a diet with 10% sodium alginate (equivalent to 12,000 mg/kg bw per day) at the expense of starch (Mokady, 1973). Analysis of faecal lipids revealed an increase in the treatment group. Total blood cholesterol and total faecal sterols were not altered. No other parameters were investigated.

Groups of 12 male Sprague–Dawley rats received a diet containing 0 (control) or 10% sodium alginate (equivalent to 11,800 mg/kg bw per day) for 8 days. No effects on body weight gain or food consumption were observed. The excreted faeces dry weight was increased (no further data given) (Harmuth-Hoene and Schelenz, 1980).

When male Sprague–Dawley rats (n = 5–7/group) received for 2 weeks a diet in which 5% sucrose was substituted by 5% sodium alginate (equivalent to 6,000 mg/kg bw per day), no effects on body weight were detected but relative organ weight of stomach, pancreas, small intestine, caecum and large intestine were increased, and small and large intestine lengthened (Ikegami et al., 1990). The pancreas amylase was elevated as well as protease and lipase in the small intestine content. In further experiments, groups of five male Sprague–Dawley rats received alginic acid, sodium alginate or calcium alginate at a level of 5% in the feed for 4 weeks. In all trials, the faecal dry weight was increased and the digestibility of protein was reduced. The alginic acid treatment resulted in final body weight increase but not its salts. The relative organ weights of stomach, pancreas, small intestine, caecum and large intestine were increased in the sodium alginate group; no such effects were found with the other test materials (no further parameters tested). However, in all experiments, the controls received a non-fibre diet containing 66% sucrose, which did not correspond to the standard diet used at present, and which might have influenced the outcome of this study.

In another study, male Wistar rats (n = 10/group) received for 4 weeks 0%, 0.5%, 1%, 2% or 3% sodium alginate in their diet (equivalent to 0, 590, 1,180, 2,360, 3,540 mg/kg bw per day) containing also 10% protein. No effects on body weight gain, protein consumption and protein efficiency ratio were found (other parameters not tested) (Mouecoucou et al., 1990).

A group of 15 male rats (strain not stated) received 5% sodium alginate in the diet (equivalent to 5,900 mg/kg bw per day) for 30 days; the control was not specified. No clinical signs were observed including diarrhoea. The standard urinalysis did not reveal any effects but necropsy showed a distended ileum (n = 2), caecum (n = 10) and colon (n = 8) (no further data; Anderson et al., 1991).

3.5.3.2. Subchronic toxicity studies

In a feeding study (Nilson and Wagner, 1951), performed without a control group, rats (n = 6 per group; no data about strain and sex) were exposed for 10 weeks to 5%, 10%, 20% or 30% sodium alginate in the diet (4,500, 9,000, 18,000 and 27,000 mg/kg bw per day). Mortality (2/6 animals) occurred even at the low dose. In comparison with the low-dose group, a dose of 9,000 mg/kg bw per day, or more, in the diet led to increased food and water consumption but decreased body weight gain. In a study with the same experimental design (Nilson and Lemon, 1942; cited by the Food and Drug Administration (FDA), 1972), the authors reported mortality (2/6 even at the low dose) due to infections in the rats. The Panel noted that the reliabilities of both studies are limited.

A study from the Netherlands Organisation for Applied Scientific Research (TNO, 1967; Documentation provided to EFSA n. 8) investigated the subchronic toxicity of sodium alginate in rats. Groups of 10 male and 10 female Wistar rats (bw 46.0–47.3 g) received for 4 or 13 weeks 0%, 5%, 15% or 45% low viscosity sodium alginate in their diet (equivalent to 4,500, 13,500 or 40,500 mg sodium alginate/kg bw per day, respectively). Reproductive organs were weighed and examined for histopathology. After 4 weeks, one control group and the 5% and 45% groups were discarded. In the first weeks of the study, rats on 45% sodium alginate showed heavy diarrhoea and abnormal hair loss resulting in practically complete baldness, whereas growth retardation was observed. The test was continued with only one control group and the group receiving 13,500 mg/kg bw per day. In the 15%

group, slightly abnormal faeces were produced during the first weeks and growth was normal. In this group and for the final 2 weeks of the study, the batch of sodium alginate was replaced by another sample, resulting in a lower food intake ascribed by the authors to the change of the test batch. The amount of faeces produced per 100 g of food consumed was considerably increased in rats that were fed sodium alginate. Haematology tests did not show abnormalities, whereas increased weight of the caecum was observed. Macroscopy revealed enlarged, distended, heavy caeca. Histopathology specimens showed a thickened urothelium with papillomatous appearance in the urinary bladder of 6/10 male and 3/10 female rats. Small calcium deposits under the thickened urothelium of the renal pelvis and/or under the surface of the renal papilla were observed in 6/10 male and 2/10 female rats. These changes were not seen in the control group. According to the authors, these histopathological renal changes were related to the treatment with the test substance. The Panel noted that the 15% concentration in feed (equivalent to 13,500 mg/kg bw per day) caused physiological disturbances, and therefore, the histopathological changes observed at this dose, although treatment-related, were considered not relevant for human risk assessment.

The Panel noted that an increased caecum weight in animals fed high amounts of carbohydrates is considered a physiological response to an increased fermentation. Increased caecum weight has been observed in rats fed carbohydrates other than alginic acid and its salts (Leegwater et al., 1974; Licht et al., 2006). Animals fed diets containing potato starch, inulin or oligofructose had significantly higher caecum weights and lower pH values than the reference animal group (Licht et al., 2006). Different groups of animals fed modified diets containing increased concentrations of potato starch, hydroxypropyl starch and hydroxypropyl distarch glycerol showed increases in the relative caecal weights, filled and emptied, with increasing concentrations of the various hydroxypropyl starches. These increases were accompanied by increased severities of diarrhoea that was related to an increased osmotic activity of the caecal fluid in the animals (Leegwater et al., 1974). The authors hypothesised that dietary components were not completely digested and/or absorbed in the small intestine, and were fermented further by the gut microflora, enhancing the amounts of osmotically active material and resulting in an increase in water retention. The animals drank more water and this led to the caecum distention to a size larger than normal.

Watt and Marcus (1971) treated groups of six male guinea pigs with sodium alginate for 7 months at dose levels of 0% or 1% in the drinking water (0 or 660 mg/kg bw per day; calculation according to WHO, 1987). No clinical signs including diarrhoea and no occult blood in faeces were detected. No effects were noted in the large bowel at necropsy. The Panel noted that there are limited parameters investigated.

