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SCIENTIFIC OPINION

Re-evaluation of guar gum (E 412) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as food additive for uses in foods for all population groups

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Abstract

Guar gum (E 412) was re-evaluated in 2017 by the former EFSA Panel on Food Additives and Nutrient sources added to Food (ANS). As a follow-up to this assessment, the Panel on Food Additives and Flavourings (FAF) was requested to assess the safety of guar gum (E 412) for its uses as food additive in food for infants below 16 weeks of age belonging to food categories 13.1.1 (Infant formulae) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). In addition, the FAF Panel was requested to address the issues already identified during the re-evaluation of the food additive when used in food for the general population. The process involved the publication of a call for data to allow the interested business operators to provide the requested information to complete the risk assessment. In the response to EFSA requests, one IBO stated that E 412 is not used in food categories 13.1.1 and 13.1.5.1, but it is present in products under food category 13.1.5.2. The Panel concluded that the submitted data are not sufficient to support the safe use of guar gum (E 412) in food for infants (below and above 16 weeks of age) and young children under FC 13.1.1, 13.1.5.1 and 13.1.5.2. Additionally, the Panel concluded that the technical data provided by the IBO support further amendments of the specifications for E 412 laid down in Commission Regulation (EU) No 231/2012.

KEYWORDS

E 412, food additive, guar gum, infants

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SUMMARY

In accordance with Regulation (EU) No 257/2010, the European Food Safety Authority (EFSA) is currently re-evaluating the safety of food additives already permitted in the Union before 20 January 2009 and issuing scientific opinions on their safety when used in food as per Annexes II and III to Regulation (EC) No 1333/2008. The risk assessment approach followed in the EFSA ANS Panel 2017 re-evaluation has not covered the use of food additives in food for infants below 12 weeks of age. Additionally, while re-evaluating the safety of food additives referred to above, EFSA identified some concerns, namely (1) data gaps that have triggered recommendations in the published scientific opinions; and/or (2) data gaps that have increased uncertainties linked to the risk assessment and/or which prevented the Panel from concluding on some aspects of it.

On 31 May 2017, EFSA published a guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age, thus enabling EFSA to assess the safety of food additive used in food for infants below this age. The age up to 16 weeks was selected in the guidance because infants are exposed to formula feeding until this age as the only source of food since complementary feeding is not supposed to be introduced before.

As follow-up of the above, this Opinion addresses the data gaps previously identified during the re-evaluation of guar gum (E 412) as food additive and the safety in the special subpopulation of infants below 16 weeks of age.

The process followed involved the publication of a dedicated call for data allowing all interested parties to provide the requested information for completing the assessment and to confirm that the additive is used in food categories 13.1.1 (Infant formulae) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). The data submitted in response to the call for data on guar gum (E 412) comprised technical information and a repeated dose toxicity study in neonatal piglets.

Guar gum (E 412) is the endosperm of the seeds of strains of the guar plant, *Cyamopsis tetragonolobus* (L.) Taub. (Family *Leguminosae*). It consists mainly of a high molecular weight hydrocolloidal polysaccharide composed of galactopyranose and mannopyranose units combined through glycosidic linkages, which may be described chemically as galactomannan. The gum may be partially hydrolysed by either heat treatment, mild acid or alcaline oxidative treatment for viscosity adjustment. Specifications for guar gum (E 412) have been defined in Commission Regulation (EU) No 231/2012.

In the response to EFSA requests, one IBO stated that E 412 is not used in food categories 13.1.1 and 13.1.5.1, but it is present in products under food category 13.1.5.2. Specifically, the IBO clarified that E 412 is used in FC 13.1.5.2 products for toddlers aged 1–3 years, excluding infants under 16 weeks. It is employed in liquid products containing amino acids designed for children diagnosed with specific medical conditions.

In the 2017 opinion, the ANS Panel recommended to consider separate specifications in the EU regulation for guar gum and clarified guar gum differing significantly in the protein content. For the present opinion, the Panel further reviewed the ANS Panel recommendation and considering toxicity data already assessed at the time of the re-evaluation and the information provided for current assessment did not find the need to separate specifications concerning the protein content in E 412. Therefore, the Panel considered single specifications for E 412 as appropriate.

In response to the call for data, analytical data for levels of toxic elements (Pb, Hg, Cd and As) in commercial samples of guar gum (E 412) were provided by one interested business operator. The IBO proposed lowest technologically achievable levels for Pb, Hg, Cd and As identical with the current limits in the EU specifications of E 412.

The Panel performed the risk assessment that would result if these toxic elements were present in E 412, at (i) the current maximum limit for toxic elements in the EU specifications that are identical to the proposed lowest technologically achievable levels by the IBO and (ii) at the highest measured value for Pb or, in the absence of any measured value(s) at the lowest reported limit of quantification (LOQ) for Hg, Cd and As modulated by the Panel by applying a factor of 10, to allow for a need for flexibility with respect to representativeness, homogeneity and differing analytical methods.

Considering that E 412 is permitted in FC 13.1.1 and 13.1.5.1 for infants < 16 weeks and in FC 13.1.5.2 for those above 12 weeks, the Panel calculated potential exposure to toxic elements from dietary exposure to E 412. Additionally, the Panel considered dietary exposure to E 412 for toddlers (consumers of FSMP (FC 13.1.5.2)) at the highest mean and 95th percentile exposure estimates calculated in this opinion, which were 498 and 548 mg/kg body weight (bw) per day, respectively.

For the general population, the Panel referred to exposure calculations for E 412 from the re-evaluation of the food additive. In the current risk assessment, the highest exposure levels in the brand-loyal refined scenario for the mean and 95th percentile among different population groups were considered: 449 mg/kg bw per day for toddlers and 865 mg/kg bw per day for children, respectively.

The Panel concluded that the potential exposure to toxic elements resulting from the exposure to E 412 could be substantial, this is particularly pronounced in the calculations conducted for infants under 16 weeks of age and those aged between 12 weeks and 11 months. For Pb, the MOE is insufficient in all cases, except for the general population and toddlers, consumers of FSMP only, where the MOE is deemed sufficient when considering values modulated by the Panel.

The Panel also calculated the impact of the potential level of the toxic elements Pb, Cd and As in the food additive (i.e. up to the specifications limit values) on the final product and compared that with the legal limits for these elements in the final formula for infants below 16 weeks of age set by Regulation (EC) 2023/915. Considering the results of these calculations and the fact that the food additive is not the only potential source of toxic elements in the infant formula, the Panel emphasises the need to reduce the specification limits for Pb, Cd and As in Regulation (EU) no 231/2012.