Groups of three male and three female Beagle Dogs received daily a diet containing 0%, 5% or 15% sodium alginate for 12 months (Woodard Res. Corp., 1959; Documentation provided to EFSA n. 3). The high dose corresponded to 3,000 mg/kg bw per day (calculated by the authors of the study). On Saturdays, double feeding was given to carry over Sunday without treatment. Dogs were observed daily for clinical signs. The body weight was recorded once weekly. Haematology was performed at week -1, 0, 2, 6, 13, 26, 39, 52 (parameters: haemoglobin, packed cell volume, white blood cell count, differential blood count) and clinical chemistry at termination (parameters: urea nitrogen, alkaline phosphatase, glucose) as well as urinalysis (parameters: sugar, albumin, microscopy, occult blood). Necropsy was performed and organ weights measured (including liver, kidney, heart, spleen, testis, ovary, uterus, prostate, adrenals, thyroid gland). Organs and tissues were examined histopathologically: analysed organs: cerebrum, pons, midbrain, pituitary, heart, salivary gland, heart, liver, lung, kidney, spleen, pancreas, stomach, ileum, jejunum, duodenum, large bowel, testis, ovary, urinary bladder, prostate, uterus, lymph nodes (only in the experiment with sodium alginate: parathyroid, spinal cord, adrenals). No clinical signs and no treatment-related effects on food consumption and body weight gain were noted. Haematology, clinical chemistry and urinalysis results were within the normal limits. No treatment-related effects were detected at necropsy and histopathology. A no-observed-adverse effect level (NOAEL) was not allocated by the authors of the study.

The Panel considered the NOAEL of this study in dogs to be 15% sodium alginate in the diet, corresponding to 3,000 mg/kg bw per day, the highest dose tested.

3.5.4. Genotoxicity

3.5.4.1. *In vitro* studies

In the study by Ishidate et al. (1984), sodium alginate was not mutagenic in *Salmonella* Typhimurium strains TA92, TA1535, TA100, TA1537, TA94 and TA98 both in the absence or presence

of S9 metabolic activation. Sodium alginate was not tested in the TA102 or *Escherichia coli* WP2 tester strains and only the pre-incubation method was applied. However, the Panel considered that the results obtained are sufficient because the oxidising or cross-linking properties of sodium alginate are not expected.

Low-density and high-density alginic acid were tested in the Ames test both in the absence or presence of S9 metabolic activation and negative results were obtained (de Veer et al., 1994). However, the Panel noted that only two *S*. Typhimurium tester strains (TA98 and TA 100) and one dose level (3.2 and 4.2 mg/mL), respectively, were used. On this basis, the study was considered to be unreliable for risk assessment.

In a chromosome aberration assay on 242 food additives, sodium alginate was assayed for its clastogenic properties in a Chinese hamster lung (CHL) cell line. Treatments were performed for 24 or 48 h at three different dose levels. The maximum dose level employed for sodium alginate was 1 mg/mL, selected in a preliminary toxicity test as the dose causing 50% cell-growth inhibition only without metabolic activation. Results obtained indicated that sodium alginate did not induce polyploidy or clastogenic effects. However, the Panel noted that treatments were not performed in the presence of S9 metabolic activation (Ishidate et al., 1984).

A chromosome aberration test with sodium alginate was also performed with Chinese hamster ovary cells (Larripa et al., 1987) without S9 metabolic activation and no clastogenic effects were detected. However, no data were given about the cytotoxicity and the sodium alginate was tested only up to 0.1 mg/mL which is well below the maximum dose level of 2 mg/mL recommended in current Organisation for Economic Co-operation and Development (OECD) guideline No 413.

In the sister chromatid exchange assay (SCE), V79 Chinese hamster cells were exposed to low-viscosity and high-viscosity alginic acid at single dose levels of 3.2 and 4.2 mg/mL, respectively, both in the absence or presence of S9 metabolic activation and no significant increases of SCE, compared with vehicle control values were observed. However, the Panel noted that the study was only performed with a single dose level and that no data about cytotoxicity were reported. Furthermore, the SCE assay is considered to be an ancillary test for genotoxicity and is not currently recommended for risk assessment. Overall, this study was judged of limited value (de Veer et al., 1994).

The possible DNA-damaging activity of sodium alginate was tested in the Rec-assay (DNA repair test) using the *Bacillus subtilis* mutant strain M45 rec^-, unable to repair DNA damage, and the wild-type strain H17 rec^+ as $control^-$ at dose level of 2.0 mg/disc both in the absence or presence of S9 metabolic activation and negative results were obtained (Ishizaki and Ueno, 1987). The Panel noted that the Rec-assay is no longer included in genotoxicity test batteries and did not receive sufficient validation.

3.5.4.2. *In vivo* studies

In a dominant lethal test, 7–10 male ICR/Ha Swiss mice per group (8–10 weeks old at initiation) received a single intraperitoneal (i.p.) injection of 0, 82, 200 or 1,000 mg/kg bw alginic acid. Each male was subsequently mated with three virgin females that were replaced weekly for 8 consecutive weeks. Each female mouse was sacrificed 13 days after the presumptive mating and early and late fetal deaths as well as total implants were determined. Alginic acid did not induce an increase in early fetal death and preimplantation losses. A concurrent positive control was not performed but positive results were obtained with known alkylating agents in parallel trials (Epstein et al., 1972). The author concluded that, under the reported experimental conditions, alginic acid did not cause dominant lethal mutations in mice. The Panel agreed with this conclusion..

Overall, alginic acid and sodium alginate were tested in several *in vitro* assays and in one *in vivo* assay that, despite some limitations, did not reveal any genotoxic effect for alginic acid and sodium alginate. No studies were available for calcium alginate, potassium alginate and ammonium alginate. However, the Panel considered that a read-across approach can be applied to calcium alginate, potassium alginate and ammonium alginate to exclude a potential genotoxicity also for these compounds. The Panel also noted that alginic acid would not be absorbed unchanged and would not be metabolised by enzymes present in the gastrointestinal tract but partially fermented during its passage through the large intestine by the action of the intestinal tract microflora leading to the production of its fermentation products such as SCFA which do not raise concerns for genotoxicity (OECD Toolbox 4.0[22]). On this basis, the Panel concluded that there is no concern with respect to the genotoxicity for alginic acid and its salts (E 400–E 404).

[22] Available on: https://www.qsartoolbox.org/

3.5.5. Chronic toxicity and carcinogenicity

3.5.5.1. Mice

In a combined chronic and carcinogenicity feeding study (according to OECD TG 453) in mice (Til et al., 1986), a total of 75 male and 75 female Swiss mice (6 weeks old at initiation) received for 87 weeks (recovery group) or 89 weeks a diet that contained sodium alginate at a dose level gradually increasing to 25% (week 39; no further details available, equivalent to 37,500 mg/kg bw per day). Sodium alginate was incorporated into the control diet at the expense of equal amounts of the pre-cooked potato starch. Controls (75 mice of each sex) received a standard diet containing 55% of the starch. In week 87, half the total number of the surviving male and female mice in the treated group were placed on control diet and 2 weeks later urinalysis was repeated. The pH of faeces was measured in pooled samples of 4–5 males/group at weeks 82 and 85. In week 80, 10 mice/sex per group were killed, necropsy performed, organ weights determined (heart, kidneys, liver, spleen, brain, testes; caecum and colon filled and empty) and tissues (including epididymides, prostate, seminal vesicles, ovaries and uteri) examined histopathologically. Mice found moribund were killed and necropsied. At weeks 89–92, all survivors were killed and subjected to autopsy. The weights of the caecum and colon, both filled and empty, were recorded. Histopathological examinations were carried out on the kidneys and urinary bladder of all mice, as well as on all organs bearing or suspected of bearing tumours.

Clinical signs were limited to urinary incontinence found in eight males and two females. There was no treatment-related effect on survival. Mean body weights in the treatment group were decreased from week 8 onwards in males and from week 20 onwards in females. No treatment-related effects were detected in haematology and no effects on faecal pH were found. Sodium alginate resulted in extremely high water consumption (5–10 times the control value) considered by the authors to be related to sodium intake. Urinalysis revealed high urine volume, increased urine pH and decreased specific gravity in males and females; the level of blood urea nitrogen was increased. The concentration of calcium, sodium and phosphor in urine was significantly increased in males and females. The urinalysis after the 14-day recovery period showed the reversibility of these effects. Also, the increased relative organ weights of caecum and colon in males and females were reversible after the recovery period. Slightly increased kidney and liver weights were found in females (no further details, presumably not significant). Histopathological examination of organs other than the kidneys and urinary bladders of mice killed in week 80 (n = 10) revealed no treatment-related effects including caecum and colon. Histopathology of kidney and bladder in all control and treated mice (n = 66–75 per dose/sex) showed the increased incidence and severity of chronic nephropathy and the increased incidence in intratubular calcareous deposits in treated female mice as well as distension of renal pelvic space. In male and in female mice, the incidence of dilated distal renal tubules was increased, accompanied by epithelial hyperplasia and hypertrophy. An increased number of female mice showed subepithelial round cell infiltrates in the urinary bladder that was in several instances accompanied by cystitis (considered by the authors to be not treatment related); a proliferation of the epithelium was not found. Histopathology gave no indication for carcinogenic activity under the conditions of this study (Til et al., 1986).

According to the authors, the findings in urinalysis were probably due to the high sodium intake followed by extremely high water intake and the findings in the histopathology of the kidney might have been also related to the high water intake (Til et al., 1986). Furthermore, the authors discussed the enlargement of the caecum and colon as a consequence of increased load of non-digestible and osmotically active substances. These findings were not considered to be of toxicological significance. The toxicological relevance of the nephrotoxic effects was not evaluated by the authors or in the JECFA evaluation (1993a).

The Panel could not use this study to identify a NOAEL for the observed effects on kidneys and bladders of female and male mice because only one dose of sodium alginate was tested, and moreover, the dose of sodium alginate was gradually increased to 25% in the diet (equivalent to 37,500 mg/kg bw per day).

3.5.5.2. Rats

The Panel considered that the following studies were of limited relevance for evaluation of the chronic toxicity after oral administration of sodium alginate.

In a study with limited information, rats exposed for 2 years to 10,000 mg/kg bw per day showed reduced body weight gain but no effects at necropsy and histopathology (no data about strain, sex, number of animals per group and vehicle). A control group was not specified (Stara and Waldron-Edward, 1968; cited in BIBRA, 1988; also no further data in the primary source).

In another study, 10 male Yokelson's rats were fed a diet containing 5% sodium alginate (equivalent to 2,500 mg/kg bw per day) for up to 128 weeks (rats died naturally). Control males (n = 12) received the basal diet and survived up to 132 weeks. Treated rats showed no effect on final body weight or food and water consumption and at necropsy (no further data; Nilson and Wagner, 1951).

Overall, from the results of the long-term toxicity studies in mice and rats, the Panel considered that alginic acid and its salts were not of concern with respect to carcinogenicity.

3.5.6. Reproductive and developmental toxicity

3.5.6.1. Reproductive toxicity

In a two-generation reproductive toxicity study, groups of 20 male and 20 female Sprague–Dawley rats (F0 rats; 36 days of age) were fed diets containing 0 or 5% sodium alginate (equivalent to 0 and 2,500 mg/kg bw per day) for a period of 2 years. During this period the F0-generation rats were bred once to produce the F1-generation 5–6 months after initiation of treatment. The 4-month-old F1-rats (n = 7 per sex in control and n = 9 or 10 in the treatment group) were subsequently used for breeding of an F2-generation (n = 8–10 per sex per group). F1- and F2-rats were placed on the same diet as the F0-generation (no further details on methods used for the end-point reproduction). The reproductive performance was comparable to controls and no effects were seen during the lactation period (no further details available). There were no significant effects on body weight gain (measured weekly during the first 4 months, then monthly) of the F0- and the F1- or F2-generation except higher body weight in the F2-females (not considered to be treatment related by the authors of the study). Haematology, including red and white blood cell counts, haematocrit and differential blood counts of the F0-rats (blood sampling at study month 5, 8, 12 and 23) and F2-rats (sampling after 3 and 6 months postnatal) were normal. Necropsy of F0-, F1- and F2-rats and histopathology of lung kidney, liver, stomach, intestine and pancreas of the parent groups after 2 years, and of the F1- and F2-generation at the conclusion of the rapid growth period, were normal (Georgetown University Medical School, 1959; Documentation provided to EFSA n. 5). The Panel noted that the data presented in this study are insufficient to conclude that there are no effect on reproduction due to low number of animals used to generate the F2-generation and limited reporting of data.

3.5.6.2. Developmental studies

Only one study of minor relevance (Krentz et al., 1993) on encapsulation of mouse morulae in 2% sodium alginate was found. The Panel considered this study of minor relevance for evaluation of the safety.

Overall, the data on reproductive and developmental toxicity were too limited to evaluate this end-point.

3.5.7. Hypersensitivity, allergenicity and food intolerance

3.5.7.1. *In vitro* studies

Yang and Jones (2009) showed that sodium alginate (low viscosity purified from brown algae) induced activation of macrophage-like cells (RAW264.7) through the NF-κB pathway. Production of proinflammatory cytokines, such as IL-1β, IL-6, IL-12, and tumour necrosis factor (TNF)-α was time dependent and dose dependent. Treatment with sodium alginate solution (1–3 mg/mL) caused responses that closely paralleled stimulation by lipopolysaccharide in timing and magnitude. According to the authors, these data suggested that sodium alginate causes initiate immune responses through NF-κB activation and probably activates the same pathways as pathogen recognition. The Panel noted that the doses used were much higher than what can be expected *in vivo*.

Ueno and Oda (2014) examined the effect of alginates with varying molecular weights and an M/G ratio on the murine macrophage cell line RAW264.7, in terms of induction of TNF-α secretion. Among the alginates tested, the alginate with the highest molecular weight (MW 38,000, M/G 2.24) showed the most potent TNF-α-inducing activity. Alginates that had higher M/G ratios tended to show higher activity. According to the authors, these results suggested that molecular size and M/G ratio are important structural parameters influencing TNF-α-inducing activity.

The Panel noted that it is difficult to evaluate the relevance of these data obtained with material that are not clearly identical to the food additives alginic acid and its salts (E 400–E 404).