The Panel noted that the maximum limits in the EU specifications for toxic elements should be established based on actual levels in the commercial food additive. Therefore, the Panel recommended that the maximum limits be lowered on the basis of the information provided by the IBO and on the considerations of the Panel.

On the question of residual proteins, data were provided using the Kjeldahl method and other not described methods for total nitrogen and all gum samples were within the EU specification of 10% (N content × 6.25). The Panel is of the view that, for harmonisation, the Kjeldahl method should be indicated to be used for the determination of the residual protein content in E 412.

Regarding the question on specifications for guar gum use in special formulae intended for infants below 16 weeks of age under special medical conditions, the IBO explained that E 412 is not used in the food categories FC 13.1.1 and FC 13.1.5.1, and in FC 13.1.5.2 is used only for children from 1 year of age onwards, and no information was provided. The IBO further stated that there are no special requirements on purity criteria for guar gum E 412 intended for infant formulae/food.

One IBO provided data showing the absence of *Salmonella* spp. and *Escherichia coli* in analysed samples of E 412 and on the levels of TAMC (including TBC) and TYMC determined for analysed samples. The Panel noted that guar gum (E 412) may be prone to microbiological contamination, and therefore, microbiological specifications should be set for E 412 and should also include *Cronobacter (Enterobacter) sakazakii*; however, no data were provided.

Taking all these aspects into consideration, the Panel has made proposals for an update of the EU specifications for guar (E 412).

The toxicological studies evaluated in the opinion on the re-evaluation, in which NOAELs of up to 18,000 mg/kg bw per day were identified, are not fully appropriate for the assessment of the safety of guar gum when used in food for infants below and above 16 weeks of age and young children consumers of food under FCs 13.1.1, 13.1.5.1 and 13.1.5.2. Therefore, the conclusion of the ANS Panel on the safety of E 412 used as food additive is not applicable for this population.

The IBOs did not provide clinical data, post-marketing surveillance reports on undesired and adverse reactions and published and unpublished case reports. A repeated dose study of guar gum in neonatal piglets with 2-week recovery period was provided. The design of this study followed the EMA and ICH guidelines and the relevant EFSA guidance. The study was performed according to good laboratory practice (GLP). The study was assessed by means of a risk of bias (RoB) scoring scheme and was allocated to tier 3 (high risk of bias) because of several flaws. In this study, a statistically significant reduction of body weights in the high-dose group in males was noted by the Panel. In the ANS Panel opinion on the re-evaluation of guar gum, effects on the body weight at high doses in rats, mice and rabbits were attributed to the bulk properties of guar gum when in contact with water or intestinal juices and have not been considered as adverse effects. In the context of the assessment of the piglet study, the observed statistically significant body weight reduction in male piglets (highest dose, nominally 4500 mg/kg bw per day) was considered adverse by the Panel taking into account that the piglet is a model for developing infants and weight reduction would indicate adverse effects in this population. Whereas there are indications of adverse effects in male piglets, because of the high risk of bias of this study, the available data are not adequate to support the derivation of a reference point. The high risk of bias of the piglet study precludes its use to assess the safety of guar gum (E 412) in food for infants below and above 16 weeks of age and young children (FC 13.1.1, 13.1.5.1 and 13.1.5.2). As reported above, industry declared that guar gum is used only in FC 13.1.5.2 in food for toddlers for which also no adequate toxicological/clinical data were submitted to support its use.

Overall, the Panel concluded that the submitted data are not sufficient to demonstrate that the use of guar gum (E 412) in food for infants (below and above 16 weeks of age) and young children consumers of food under FC 13.1.1, 13.1.5.1 and 13.1.5.2 is safe.

1 | INTRODUCTION

The present opinion deals with:

- The risk assessment of guar gum (E 412) in food for infants below 16 weeks of age in the food categories (FC) 13.1.1 (Infant formulae as defined in Commission Delegated Regulation (EU) 2016/127) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants).
- The follow-up on issues that have been expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of guar gum (E 412) as a food additive (EFSA ANS Panel, 2017) including the safety assessment for the use of guar gum in food category 13.1.5.2 (Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC).

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

1.1.1 | Background

The composition of food intended for infants and young children, as defined by Regulation (EU) No 609/2013,[1] is regulated at EU level and such rules include requirements concerning the use of substances as food additives.

The use of food additives is regulated by Regulation (EC) No 1333/2008 on food additives. Only food additives that are included in the Union list, in particular in Annex II and III to that Regulation, may be placed on the market and used in food under the conditions of use specified therein.

In accordance with Regulation (EU) No 257/2010,[2] EFSA is currently re-evaluating the safety of food additives already permitted in the Union before 20 January 2009 and issuing scientific opinions on their safety when used in food as per Annexes II and III to Regulation (EC) No 1333/2008. However, the risk assessment approach followed until now has not covered the use of food additives in food for infants below 12 weeks of age. Consequently, EFSA published several scientific opinions on the re-evaluation of the safety of food additives permitted in food category 13.1 but not addressing their use in food for infants below 12 weeks of age.

In addition, in these opinions EFSA identified some concerns, namely (1) Data gaps that have triggered recommendations in the (to be) published scientific opinions, and/or; (2) Data gaps that have increased uncertainties linked to the risk assessment and/or which prevented the EFSA from concluding on some aspects of it.

On 31 May 2017, EFSA published a guidance document (EFSA Scientific Committee, 2017) on the risk assessment of substances present in food intended for infants below 16 weeks of age, thus enabling EFSA to assess the safety of food additives used in food for infants below 12 weeks of age.[3] Now EFSA is expected to launch dedicated calls for data to be able to perform such risk assessments.

The EC considers it is more effective that EFSA, in the context of these dedicated calls for data, also addresses all the issues and data gaps already identified in the relevant (to be) published scientific opinions on the re-evaluation of the safety of food additives permitted in food category 13.1.

In accordance with the current EC approach for the follow-up of EFSA's scientific opinions on the re-evaluation of the safety of permitted food additives for which some concerns have been identified, a specific call for data would be published by the EC on DG SANTE's website[4] on food additives and additional (missing) information would then be provided by interested business operators to the EC.

However, for those scientific opinions on the re-evaluation of the safety of permitted food additives in food category 13.1 for which the risk assessment does not address their uses in food for infants below 12 weeks of age and for which some concerns have been identified by EFSA, the EC considers that for the sake of efficiency it would be appropriate to streamline the approach as described above.

Therefore, the EC requests EFSA to address all the issues and data gaps already identified in the relevant published scientific opinions of those food additives (or groups of additives that can be addressed simultaneously) as part of the upcoming work on the safety assessment of food additives uses in food for infants below 12 weeks of age.