3.5.7.2. Animal studies

Effects on the humoral immune response in mice were examined (Mayer et al., 1987). In the first trial (BALB/c × DBA/2), F1 hybrid mice (n = 4; sex not stated) received an injection (route not stated but presumably i.p.) with 100 μg of sodium alginate in physiological saline at 4 days before the inoculation with sheep red blood cells and at the day of inoculation. Blood samples were collected 7 days after inoculation and serum was assayed for antibodies against sheep red blood cells by haemagglutination test. Sodium alginate caused a significant increase in antibody titre compared with the control (n = 12), which was treated with physiological saline. However, no effect on the humoral immune response was found in a second trial using the same experimental design (n = 5); the antibody titre was comparable with the control value.

3.5.7.3. Human data

Gangemi et al. (2009) reported one case of fatal anaphylaxis that appeared immediately after the oral mucosa came into contact with an alginate paste used for dental impressions. The patient was affected by both cardiovascular and lung diseases that worsened the condition and forbade the use of adrenaline. To the authors' knowledge, dental impression materials, and alginate in particular, have not been reported previously as being a cause of anaphylaxis.

No such case reports of hypersensitivity and anaphylaxis after exposure to products containing alginic acid or its salts via ingestion have been identified by literature research. Overall, the Panel considered that there is no indication for immunotoxicity or an allergenic potential of alginic acid and its salts used as food additives.

3.5.8. Other studies

3.5.8.1. *In vitro*

An *in vitro* continuous flow dialysis model with a preliminary intraluminal digestive phase[23] was used to measure calcium, iron and zinc availability from casein-based and whey-based infant formulae supplemented with soluble fibre fractions, among them alginic acid (Bosscher et al., 2001). Availability was calculated from the amount of guar gum (and other soluble fibre fractions) that had passed the dialysis membrane proportional to the total element content of the sample. In the whey-based formula, the addition of alginic acid at 2.0 g/100 mL decreased the availability of calcium from 13.3% to 5.3% and increased that of iron or zinc from 1.28% to 6.05% and from 6.7% to 10.2%, respectively.

3.5.8.2. Animal studies

The effect of polysaccharides, including sodium alginate, fed at the level of 10% in a semi-synthetic diet, on absorption of Ca, Fe, Zn, Cu, Cr and Co, on weight gain and on faecal dry matter excretion was assessed over a period of 8 days in five groups of 12 weanling male rats each and compared with a control group (Harmuth-Hoene and Schelenz, 1980). Sodium alginate reduced significantly the absorption of Fe, Cr and Co.

Wölbling et al. (1980) studied *in situ* the effect of sodium alginate in the absorption of ^{59}Fe-labelled iron in tied-off jejunal segments of normal or iron-deficient anesthetised female Wistar rats. Tied-off jejunal segments were filled with 2 mL of a solution containing 360 nmol ^{59}Fe-labelled ferric chloride (pH 2) and increasing amounts of 1.2, 8, 30 and 100 mg of sodium alginate. After 1 h of exposure, the animals were sacrificed and the tied-off segments removed. The ^{59}Fe activity in the carcasses was determined in a whole body counter. The amount of ^{59}Fe detected (called 'absorption') in the carcasses was calculated in % of the dose administered. Increasing doses of guar gum inhibited the 'absorption' of iron in normal rats. The highest dose of sodium alginate inhibited iron 'absorption' by 60%. In iron-deficient rats, the 'absorption' of iron was reduced by about 15%. When ^{59}Fe was given in the diet containing 10% of sodium alginate for 3 days and on the sixth day after administration of iron the retention of ^{59}Fe was measured. Under these conditions, sodium alginate inhibited the

[23] The method consists of the so-called 'gastric and intestinal phases'. During the 'gastric phase', the sample pH is adjusted to pH 4.0 and pepsin solution is added under incubation. During the 'intestinal phase' done in an Amicon stirred cell, a small dialysis bag containing $NaHCO_3$ is added to neutralise the gastric phase. After 30 min, a mixture of pancreatin/bile acid is added and dialysis continued for another 2 h.

'absorption' of iron in normal rats (by about 40%) but did not inhibit the 'absorption' of iron in iron-deficient rats.

3.5.8.3. Human data

Pharmaceutical uses

Information on pharmaceutical uses was obtained by searches of the literature, the websites of national competent authorities for medicinal products and publicly available SmPC on the nationally available authorised products indicated to the EFSA by the EMA communication (Documentation provided to the EFSA, n. 9).

Alginic acid, magnesium alginate and sodium alginate, are given as active ingredients to treat GERD. In the presence of gastric acid, a viscous alginic acid gel (ranft) is formed, which is strengthened under the influence of Ca^{2+} and acts as mechanical barrier to reduce reflux. If combined with carbonates, CO_2, released upon contact with gastric acid, is trapped within the alginic acid gel to provide aeration and buoyancy of the gel floating on the gastric content (e.g. Dettmar et al., 2011; Martindale, 2014).

Adults, adolescents and children 6–12 years

Alginic acid in combination with carbonates

Tablets with alginic acid are given to impede gastroesophageal reflux and may contain 300 mg active substance per single dosage (administered not more than six times per day) in combination with calcium carbonate and heavy magnesium carbonate[21] or 200–400 mg active substance per single dosage (administered not more than four times per day) in combination with dried aluminium hydroxide gel, magnesium trisilicate and sodium bicarbonate.[24] Overall, this amount corresponds approximately to a single dose of 3–6 mg/kg bw and a daily dose of up to 26 mg/kg bw of alginic acid. Flatulence may occur as an undesirable effect. Anaphylactic and hypersensitivity reactions as well as respiratory effects are indicated as very rare side-effects.

Sodium alginate in combination with carbonates

Sodium alginate is used in different medicinal combination products (solid and liquid formulae) as the active ingredient (often combined with sodium bicarbonate and calcium carbonate or potassium bicarbonate) in cases of gastric reflux. The dosage[20] is given for adolescents and adults as 500–1,000 mg sodium alginate after meals and at bedtime (up to four times daily) corresponding approximately to a single dose of 7–14 mg/kg bw and a daily dose of up to 56 mg/kg bw. For children 6–12 years of age, the dosage is given as 250–500 mg sodium alginate after meals and at bedtime (up to four times daily). Usage in pregnancy and lactation is possible, if clinically needed. Side-effects are very rare and may affect the immune system (anaphylactic and anaphylactoid reactions; hypersensitivity reactions such as urticaria) and the respiratory system (e.g. bronchospasms).

Infants and young children

Sodium alginate combined with magnesium alginate

A combination of sodium alginate and magnesium alginate in the form of powder to be administered after mixing with water or formula is authorised for infants and young children in the treatment of gastric regurgitation, gastroesophageal reflux and reflux associated with hiatus hernia.[25] It should not be used in premature infants or infants under 1-year-old except under medical supervision. The posology for toddlers aged 1–2 years is given as 225 mg sodium alginate and 87.5 mg magnesium alginate for infants under 4.5 kg bw and 450 mg sodium alginate and 175 mg magnesium alginate for infants over 4.5 kg bw per meal, not more than six times in any 24-h period. When the sum of total alginates is expressed as sodium alginate, the single dosage corresponds to a range of 69–139 mg sodium alginate/kg bw and maximum daily dosage corresponds to a range of 417–834 mg sodium alginate/kg bw. It is advised that the medicinal product should not be used with thickening agents or infant milk preparations containing a thickening agent, as this could lead to over-thickening of the stomach contents. Side-effects described are hypersensitivity, constipation, diarrhoea, intestinal obstruction, flatulence, abdominal distension and bezoar. Contraindications are hypersensitivity to alginates or cases of intestinal obstruction or established diarrhoea. It is reported that rare instances have occurred in which an intragastric mass has developed comprising the

[24] Gastrocote tablets: https://www.medicines.org.uk/emc/medicine/21184
[25] Gaviscon infant: https://www.medicines.org.uk/emc/medicine/21981

medicinal product and milk proteins. It is assumed that overdosage may have contributed to the development of such masses. The majority of these events resolved spontaneously when the child was admitted to hospital, the administration of the product was discontinued and a regime of adequate fluid intake and monitoring of fluid and electrolyte balance was installed. Furthermore, it is indicated that if spontaneous resolution of the mass does not occur, removal by surgical or endoscopic means may be required[25] (Keady, 2007; Tighe et al., 2014).

Sodium alginate in combination with carbonates

A combination of sodium alginate and sodium bicarbonate in form of a suspension is authorised for the treatment of symptoms of reflux in infants and toddlers. The posologies are: infants up to 1 month: 50 mg sodium alginate after each meal (up to six times daily); infants 1–2 months of age: 75 mg sodium alginate after each meal (up to five times daily) and infants 2–4 months of age: 100 mg sodium alginate after each meal (up to five times daily) infants/toddlers 4–18 months: 125 mg sodium alginate after each meal (up to four times daily), toddlers from 18 months onwards: 250 mg sodium alginate after each meal (up to four times daily). Indicated undesirable effects are allergic reactions or difficulty in breathing.[26]

3.5.8.4. Case reports

Rare cases of intra-abdominal bezoar formation in infants and children have been reported after antireflux treatment with alginates (Sinaasappel et al., 1984; Sorbie et al., 1984; Kaneko et al., 2004). For example, large mobile masses were detected in the abdomen by barium meal examination in two male infants (3 and 6 months of age) after administration of an alginate containing medicinal product[27] (Sorbie et al., 1984).

The United States Food and Drug Administration (US FDA) concluded, that for over-the-counter (OTC) drug products for human use, containing alginic acid or another water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient, when marketed in a dry or incompletely hydrated form (e.g. capsules, granules, powders, tablets, wafers) the following labelling is needed to prevent oesophageal obstruction or asphyxiation: 'Taking this product without adequate fluid may cause it to swell and block your throat or oesophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention' (FDA, 2015).

3.5.8.5. Clinical studies

Adults

Alginic acid

Three male patients whose clinical condition warranted sodium restriction and one healthy male subject (no illness other than Ménière's syndrome) were given oral doses of 15 g of alginic acid three times daily (corresponding approximately to single doses of 214 mg/kg bw and daily doses of 643 mg/kg bw of alginic acid) for 7 days, completed by a diet containing 500 mg sodium/day (also given in the pre-exposure period for 7 days). In a repeat trial with three patients (no further data), the diet contained 1,500 mg sodium/day. In the first 2 days after the start of alginic acid treatment, the patients in both trials reported a transient unpleasant taste and a brief sensation of fullness. Mild laxative effects were noted and significantly increased faecal sodium and potassium excretion, but no changes in plasma electrolyte concentration or in electrocardiogram (Feldman et al., 1952).

Six patients with essential hypertension (no further details) were given 45 g/day (corresponding to 643 mg/kg bw per day) of alginic acid containing 10% of potassium alginate for a period of 5–9 weeks. The treatment was well tolerated and produced no gastrointestinal disturbance or electrolyte disorders (no further details). Similar results were found in a second experiment with three patients in an oedematous state after receiving the same dosage for 1–2 weeks (Gill and Duncan, 1952).

Sodium alginate

Five healthy male volunteers (26–48 years old; body weight: 51–92 kg) received 175 mg sodium alginate/kg bw per day for 7 days, followed by 200 mg/kg bw per day for a further 16 days period (Anderson et al., 1991). The daily doses were consumed in three portions at intervals each day (no further details). The individual portions of sodium alginate were mixed with 220 mL of water and

[26] Gaviscon Baby: https://www.arcofarma.be/files/pdf/2805513_DE.PDF
[27] https://www.medicines.org.uk/emc/medicine/21981

allowed to fully hydrate for 24 h to give a thick, but fluid, gel to which orange juice was added before consumption. At day 3 of the initial control week, a history of allergenicity was recorded. During the treatment period, queries were made with respect to apparent allergic reactions. At day 3 of the initial control period, on the last day of the 23-day treatment period and at day 7 day of the 1 week post-exposure observation period the following parameters were evaluated: glucose tolerance test, plasma insulin, exhaled hydrogen concentrations during the glucose tolerance test, from fasting blood samples haematological parameters and clinical chemistry parameters. Routine urinalysis of 24-h samples was performed during the initial control week and during the third week of treatment (no details available). Complete 5-day faecal collections were made during days 2–6 of the initial control period and during days 16–20 of the treatment period. Faecal transit time (after ingestion of a marker), stool wet weight and dry weight, water content, pH, occult blood, neutral sterols, fat, volatile fatty acids and bile acids in faeces were calculated. No differences in the composition of the diet were found during control and treatment period. None of the volunteers reported allergic reactions, gastrointestinal disturbances or discomfort. At the dose levels applied in this study, sodium alginate acted as a bulking agent without a significant change in transit time. Total faecal volatile acids increased in four volunteers but diminished in one. No changes were seen in other parameters of faecal analysis. Haematology, clinical chemistry and urinalysis did not show treatment-related significant changes. According to the authors, the ingestion of sodium alginate at a high level for 23 days caused no effects other than those normally associated with a polysaccharide bulking agent; in particular, the enzymatic and other sensitive indicators of adverse toxicological effects remained unchanged.

In a recent randomised placebo-controlled clinical trial, the influence of sodium alginate (in combination with sodium bicarbonate) on reflux symptoms was investigated in patients with persistent symptoms (Reimer et al., 2016). In that study (on 136 patients), it could be shown that in patients with residual reflux symptoms, despite proton pump inhibitor treatment, the addition of sodium alginate decreased the burden of reflux symptoms. The daily dosage was 1,000 mg sodium alginate four times per day (corresponding approximately to single doses of 14 mg/kg bw and daily doses of 56 mg/kg bw) for 7 days. Altogether 33 patients (24.3%) experienced a total of 43 treatment emergent adverse events. In the group that received sodium alginate, 16 patients (24.2%) experienced 21 adverse events, while in the placebo group 17 patients (24.3%) experienced 22 adverse events. The most frequently reported adverse events in both groups were nausea and headache.