This follow-up aims at completing the re-evaluation of the food additives in question for all food categories and includes calls for data covering the actual use and usage levels of food additives in food for both infants below 12 or 16 weeks of age as well as for older infants, young children and other groups of the population for which EFSA has already finalised its assessment.

[1]Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35–56.

[2]Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a program 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, p. 19–27.

[3]See Section 1.1.3.

[4]https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en

The future evaluations of EFSA should systematically address the safety of use of food additives for all age groups, including the infants below 12 or 16 weeks of age.

1.1.2 | Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[5] and as part of EFSA 's work in completing its risk assessments concerning the use of food additives in food for infants below 12 weeks of age,[5] covered by the re-evaluation programme and its terms of reference, the European Commission requests the European Food Safety Authority to address all the data gaps specified in the recommendations made in this scientific opinions on the re-evaluation of the safety of food additives permitted in food category 13.1 (food for infants and young children) of annex II to Regulation (EC) No 1333/2008.

1.1.3 | Interpretation of Terms of Reference

Before the publication of the EFSA Scientific Committee Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017), EFSA has taken 12 weeks as a cut off age for the applicability of the safety assessment. However, according to EFSA Scientific Committee (2017), the assessment will include infants up to 16 weeks of age because they are exposed to formula feeding until this age as the only source of food since complementary feeding is not supposed to be introduced before this age (see EFSA Scientific Committee, 2017).

The Panel noted that according to the information provided by one IBO, guar gum (E 412) is not used in food categories (FC) 13.1.1 and 13.1.5.1 but *'there are products in category 13.1.5.2 with guar gum usage*' (Documentation provided to EFSA n. 3, 4). Upon request, the same IBO confirmed that E 412 is used in the food category 13.1.5.2 in products for toddlers (1 to 3 years of age) diagnosed with inborn errors of metabolism (Documentation provided to EFSA n. 4). Despite the information that guar gum is not used in FC 13.1.1 and FC 13.1.5.1 the Panel performed risk assessments for infants below 16 weeks of age and for infants between 12 weeks and toddlers based on the regulatory maximum permitted levels (MPLs) according to Regulation (EC) No 1333/2008 for FC 13.1.1, 13.1.5.1 and 13.1.5.2.

1.2 | Previous evaluations of guar gum (E 412)

Guar gum was evaluated by JECFA in 1970, 1974 and 1975 (JECFA, 1970, 1974, 1975a, 1975b). Based on the lack of adverse effects in the toxicity studies available at the time, an ADI 'not specified' was allocated.

Guar gum has been also evaluated by the Scientific Committee for Food (SCF) in 1977 (SCF, 1978) who endorsed the ADI 'not specified' allocated by JECFA. No detailed information was given on the basis for the evaluation.

In 1998, the SCF accepted the use of guar gum in foods for special medical purposes (FSMP) for infants and young children at levels up to 10 g/L in ready-to-use liquid formulae containing extensively hydrolysed protein and in ready-to-use liquid formulae containing partially hydrolysed proteins for infants in good health at levels up to 1 g/L. In 2001, the SCF accepted the use of guar gum in all weaning foods at levels up to 10 g/kg and in gluten-free cereal-based foods up to 20 g/kg, singly or in combination with other emulsifiers (SCF, 1991).

In 2003, the SCF re-evaluated guar gum in the revision of the essential requirements of infant formulae and follow-on formulae intended for the feeding of infants and young children (SCF, 2003):

- The Committee recommended guar gum should not be used in infant formulae.
- Considering that guar gum has been used for quite some time in follow-on formulae without the appearance of reports on adverse events, the Committee finds it acceptable to maintain the current maximum level of the use of guar gums in follow-on formulae of 1 g/L.
- The Committee further recommended maintaining the concept that if more than one of the three substances, locust bean gum, guar gum or carrageenan, are added to a follow-on formula, the maximum level established for each of those substances is lowered with that relative part as is present of the other substances together.

Guar gum is one of the food additives that composed jelly mini-cups which were suspended in 2004 by the European Commission to be placed on the market and import (Commission Decision 2004/37/EC[6]), following the measures taken and information provided by different Member States. Jelly mini-cups are defined as 'jelly confectionery of a firm consistence,

[5]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[6]European Commission. (2004). Commission Decision of 13 April 2004 suspending the placing on the market and import of jelly mini-cups containing the food additives E 400, E 401, E 402, E 403, E 404, E 405, E 406, E 407, E 407s, E 410, E 412, E 413, E 414, E 415, E 417 and/or E 418 (2004/37/EC). Official Journal of the European Union, L118/70, 23.4.2004.

contained in semi rigid mini-cups or mini-capsules, intended to be ingested in a single bite by exerting pressure on the mini-cups or mini-capsule to project the confectionery into the mouth'. In 2004, the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) 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 guar gum (E 412) in jelly mini-cups (EFSA, 2004a). 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 mini-cups, would give rise to a risk for choking (EFSA, 2004a). The use of these additives in jelly mini-cups is not authorised in the EU.[7]

In 2007, the EFSA AFC Panel issued an opinion on the use of partially depolymerised guar gum as a food additive (EFSA, 2007a). The safety of depolymerised guar gum was assessed from a 90-day study in rats fed with a depolymerised guar gum prepared by alcaline oxidation which showed no adverse effect up to dose levels of 50 g/kg diet, estimated to be equal to 2500 mg/kg body weight (bw) per day. Furthermore, based on the documented safety of native guar gum and considering that depolymerised guar gum appears to fall within the specifications of native guar gum, the Panel concluded that there is no safety concern for the partially depolymerised guar gum prepared by either heat treatment, acid hydrolysis or alcaline oxidation at the estimated levels of intake (between 41 and 57 mg/kg bw per day based on a worst case scenario). Finally, the Panel considered that the specifications for guar gum may need to be modified to take account of the increased level of salts and the possible undesirable by-products, e.g. furfural and peroxides, that may result from the described processes to produce partially depolymerised guar gum.

In 2010, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) prepared a scientific opinion on the substantiation of health claims related to guar gum (EFSA NDA Panel, 2010). No cause-and-effect relationship could be established between the consumption of guar gum and maintenance of normal blood glucose concentrations, increase in satiety and maintenance of normal blood cholesterol concentrations.

In 2011, the EFSA NDA Panel prepared a scientific opinion on the substantiation of health claims related to partially hydrolysed guar gum (EFSA NDA Panel, 2011). No cause-and-effect relationship could be established with decreasing potentially pathogenic gastrointestinal microorganisms, changes in short-chain fatty acid (SCFA) production and/or pH in the gastrointestinal tract, changes in bowel function and reduction in gastrointestinal discomfort.