In a randomised double-blinded clinical trial, 1107 patients (18–65 years of age) with GERD received either two tablets containing 250 mg sodium alginate, 106.5 mg sodium bicarbonate and 187.5 mg calcium carbonate as active ingredients or two placebo tablets four times daily for 7 consecutive days (corresponding to a daily dose of 29 mg sodium alginate/kg bw) (Sun et al., 2015). The placebo tablets were composed mainly of mannitol and xylitol. The incidence of adverse events was similar in the alginates and placebo groups. Twenty-nine participants (5.3%) in the alginates group and 19 participants (3.5%) in the placebo group had adverse events that were at least possibly related to the study medication. Most adverse events (alginates/placebo) were gastrointestinal disorders (3.3%/2.4%) such as constipation (1.5%/0.7%), abdominal distension (0.7%/0.4%) and flatulence (0.2%/0.7%). Similar results were obtained in a randomised double-blinded clinical pilot study performed in 110 patients with symptoms of GERD (Thomas et al., 2014).

Calcium alginate

In total, 14 patients on continuous ambulatory dialysis received calcium alginate for phosphate binding orally in capsules over a period of 1 year (Passlick et al., 1989). The dosage of calcium alginate was 6,900 mg per day at the beginning of the study and 8,300 mg per day at the end of the study, corresponding to 99 and 119 mg/kg bw per day, respectively. The daily dosage was administered divided in three single dosages and was given with the meals. Treatment was stopped in two patients after 12 and 20 weeks, because of difficulties in swallowing the capsules. Besides this difficulty no other adverse reactions such as constipation, diarrhoea, flatulence or indigestion, occurred in the patients.

In a second study, 12 patients on haemodialysis were treated orally with calcium alginate in divided doses with meals amounting to a maximum of 8,400 mg per day, corresponding to 120 mg/kg bw per day, for 6 months. The only side-effect reported was mild diarrhoea in one patient (Harris and Yuill, 1993).

Infants

In a double-blinded, randomised, parallel-group study conducted in 25 general practice centres in the UK, 90 paediatric patients with gastroesophageal reflux, 0–12 months of age, received alginates (42 patients) or placebo (48 patients). Infants were assessed before treatment and again after 7 and

14 days of treatment. For the alginates, treatment sachets each containing 225 mg sodium alginate and 87.5 mg magnesium alginate were used and administered in liquids. On feeding occasions, infants weighing < 4.54 kg were given one sachet in and infants weighing ≥ 4.54 kg were given two sachets in formula or water. When the sum of total alginates is expressed as sodium alginate, single dosage corresponds to a range of 69–139 mg sodium alginate/kg bw and daily dosage to a range of 417–834 mg sodium alginate/kg bw. The alginate treatment achieved a significantly greater reduction in the mean severity of vomiting episodes. More than one-half of the total number of all patients experienced at least one adverse event (alginate, 55%; placebo, 59%), with no significant treatment difference being observed between the two groups. Gastrointestinal effects (alginates/placebo) included functional diarrhoea (14.3%/10.9%), emesis (2.4%/10.9%) and constipation (9.5%/2.2%). (Miller, 1999; Tighe et al., 2014).

Overall, the Panel noted that the oral intake of 175 mg sodium alginate/kg bw per day for 7 days, followed by 200 mg/kg bw per day for further 16 days was well tolerated in five healthy male adults. In addition, in several larger placebo-controlled clinical trials in adults, investigating the safety of the medicinal use of sodium alginate in GERD, daily dosages up to 56 mg/kg bw in combination with carbonates have been well tolerated. Furthermore, oral treatment of 14 patients on dialysis with approximately 120 mg calcium alginate/kg bw per day over a period of 1 year was well tolerated without adverse reactions.

The Panel also noted that for the medicinal use of a combination of sodium alginate and magnesium alginate in infants and young children with a maximum daily dosage corresponding in total to 417–834 mg sodium alginate/kg bw, constipation, diarrhoea, intestinal obstruction, flatulence, abdominal distension and bezoar are indicated as adverse effects. However, cases of development of an intragastric mass are reported to be rare and possibly due to overdose. In a multicentre study in infants, no significant differences in the incidences of adverse events between the groups treated with the combination of sodium alginate and magnesium alginate or with placebo were observed.

4. Discussion

Alginic acid (E 400) as defined by Commission Regulation (EU) No 231/2012, is a linear glycuronoglycan polymer consisting mainly of β-(1→4)-linked D-mannuronic and α-(1→4)-linked L-guluronic acid units extracted from natural strains of various species of brown seaweeds (Phaeophyceae). Sodium (E 401), potassium (E 402), ammonium (E 403) and calcium alginates (E 404) are sodium, potassium, ammonium and calcium salts of alginic acid, respectively.

Specifications for these food additives have been defined in Commission Regulation (EU) 231/2012.

Based on the information on ranges of protein content (N × 6.25%) in food additives E 400, E 401, E 402, E 404 and E 404 of 0–3.2% provided by the interested party, the Panel noted that, due to the possible hypersensitivity issues, limits for protein should be reduced as much as possible and included in the EC specifications.

The Panel noted that toxicological studies with PGX were available for its evaluation as novel food by the EFSA NDA Panel. The EFSA ANS Panel did not consider results of these studies in its re-evaluation of the individual substance alginic acid and its salts (E 400–E 404). It is not possible to conclude to what extent are the reported effects attributable to one of the individual components of the complex. The physicochemical properties of the individual components might also have changed during the manufacturing process of PGX (see Section 1.2).

The *in vitro* degradation by microbiota from human colon and the *in vivo* metabolism of alginic acid and its salts in animals have been investigated. These studies demonstrated that the *in vivo* biological fate of alginic acid and its salts are similar. Alginic acid and its salts would not be absorbed intact regardless of the form administered; they would not be metabolised by enzymes present in the gastrointestinal tract. However, they would be partially fermented during their passage through the large intestine by the action of the intestinal microbiota. The rate of breakdown in the gastrointestinal tract in humans is unknown. However, it is expected that fermentation of alginic acid and its salts would lead to the production of products such as SCFA, which were considered to be of no concern by the Panel.

One short-term toxicity study performed in rats with alginic acid up to 24,000 mg/kg bw per day, seven short-term toxicity studies performed in rats with sodium alginate up to 12,000 mg/kg bw per day, one subchronic toxicity study performed in rats with sodium alginate up to 13,500 mg/kg bw per day and one subchronic study in dogs with sodium alginate up to 3,000 mg/kg bw per day were available. No adverse effects were observed. In the rat studies, the caecal enlargement described by the authors was considered by the Panel as an adaptive process related to the high doses tested.