Under the frame of Regulation (EC) No 257/2010, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) has re-evaluated the safety of guar gum (E 412) when used as a food additive (EFSA ANS Panel, 2017). Following the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSAANS Panel, 2014), the Panel concluded that there is no need for a numerical ADI for guar gum (E 412), and that there is no safety concern for the general population at the refined exposure assessment for the reported uses of guar gum (E 412) as a food additive.

The Panel considered that for uses of guar gum in foods intended for infants and young children the occurrence of abdominal discomfort should be monitored and if this effect is observed doses should be identified as a basis for further risk assessment.

Concerning the use of guar gum (E 412) 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 ANS Panel concluded that the available data do not allow an adequate assessment of the safety of guar gum (E 412) in infants and young children consuming these FSMP.

In 2017, the EFSA ANS Panel prepared a scientific opinion on the re-evaluation of guar gum as food additive (E 412) (EFSA ANS Panel, 2017).[8]

The following recommendations were made:

- The Panel recommended that the maximum limits for the impurities of toxic elements (lead, mercury and arsenic) in the European Commission specification for guar gum (E 412) should be revised in order to ensure that guar gum (E 412) as a food additive will not be a significant source of exposure to those toxic elements in food in particular for infants and children. The Panel noted that currently detected levels of these toxic elements were orders of magnitude below those defined in the EU specifications, and therefore, the current limits could be lowered.
- The Panel recommended to harmonise the microbiological specifications in the EU Regulation for polysaccharidic thickening agents, such as gums, and to include criteria for the absence of *Salmonella* spp. and *E. coli*, for TAMC and for TYMC into the EU specifications of guar gum (E 412).
- The Panel recommended to give separate specifications in the EU regulation for guar gum and clarified guar gum differing significantly in the protein content.
- The Panel considered that no threshold dose can be established for allergic reactions. Therefore, it is advisable that exposure to eliciting allergens, such as proteinaceous compounds, is avoided as much as possible, and therefore, the Panel recommended that their content should be reduced as much as possible, which can be achieved for example by clarification of guar gum.

[7]Annex II to Regulation (EC) No 1333/2008.

[8]https://www.efsa.europa.eu/en/efsajournal/pub/4669

- The Panel recommended that additional data should be generated to assess the potential health effects of guar gum (E 412) when used in 'dietary foods for infants for special medical purposes' (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).

2 | DATA AND METHODOLOGIES

2.1 | Data

For the current opinion, the Panel based its assessment on the:

- Information submitted by interested business operators (IBOs) in response to the EFSA public call for data[9] and the subsequent requests for clarifications and/or additional information, and the conclusions and recommendations from previous evaluations;
- Information from Mintel's Global New Products Database (GNPD) to identify the use of the food additive guar gum (E 412) in food 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 guidance documents from the EFSA Scientific Committee and in particular the EFSA Guidance of the Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017).

In order to conclude on the safety of guar gum (E 412) for all population groups and to address the data gaps identified during the re-evaluation in 2017, the FAF Panel assessed the information provided:

- For the risk assessment of guar gum (E 412) in food for infants below 16 weeks of age in the food categories (FC) 13.1.1 (Infant formulae as defined Directive 2006/141/EC) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants).
- For the follow-up on issues that have been expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of guar gum (E 412) as a food additive (EFSA ANS Panel, 2017) including the safety assessment for the use of guar gum in food category 13.1.5.2.

Dietary exposure to guar gum (E 412) from its use as a food additive in foods for infants below 16 weeks of age was estimated combining the mean and high-level consumption values for infant formulae reported for the period of 14–27 days of life which correspond, respectively, to 200 and 260 mL/kg bw per day (EFSA Scientific Committee, 2017, see section 3.3.3.1), with the maximum permitted levels according to Annex II. Different scenarios were used to calculate dietary exposure (see Section 3.5). Uncertainties on the exposure assessment were identified and discussed.

An exposure assessment considering FC 13.1.5.2 was performed to estimate the exposure of infants above 12 weeks and toddlers who may eat and drink foods for special medical purposes (FSMP). The consumption of these foods is not reported in the EFSA Comprehensive database. To consider potential exposure to guar gum (E 412) via these foods, the Panel assumes that the amount of FSMP consumed by infants and toddlers resembles that of comparable foods in infants and toddlers from the general population. Thus, the consumption of FSMP categorised as FC 13.1.5 was assumed equal to that of formulae and food products categorised as FCs 13.1.1, 13.1.2, 13.1.3 and 13.1.4.

3 | ASSESSMENT

3.1 | Identity and specifications of E 412

According to Commission Regulation (EU) No 231/2012,[10] sthe food additive E 412 is named as guar gum.

The specifications for guar gum (E 412) as defined in the Commission Regulation (EU) No 231/2012 and as proposed by JECFA (2008) are listed in Table 1.

In the JECFA specifications a distinction is made between guar gum and clarified guar gum (Table 1) whereas no such distinction is made in the definition of guar gum (E 412) in the EU specifications.

[9]Call for technical and toxicological data on guar gum (E 412) for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-guar-gum-e-412-uses-foods

[10]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 Text with EEA relevance. OJ L 83, 22.3.2012, p. 1–295.

TABLE 1 Specifications for guar gum (E 412) according to Commission Regulation (EU) No 231/2012 and proposed by JECFA (2008).

	Commission Regulation (EU) No 231/2012	JECFA (2008) guar gum	JECFA (2008) (clarified guar gum)
Definition	Guar gum is the ground endosperm of the seeds of strains of the guar plant, *Cyamopsis tetragonolobus* (L.) Taub. (family *Leguminosae*). Consists mainly of a high molecular weight hydrocolloidal polysaccharide composed of galactopyranose and mannopyranose units combined through glycosidic linkages, which may be described chemically as galactomannan. The gum may be partially hydrolysed by either heat treatment, mild acid or alcaline oxidative treatment for viscosity adjustment	Primarily the ground endosperm of the seeds from *Cyamopsis tetragonolobus* (L.) Taub. (Fam. *Leguminosae*) mainly consisting of high molecular weight (50,000–8000,000) polysaccharides composed of galactomannans; the mannose: galactose ratio is about 2:1. The seeds are crushed to eliminate the germ, the endosperm is dehusked, milled and screened to obtain the ground endosperm (native guar gum). The gum may be washed with ethanol or isopropanol to control the microbiological load (washed guar gum)	Primarily the ground endosperm of the seeds from *Cyamopsis tetragonolobus* (L.) Taub. (Fam. *Leguminosae*) mainly consisting of high molecular weight (50,000–8000,000) polysaccharides composed of galactomannans; the mannose: galactose ratio is about 2:1. The seeds are crushed to eliminate the germ, the endosperm is dehusked, milled and screened to obtain the ground endosperm (native guar gum). The gum is clarified by dissolution in water, filtration and precipitation with ethanol or isopropanol. Clarified guar gum does not contain cell wall materials. Clarified guar gum in the market is normally standardised with sugars
Einecs	232-536-0	–	–
CAS number	–	9000-30-0	9000-30-0
Molecular weight	50,000–8,000,000	–	–
Assay	Galactomannan content not less than 75%	–	–
Description	A white to yellowish-white, nearly odourless powder	White to yellowish-white, nearly odourless, free-flowing powder	White to yellowish-white, nearly odourless, free-flowing powder
Functional uses	–	Thickener, stabilizer, emulsifier	Thickener, stabilizer, emulsifier
Identification			
Test for galactose	Passes test	–	–
Test for mannose	Passes test	–	–
Solubility (Vol. 4)	Soluble in cold water	Insoluble in ethanol	Insoluble in ethanol
Gel formation	–	Method described in JECFA (2008)	Method described in JECFA (2008)
Viscosity	–	Method described in JECFA (2008)	Method described in JECFA (2008)
Gum constituents	–	Method described in JECFA (2008)	Method described in JECFA (2008)
Microscopic examination	–	Method described in JECFA (2008)	–
Purity			
Loss on drying (Vol. 4)	Not more than 15% (105°C, 5 h)	Not more than 15.0% (105°, 5 h)	Not more than 15.0% (105°, 5 h)
Borate	–	Method described in JECFA (2008)	Method described in JECFA (2008)
Total ash	Not more than 5.5% determined at 800°C	Not more than 1.5% (800°, 3–4 h)	Not more than 1.0% (800°, 3–4 h)
Acid-insoluble matter	Not more than 7%	Not more than 7.0%	Not more than 1.2%
Residual solvents	–	Not more than 1% of ethanol or isopropanol, singly or in Combination	Not more than 1% of ethanol or isopropanol, singly or in Combination
Protein	Not more than 10% (factor N×6.25)	Not more than 10.0%[a]	Not more than 1.0%[a]
Starch	Not detectable by the following method: to a 1 in 10 solution of the sample add a few drops of iodine solution. (No blue colour is produced)	–	–
Organic peroxides	Not more than 0.7 mg active oxygen/kg sample	–	–
Furfural	Not more than 1 mg/kg	–	–
Pentachlorophenol	Not more than 0.01 mg/kg	–	–

TABLE 1 (Continued)

	Commission Regulation (EU) No 231/2012	JECFA (2008) guar gum	JECFA (2008) (clarified guar gum)
Arsenic	Not more than 3 mg/kg	–	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg[a]	Not more than 2 mg/kg[a]
Mercury	Not more than 1 mg/kg	–	–
Cadmium	Not more than 1 mg/kg	–	–
Microbiological criteria			
Total (aerobic) plate count		Not more than 5000 CFU/g[a]	Not more than 5000 CFU/g[a]
Yeasts and moulds		Not more than 500 CFU/g[a]	Not more than 500 CFU/g[a]
E. coli:		Negative in 1 g[a]	Negative in 1 g[a]
Salmonella spp.		Negative in 25 g[a]	Negative in 25 g[a]

Abbreviations: CAS, Chemical Abstract Service; CFU, colony forming units; EINECS, European Inventory of Existing Commercial Chemical Substances.

[a]Further information on the test methods to be used is provided in the JECFA specifications directly and/or by reference to Volume 4 (under 'General Methods)' (JECFA, 2016). These method details are omitted here for reasons of brevity and clarity.

The Panel noted that in the JECFA specifications both for guar gum and clarified guar gum the Kjeldahl method is requested for the determination of the residual protein content in the food additive whereas, in the EU specification, no specific method for the determination of the protein levels is provided.

The Panel further noted that, contrary to JECFA, the EU specifications for E 412 do not include a test for the absence of borate nor maximum limits for residual solvents ethanol and isopropanol. Additionally, the EU specifications for E 412 do not include the CAS number.

3.2 | Technical data submitted

In order to support the revision of the existing specifications, the Panel has assessed the data provided by the IBOs in response to the EFSA call for data.[11]

One IBO, an association (Documentation provided to EFSA n. 1 and 2), submitted analytical data on the levels of toxic elements, residual protein and microbiological data in guar gum (E 412) (Documentation provided to EFSA n.1 and 2).

One IBO (SNE) provided data on use of E 412 in FC 13.1.1, 13.1.5.1 and 13.1.5.2 (Documentation provided to EFSA n.3 and 4).

The EFSA ANS Panel in 2017 recommended to explore the need to separate the current EU specifications of E 412 to guar gum and clarified guar gum. In the EFSA call for technical data, data for clarified and unclarified guar gum preparations used as E 412 were requested; however, no data for clarified guar gum were received. Furthermore, the IBO (AIPG) stated that '*to the best of their knowledge clarified guar gum is not a commercial product and none of the members of the association have produced, marketed or been informed about commercial clarified guar gum*' (Documentation provided to EFSA n. 1).

3.2.1 | Toxic elements

The following was requested in the EFSA call for data:

- Analytical data on current levels of lead, mercury, cadmium and arsenic, in commercial samples of the food additive;
- The lowest technologically achievable level for lead, mercury, cadmium and arsenic in order to adequately define their maximum limits in the specifications;
- A proposal for separate specifications for clarified and unclarified guar gum (E 412).

One IBO, an association, provided analytical data on levels of lead (Pb), mercury (Hg), cadmium (Cd) and arsenic (As) in eight commercial samples of guar gum (E 412) analysed by several different laboratories (Documentation provided to EFSA n. 1 and 2). Analyses were conducted mainly by using inductively coupled plasma mass spectrometry (ICP-MS), with the levels of toxic elements reported in various formats, such as numerical values, < LOQ or < LOD or as not detected without provided LOQ or LOD.

Pb, As, Hg and Cd were reported as not detected in four samples analysed by three different laboratories. For two of these samples, analysed by two different laboratories the limit of detection (LOD) was reported as 0.1 mg/kg for each of the toxic elements.

[11]https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-guar-gum-e-412-uses-foods

For three samples, analysed by another laboratory, the levels of As, Hg and Cd were reported as below their respective LOQ of 0.02 mg/kg. The levels of Pb in these three samples were reported as below the LOQ (0.02 mg/kg), 0.029 mg/kg and 0.5 mg/kg, respectively.

In another sample, levels of all four toxic elements were reported as below their respective LOQ of 0.1 mg/kg.