Alginic acid and sodium alginate were tested in several *in vitro* assays and in one *in vivo* assay that, despite some limitations, did not reveal any genotoxic effect for alginic acid and sodium alginate. No studies were available for calcium alginate, potassium alginate and ammonium alginate. However, the Panel considered that a read-across approach can be applied to calcium alginate, potassium alginate and ammonium alginate to exclude a potential genotoxicity also for these compounds. The Panel also noted that alginic acid would not be absorbed unchanged and would not be metabolised by enzymes present in the gastrointestinal tract but partially fermented during its passage through the large intestine by the action of the intestinal tract microflora leading to the production of its fermentation products such as SCFA which do not raise concerns for genotoxicity (OECD Toolbox 4.0[22]). On this basis, the Panel concluded that there is no concern with respect to the genotoxicity for alginic acid and its salts (E 400–E 404).

The chronic exposure of mice to 25% sodium alginate (corresponding to 37,500 mg/kg bw per day) for 89 weeks resulted in nephrotoxic effects that were considered to be due to high sodium intake followed by extremely high water intake and not related to the alginate moiety. According to the results of long-term toxicity studies in mice and rats, the Panel considered that alginic acid and its salts were not of concern with respect of carcinogenicity.

In a two-generation study, male and female Sprague–Dawley rats were fed diets containing 0% or 5% sodium alginate (equivalent to 0 and 2,500 mg/kg bw per day) for a period of 2 years. The Panel noted that the data presented in this study were insufficient for hazard characterisation. However, the Panel noted that in the 90-day study in rats (TNO, 1967; Documentation provided to EFSA n.8), no effects were observed on testes and ovary weights and also no histopathological changes were observed in testes, ovaries and uteri. In the chronic study in mice (Til et al., 1986), no effect was observed on testes weights and no histopathological changes were observed on testes, epididymides, prostate, seminal vesicles, ovaries and uteri.

No prenatal developmental toxicity studies were available.

From the publications available, the Panel considered that there was no indication for immunotoxicity or for an allergenic potential of alginic acid and its salts used as food additives.

In humans, the oral intake of 175 mg sodium alginate/kg bw per day for 7 days, followed by 200 mg/kg bw per day for further 16 days was well tolerated in five healthy male adults under conditions in which the sodium alginate has been fully hydrated for 24 h. All biochemical and haematological parameters remained unchanged, whilst no allergic responses were observed in any of the volunteers. In several larger placebo-controlled clinical trials in adults that investigated the safety of the medicinal use of sodium alginate in GERD, daily dosages up to 56 mg/kg bw in combination with carbonates have been well tolerated. Furthermore, oral treatment of 14 patients on dialysis with approximately 120 mg calcium alginate/kg bw per day over a period of 1 year was well tolerated without adverse reactions.

The Panel also noted that for the medicinal use of a combination of sodium alginate and magnesium alginate in infants and young children with a maximum daily dosage ranging from 417 to 834 mg/kg bw calculated as sodium alginate, constipation, diarrhoea, intestinal obstruction, flatulence, abdominal distension and bezoar are indicated as adverse effects. However, in a multicentre study in infants, no significant differences in the incidences of gastrointestinal adverse events between the groups treated with the combination of sodium alginate and magnesium alginate or with placebo were observed.

Furthermore, the Panel noted that no specific clinical data addressing the safety of use of alginic acid and its salts (E 400–E 404) in 'dietary foods for infants for special medical purposes and special formulae for infants' (food category 13.1.5.1) and in 'dietary foods for baby and young children for special medical purposes as defined in Directive 1999/21/EC' (food category 13.1.5.2) considering that the defined maximum use levels were available to the Panel.

To assess the dietary exposure from alginic acid and its salts (E 400–E 404) from their use as a food additive, the combined exposure was calculated based on: (1) MPLs or maximum levels of data provided to EFSA for categories in which alginic acid and its salts are authorised as QS (defined as the *maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario brand-loyal* and *non-brand-loyal consumer scenario*).

Alginic acid and its salts (E 400–E 404) are authorised in a wide range of foods. The Panel did not identify brand loyalty to a specific food category and therefore the Panel considered that the non-brand-loyal scenario covering the general population was the more appropriate and realistic scenario for risk characterisation because it is assumed that the population would probably be exposed in the long term to the food additive present at the mean reported use in processed food.

A specific estimated exposure assessment scenario taking into account the food for special medical purpose for infants and young children (FC 13.1.5.1 Dietary foods for infants for special medical purposes and special formulae for infants and FC 13.1.5.2 Dietary foods for babies and young children for special medical purposes as defined by Commission Directive 1999/22/EC) was also performed to estimate exposure for infants and toddlers and children who may be on a specific diet. Considering that this diet is required due to specific needs, it is assumed that consumers are loyal to the food brand; therefore the refined brand-loyal estimated exposure scenario was performed using the maximum permitted level for the FSMPs. The Panel noted that no data on use levels were submitted by industry for the food categories 13.1.5.1 and 13.1.5.2, which is in agreement with the absence of data in the Mintel database.

No exposure assessment was carried out for food supplements, as alginic acid and its salts are authorised in QS in this food category and no usage level data were available for the assessment.

The refined estimates are based on 23 out of 75 food categories in which alginic acid and its salts (E 400–E 404) are authorised. The Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to alginic acid and its salts (E 400–E 404) as a food additive in European countries for the refined scenario if it is considered that the food additive may not be used in food categories for which no usage data have been provided. However, the Panel noted that, given the information from the Mintel's GNPD, it may be assumed that alginic acid and its salts (E 400–E 404) are used in food categories for which no data have been provided by the food industry.

The main food categories, in term of amount consumed, not taken into account were bread and rolls, pasta, salads and savoury-based sandwiches, breakfast cereals, snacks, other confectionery including breath-freshening microsweets and some alcoholic beverages. According to the Mintel GNPD (Appendix B), in the EU market, some products in these categories are labelled with alginic acid and its salts (E 400–E 404). Also, limited use of alginic acid and its salts (n = 34) in category food supplements is found in the Mintel GNPD database. Therefore, the Panel considered that, if these uncertainties were confirmed, it would therefore result in an underestimation of the exposure.

The Panel further noted that the exposure to alginic acid and its salts (E 400–E 404) from their use according the Annex III (Parts 1, 3 and 5) was not considered in the exposure assessment.

The Panel also noted that the refined exposure estimates are based on information provided on the reported level of use of alginates (E 400–E 404). If actual practice changes, this refined estimates may no longer be representative and should be updated.