Apart from Pb, As, Hg and Cd, the reporting of other elements was not consistent among the different laboratories that had been used by the IBO. Tin (Sn) was not detected or not quantified in the three samples for which Sn was reported. Zinc (Zn) was at 4.3, 3.2 and 4.6 mg/kg in the three samples for which this element was reported. Iron (Fe) was reported in only one certificate of analysis and it was at 0.4 mg/kg. Nickel (Ni) was reported in two samples, and it was < LOD and 0.54 mg/kg. Finally, copper (Cu) was reported in two samples, and it was < LOD and 1.7 mg/kg.

The IBO explained that the manufacturing process of guar gum is not specifically intended to reduce the content of toxic elements. The IBO stated that the current maximum limits for Pb, Hg, Cd and As in E 412 as set in Eu Regulation 231/2012 reflect the lowest technologically achievable levels. The maximum limits for Pb, Hg, Cd and As proposed by the IBO for E 412 used in foods for all population groups including infants are shown in Table 2 (Documentation provided to EFSA n. 1).

TABLE 2 Lowest technologically achievable levels for the toxic elements Pb, Hg, Cd and As in commercial unclarified E 412 for all population groups including infants below 16 weeks of age, as proposed by an IBO (Documentation provided to EFSA n. 1).

Pb	Hg	Cd	As
2 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg

The Panel noted that the maximum limits proposed by the IBO for Pb, Hg, Cd and As are identical with the specifications set in EU Regulation 231/2012 for E 412 and are substantially higher than the reported levels measured in commercial samples of E 412.

The Panel further noted that, already in the EFSA ANS Panel opinion (EFSA ANS Panel, 2017), the levels of toxic elements reported by the industry were substantially lower than the maximum limits set in the EU specification for E 412.

3.2.2 | Residual proteins

The following was requested in the EFSA call for data:

- current levels of residual proteins in clarified and unclarified preparations;
- the lowest technologically achievable level for residual proteins in clarified and unclarified preparations in order to adequately define their maximum limits in the specifications in view of case reports on hypersensitivity reactions associated with guar gum.

One IBO, an association, reported the residual protein content in nine commercial samples of guar gum. The content of protein in three samples was determined by using the Kjeldahl method and for six sample an internal, not described test method was stated (Documentation provided to EFSA n. 1 and 2). Independently of the method applied, the protein content was in the range from 2.8% to 5.6% w/w.

The IBO supported the existing specification for E 412 which limits the residual proteins (factor N × 6.25) to 10% (Table 1) (Documentation provided to EFSA n. 1).

3.2.3 | Microbiological criteria

The following was requested in the EFSA call for data:

- Because of both the botanical origin and the polysaccharidic nature of guar gum, it can be a substrate of microbiological contamination. Data should be provided demonstrating the absence of *Salmonella* spp. and *Escherichia coli* and on the lowest total aerobic microbial count (TAMC) and total combined yeast and mould count (TYMC) that can be reached.
- In addition, data should be provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii*.

One IBO, an association, reported the results of microbiological analyses of 17 samples of guar gum E 412. In all analysed samples, *Salmonella* spp. (neg/25 or 375 g) and *Escherichia coli* (neg/1–12.5 g) were not detected. The levels of TYMC determined for all samples were ranging < 10–50 CFU/g. For 12 samples, total bacterial count (TBC) was reported ranging from 140 to 570 per gram, and for three samples, the level of TAMC was in the range 1200–7200 CFU/g. (Documentation provided to EFSA n. 1 and 2).

The IBO did not provide any data demonstrating the absence or presence of *Cronobacter* (*Enterobacter) sakazakii* (Documentation provided to EFSA n. 1 and 2) in the food additive E 412.

Regarding the proposal for the lowest technologically achievable levels for TAMC and TYMC, the IBO stated that the submitted data confirm the previous range of results for microbiological analysis submitted to EFSA in 2017 (EFSA ANS Panel, 2017) and that '*the lowest Total Plate Count could be set at 10,000 CFU/g*' in the EU specifications of E 412 (Documentation provided to EFSA n. 1).

The Panel noted that, for one sample, the limit of the TAMC as set in JECFA specifications for guar gum i.e. 5.000 CFU/g was exceeded.

3.2.4 | Other impurities

One IBO submitted additional information on the presence of other impurities in some samples of the food additive E 412 (Documentation provided to EFSA n. 1). In five analysed samples, pentachlorophenol (PCP) was not detected in three samples, and in two samples was reported as 'within limits'. Dioxins levels analysed in two samples were reported as 'within limits', and in two analysed samples, borate level was reported as 'not detected'.

The Panel noted that there are not limits for dioxins whereas a limit is only given for PCP (0.01 mg/kg) for guar gum in the EU regulation (EU Regulation 2019/1793).

The Panel noted that since 2008 in the EU specific regulations, e.g. 'laying down special conditions applicable to the import of guar gum originating in or consigned from India due to contamination risks by pentachlorophenol and dioxins'[12] are in force. This results in testing numerous samples of guar gum used for food and feed yearly if imported into the EU from India.

3.2.5 | Additional information on the E 412 used in food categories 13.1.1, 13.1.5.1 and 13.1.5.2

The following was requested in the EFSA call for data:

- information on the fate and the reaction products of guar gum (E 412) in the infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of that age under special medical conditions (FC 13.1.5.1);
- information on particular specification requirements for identity and the purity of guar gum (E 412) (e.g. with respect to levels of protein residues; use of clarified guar gum or content of toxic elements, furfural, pentachlorophenol, isopropanol, borate) when used in the infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of that age under special medical conditions (FC 13.1.5.1). Analytical data on impurities in the final special formulae for infants below 16 weeks of age need to be provided when no legal limit has been established;
- Information on the possibility to use clarified guar gum to cover all technological needs of the food additive E 412 especially for the use in FC 13.1.1 and FC 13.1.5.2.

The IBO did not provide data on the fate and the reaction products of guar gum (E 412) in special formulae used for infants below 16 weeks of age under special medical conditions (Documentation provided to EFSA n. 1 and 2).

The IBO stated that guar gum is a soluble dietary fiber and *'is soluble in cold and hot water developing a large range of viscosity depending upon the grade*'. Furthermore, the IBO stated that *'guar gum shows no reaction with other components of food formulae*' and *'is not metabolised in the gastrointestinal tract and is partially fermented by the intestinal micro flora*'. The Panel noted that no evidence was provided to support the IBO statement (Documentation provided to EFSA n. 1 and 2).

The IBO did not provide any information regarding particular specification requirements for identity and purity of guar gum when used as E 412 in infant formulae (FC 13.1.1. and FC 13.1.5.1). No information was provided on the impurity levels in the formulae for infants below 16 weeks of age (see Appendix B).

Regarding the possibility of using clarified guar gum to cover all technological needs of the food additive E 412, the IBO stated that: '*clarified guar gum is not commercialised by the members of the association*'. (Documentation provided to EFSA n. 1).

Moreover, another IBO clarified that E 412 is not used in food categories 13.1.1 and 13.1.5.1, but it is present in products under food category 13.1.5.2. Specifically, the IBO clarified that E 412 is used in FC 13.1.5.2 products for toddler aged 1 year and older, excluding infants, especially those under 16 weeks of age. It is employed in liquid products containing amino acids designed for children diagnosed with specific medical conditions from 1 year onwards (Documentation provided to EFSA n. 3 and 4).

3.2.6 | Particle size distribution

No new data in addition to those previously reported in the re-evaluation (EFSA ANS Panel, 2017) on the particle size distribution were submitted in response to a further, specific request from EFSA.

[12]Commission Implementing Regulation (EU) 2019/1793 of 22 October 2019 on the temporary increase of official controls and emergency measures governing the entry into the Union of certain goods from certain third countries implementing Regulations (EU) 2017/625 and (EC) No 178/2002 of the European Parliament and of the Council and repealing Commission Regulations (EC) No 669/2009, (EU) No 884/2014, (EU) 2015/175, (EU) 2017/186 and (EU) 2018/1660, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R1793.

3.3 | Authorised uses and use levels

Maximum levels of guar gum (E 412) in foods for infants below 16 weeks of age are defined in Regulation (EC) No 1333/2008 on food additives, as amended. In this opinion, these levels are termed maximum permitted levels (MPLs).

According to Regulation (EC) No 1333/2008, annex II, Part E, guar gum (E 412) is authorised in foods for infants below 16 weeks of age in 'infant formulae as defined by Directive 2006/141/EC' (FC 13.1.1) and in 'dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1) as defined in Directive 1999/21/EC', see Table 3.

TABLE 3 MPLs of guar gum (E 412) in foods for infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008.

Food category number	Food category name	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
13.1.1	Infant formulae as defined by Directive 2006/141/EC	E 412	Only where the liquid product contains partially hydrolysed proteins	1000
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 412	From birth onwards in products in liquid formulae containing hydrolysed proteins, peptides or amino acids	10,000
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 412	Only where the liquid product contains partially hydrolysed proteins	1000
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 412		1000[a]
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 412		1000[a]
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 412	From birth onwards in products in liquid formulae containing hydrolysed proteins, peptides or amino acids	10,000

Abbreviation: MPL, maximum permitted level.

[a]If more than one of the substances E 407, E 410 and E 412 is added to a foodstuff, the maximum level established for that foodstuff for each of those substances is lowered with that relative part as is present of the other substances together in that foodstuff.

3.4 | Exposure data

Some food additives are authorised in the EU in infant formulae as defined by Commission Delegated Regulation (EU) 2016/127/EC (FC 13.1.1) and in dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1) at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, actual use levels are required for performing a more realistic exposure assessment.

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[13] for technical and toxicological data on guar gum (E 412) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. No actual use levels nor analytical data of guar gum (E 412) in foods was made available to EFSA in response to this public call.

3.4.1 | Reported use levels in food categories 13.1.1, 13.1.5.1 and 13.1.5.2

Industry indicated that guar gum (E 412) is not used in FCs 13.1.1 and 13.1.5.1 (Documentation provided to EFSA n. 3).

Data were provided for special formulae (FC 13.1.5.2) for toddlers from 1 year onwards, at a typical level of 813 mg/L and maximum level of 1016.5 mg/L. (Documentation provided to EFSA n. 4).

3.4.2 | Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 3.8 million food and beverage products of which more than 1,400,000 are or have been

[13]Call for technical and toxicological data on guar gum (E 412) for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-guar-gum-e-412-uses-foods

available on the European food market. Mintel started covering EU's food markets in 1996, currently having 24 out of its 27 member countries, Norway presented in the Mintel GNPD.[14]

For the purpose of this Scientific Opinion, Mintel's GNPD[15] was used for checking the labelling of food and beverage products and food supplements for guar gum (E 412) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to Mintel's GNPD, no foods for infants below 16 weeks of age are labelled with guar gum (E 412) between January 2019 and February 2024.

3.5 | Exposure estimates

3.5.1 | Dietary exposure estimates to guar gum (E 412) for infant < 16 weeks of age

Although the Panel noted that industry indicated that guar gum (E 412) is not used in the FCs 13.1.1 and 13.1.5.1, the Panel estimated the exposure to this food additive based on the MPLs for these two food categories.

This scenario is based on the recommended consumption levels from SC Guidance (EFSA Scientific Committee, 2017). This guidance 'recommends values of 200 and 260 mL formula[16]/kg bw per day as conservative mean and high-level consumption values to be used for performing the risk assessments of substances which do not accumulate in the body present in food intended for infants below 16 weeks of age'. These recommended consumption levels correspond to 14- to 27-day-old infants consumption. Two regulatory maximum level exposure assessment scenarios were calculated, one considering the MPLs for infant formulae (FC 13.1.1 at 1000 mg/kg) and the second considering the MPL for FSMP (FC 13.1.5.1 at 10,000 mg/kg). These two food categories cover both food used by infants during the first months of life. The first one should satisfy the nutritional requirements of such infants until the introduction of appropriate complementary feeding, the second one is covering foods for infants having special medical purposes and special formulae.

Table 4 summarises the estimated exposure to guar gum (E 412) from its use as a food additive in FC 13.1.1/13.1.5.1 for infants below 16 weeks of age.

TABLE 4 Dietary exposure to guar gum (E 412) (mg/kg bw per day) in infant formulae (FC 13.1.1/13.1.5.1) for infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008.

	Infants (< 16 weeks of age)
Regulatory maximum level exposure assessment scenario (in FC 13.1.1 at 1000 mg/kg)	
• Mean consumption (200 mL/kg bw per day)	200
• High-level consumption (95th percentile, 260 mL/kg bw per day)	260
Regulatory maximum level exposure assessment scenario (in FC 13.1.5.1 at 10,000 mg/kg)	
• Mean consumption (200 mL/kg bw per day)	2000
• High-level consumption (95th percentile, 260 mL/kg bw per day)	2600

Abbreviation: bw, body weight.