5. Conclusions

5.1. General population

Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA, 2014), and given that:

- from all the data received, data were adequate for a refined exposure assessment for 23 out of 75 food categories;
- based on the reported use levels, a refined exposure (non-brand-loyal scenario) of up to 208 mg/kg bw per day in infants (from 12 weeks up to and including 11 months of age) was estimated;
- alginic acid and its salts were practically undigested, not absorbed intact, but partially fermented by intestinal microbiota in humans;
- adequate toxicity data were available;
- no adverse effects were reported in subchronic studies in rodents at the highest dose tested, of 13,500 mg sodium alginate/kg bw per day in rats;
- there was no concern with respect to the genotoxicity of alginic acid and its salts;
- no carcinogenic effects were reported at the highest dose tested of 37,500 mg sodium alginate/kg bw per day in mice;
- oral intake of 175 mg sodium alginate/kg bw per day for 7 days, followed by 200 mg/kg bw per day for further 16 days was well tolerated in healthy human adults;
- oral treatment of 14 patients on dialysis with approximately 120 mg calcium alginate/kg bw per day over a period of one year was well tolerated without side-effects;
- for higher therapeutic daily doses corresponding to 417–834 mg sodium alginate/kg bw in the treatment of infants and young children for gastric reflux, reported side-effects were gastrointestinal disorders including rare formation of intragastric 'mass';

- available data support read-across in safety parameters among alginic acid and its salts (E 400–E 404);

the Panel concluded that there was no need for a numerical ADI for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404), and that there was no safety concern at the level of the refined exposure assessment for the reported uses of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) as food additives. The Panel further concluded that exposure of infants and young children to alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) by the use of these food additives should stay below therapeutic dosages for these population groups at which side-effects could occur.

5.2. Infants and young children consuming foods for special medical purposes and special formulae

Concerning the use of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in 'dietary foods for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and 'in dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2), and given that:

- for populations consuming dietary foods for special medical purposes and special formulae, the highest refined exposure estimate (p95) calculated based on MPL were for toddlers (12–35 months) up to 290.4 mg/kg bw per day (brand-loyal scenario);
- infants and young children consuming foods belonging to these food categories may show a higher susceptibility to the gastrointestinal effects of alginic acid and its salts than their healthy counterparts due to their underlying medical condition;
- no adequate specific studies addressing the safety of use of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in this population under certain medical conditions were available;
- no data on use levels were submitted by industry for the food categories 13.1.5.1 and 13.1.5.2, which is in agreement with the absence of data in the Mintel database;

the Panel concluded that the available data did not allow an adequate assessment of the safety of alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in infants and young children consuming the food belonging to the categories 13.1.5.1 and 13.1.5.2.

6. Recommendations

The Panel recommended that the European Commission considers:

- revising the current limits for toxic elements (arsenic, cadmium, lead and mercury) in the EU specifications for alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) in order to ensure that alginic acid and its salts (E 400, E 401, E 402, E 403 and E 404) as food additives will not be a significant source of exposure to those toxic elements in food, in particular for infants and children;
- defining a suitable validated analytical method of appropriate accuracy for the determination of formaldehyde in the specifications for alginic acid and its salts (E 400–E 404).

Documentation provided to EFSA

1) Pre-evaluation documents on alginic acid and its salts E 400 E 404). Frauenhofer (ITEM). October 2012.
2) Marinalg International, 2010. Reply to EFSA: Call for data on emulsifiers, stabilisers and gelling agents. Information on alginic acid and its salts (E 400–E 404) on present usage, ADME (Metabolism and Toxicokinetics), subchronic toxicity, reproduction and developmental toxicity and other study. Submitted on 18 November 2010.
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8) TNO (Netherlands Organisation for Applied Scientific Research), 1967. Sub-chronic toxicity test with a modified potato starch (propylene oxide) and an alginate in albino rats. Unpublished Report R2456. Submitted by Intertek (formerly known as Cantox) on 14 September 2011.
9) EMA (European Medicines Agency), 2016. Communication to EFSA request for information on a certain group of substances used as food additives. Submitted on 4 January 2016.
10) Marinalg International, 2015. Reply to EFSA: Call for technical data on certain thickening agents permitted as food additives in the EU. Information on technical data including specifications on alginic acid and its salts (E 400–E 404). Submitted on 22 December 2015.
11) Marinalg International, 2016. Reply to EFSA letter of 8 February 2016: request of information on the methods used to analyse and measure formaldehyde. Technical report of the development of the Farrell method (2007). Submitted on 4 March 2016.
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13) FDE (Food Drink Europe), 2016. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 31 May 2016.
14) European Dairy Association (EDA), 2016. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 30 May 2016.
15) Marinalg International, 2016. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 31 May 2016.
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17) ASEMESA (Asociacion Espanola de Exportadores e Industriales de Aceitunas de Mesa), 2015. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 25 November 2015.
18) ICGA (International Chewing Gum Association), 2016. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 31 May 2016.
19) Aviko, 2016. Data on usage levels of alginic acid and its salts (E 400–E 404) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2015). Submitted to EFSA on 10 May 2016.
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Abbreviations

ADI	Acceptable Daily Intake
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
ALT	alanine transaminase
ANS	Panel on Food Additives and Nutrient Sources added to Food
AOAC	Association of Analytical Communities
ASEMESA	Asociacion Espanola de Exportadores e Industriales de Aceitunas de Mesa
AST	aspartate transaminase
CAS	Chemical Abstracts Service
CFU	colony forming unit
CHL	Chinese hamster lung
EC	Evaluated under Commission
EDA	European Dairy Association
EINECS	European Inventory of Existing Commercial Chemical Substances
EMA	European Medicines Agency
FAO/WHO	Food and Agriculture Organization/World Health Organisation
FC	Food for weight control
FCS	Food Classification System
FDA	Food and Drug Administration
FDE	Food Drink Europe
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FSMP	Foods for special medical purposes
GERD	gastroesophageal reflux disease
GNPD	Global New Products Database
HPLC	high-performance liquid chromatography
ICGA	International Chewing Gum Association
IL	interleukin
INS	International Numbering System for Food Additives
IOM	Institute of Medicine
i.p.	intraperitoneal
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD50	lethal dose, 50%, i.e. dose that causes death among 50% of treated animals
LOD	limit of detection
LOQ	limit of quantification
MoE	margins of exposure
MPL	maximum permissible level
NDA	Panel on Dietetic Products, Nutrition and Allergies
NOAEL	no-observed-adverse effect
OECD	Organisation for Economic Co-operation and Development
OTC	over-the-counter
PGX	alginate–konjac–xanthan polysaccharide complex
QS	*quantum satis*
SCE	sister chromatid exchange
SCF	Scientific Committee for Food
SCFA	short-chain fatty acids
SIDS	Screening Information Dataset
SmPC	Summary of product characteristics
SNE	Specialised Nutrition Europe
TNF	tumour necrosis factor
TNO	Netherlands Organisation for Applied Scientific Research
WHO	World Health Organisation

Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of alginic acid and its salts (E 400–404) provided by industry

Appendix B – Number and percentage of the food products labelled with alginic acid and its salts (E 400–404) between 2011 and September 2016, out of the total number of food products per food subcategories according to the Mintel GNPD food classification.

Appendix C – Concentration levels of alginic acid and its salts (E 400–404) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix D – Summary of total estimated exposure of alginic acid and its salts (E 400–404) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix E – Main food categories contributing to exposure to alginic acid and its salts (E 400–404) using the maximum level exposure scenario and the refined exposure scenario (> 5% to the total mean exposure)

Appendix A–E can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2017.5049