3.5.2 | Dietary exposure estimates to guar gum (E 412) for infants above 12 weeks of age up to 1 year eating food for special medical purposes (FSMP)

Industry indicated that guar gum (E 412) is not used for children below 1 year (Documentation provided to EFSA n. 3, 4). However, the Panel estimated the exposure of infants above 12 weeks of age up to 1 year who would consume these special formulae, using the maximum permitted level, and according to the FSMP consumer only scenario. This scenario is estimated as follows:

This population of infants > 12 weeks of age up to 1 year (consumers only of FSMP) is assumed to be exposed to guar gum (E 412) present at the maximum permitted level via consumption of FSMP (FC 13.1.5.2 [i.e. 10,000 mg/kg]) and at the typical reported use levels for the remaining food categories.

Mean exposure for infants (12 weeks to 1 year old) ranged between 563 mg/kg bw per day and 1103 mg/kg bw per day. At the 95th percentile, exposure ranged from 1083 mg/kg bw per day to 1386 mg/kg bw per day.

3.5.3 | Dietary exposure estimates for toddlers (12–35 months) eating food for special medical purposes (FSMP)

Industry indicated that guar gum (E 412) is used in the FC 13.1.5.2 for children from 1 year onwards diagnosed with inborn errors of metabolism. These levels were considered for estimating an exposure assessment of toddlers which would consume these special formulae. The consumer only scenario is estimated as follows:

[14]Missing Cyprus, Luxembourg and Malta.

[15]http://www.gnpd.com/sinatra/home/

[16]The term 'formula' has been added.

This population (consumers only of FSMP) is assumed to be exposed to guar gum (E 412) present at the maximum reported use level (1016.5 mg/L) via consumption of FSMP (FC 13.1.5.2) and at the typical reported use levels for the remaining food categories (EFSA ANS Panel, 2017, Appendix C).

For the consumers only of FSMP, for toddlers, mean exposure to guar gum (E 412) from its use as a food additive ranged between 70 and 498 mg/kg bw per day. The 95th percentile of exposure to guar gum (E 412) ranged between 319 and 548 mg/kg bw per day.

3.5.4 | Uncertainty analysis

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007b), the following sources of uncertainty have been considered and summarised in Table 5.

TABLE 5 Qualitative evaluation of influence of uncertainties on the dietary exposure estimate.

Sources of uncertainties	Direction[a]
Consumption data for infants below 16 weeks of age: one reference point only to estimate exposure during the period of up to 16 weeks of age	+/–
Regulatory maximum level exposure assessment scenario for infants below 16 weeks of age: – exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008	+
Consumption data for infants above 12 weeks of age and toddlers: – Consumption data: different methodologies/representativeness/underreporting/Misreporting/no portion size standard	+/–
– Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
– Correspondence of reported use levels to the food items in the EFSA Comprehensive Database: uncertainties to which types of food the levels refer	+/–
– Uncertainty in possible national differences in use levels of food categories	+/–
Refined exposure assessment scenarios for infants above 12 weeks of age: – exposure calculations based on the MPL for FC 13.1.5.1, for the remaining FCs the average of the typical level was considered	+
Refined exposure assessment scenarios for toddlers: – exposure calculations based on the maximum level for FC 13.1.5.2, for the remaining FCs the average of the typical level was considered	+/–

Abbreviation: MPL, maximum permitted level.

[a]+, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Guar gum (E 412) is authorised in food categories 13.1.1, 13.1.5.1 and 13.1.5.2 according to Annex II to Regulation (EC) No 1333/2008.

For infants < 16 weeks of age, there is uncertainty around the consumption values used since the actual formula consumption could be higher or lower than the fixed values used in the scenario(s). This gives rise to the potential both for possible over- and under-estimation of exposure (+/– in Table 5).

Regarding occurrence levels, information provided to EFSA indicates that E 412 is not used in foods belonging to FCs 13.1.1, 13.1.5.1 and 13.1.5.2 for infants < 1 year and no use levels have been reported. Exposure scenarios considered only MPLs from the legislation. In contrast, these levels cannot legally be exceeded, and this means that the uncertainty is one sided (+, Table 5). The consequence of this one-sided uncertainty is that it may overestimate the potential exposure estimates when assuming use levels are all at the MPL.

Based on the assumption that carers of children would be brand loyal to a formula for special medical purposes and considering that the maximum reported levels were used for foods under FC 13.1.5.2 while mean reported use levels were used for the rest of the diet, the Panel considered that the dietary exposure to guar gum (E 412) would in general result in reliable estimate of exposure to guar gum (E 412) from its use as a food additive according to Annex II for toddlers above 1 year of age consuming FSMP.

3.6 | Proposed revision to existing EU specifications for guar gum (E 412)

The potential exposure to impurities from the use of guar gum (E 412) can be calculated by assuming that the impurity is present in the food additive up to a limit value and then by calculation pro-rata to the estimates of exposure to the food additive itself.

One IBO confirmed that E 412 is not used in food categories FC 13.1.1 and FC 13.1.5.1, and in FC 13.1.5.2, it is used only for infants aged 1 year and above (Documentation provided to EFSA no. 3 and 4). Notably, the Panel observed that E 412 is allowed in FC 13.1.1 and 13.1.5.1 for infants < 16 weeks and in FC 13.1.5.2 also for those above 16 weeks. Consequently, the Panel conducted calculation for potential exposure to toxic elements from dietary exposure estimates to E 412 as calculated in this opinion, considering:

- Infants < 16 weeks: the mean and 95th percentile exposure estimates, calculated in two scenarios depending on the MPL applicable to specific FC, were 200 and 260 mg/kg bw per day and 2000 and 2600 mg/kg bw per day (see Section 3.5.1).
- Infants above 12 weeks of age up to 1 year (consumers of special infant formulae in FC 13.1.5.2): the highest mean and 95th percentile exposure estimates were 1103 and 1386 mg/kg bw per day (see Section 3.5.2).

Moreover, the Panel considered dietary exposure to E 412 for toddlers (consumers only of FSMP, FC 13.1.5.2) at the highest mean and 95th percentile of dietary exposure estimates, calculated in this opinion (Section 3.5.3), which were 498 and 548 mg/kg bw per day, respectively.

For the general population, the Panel considered exposure calculations for E 412 as presented in the re-evaluation of the food additive (EFSA ANS Panel, 2017). The ANS Panel selected the brand-loyal refined scenario as the most relevant exposure scenario for the risk assessment. For the current assessment, the highest exposure levels in the brand-loyal refined scenario for the mean and 95th percentile among different population groups were considered: 449 mg/kg bw per day for toddlers and 865 mg/kg bw per day for children, respectively.

The level of the impurity in the food additive combined with the estimated or potential intakes of guar gum (E 412), as explained above could result in an exposure which can be compared with the following reference points (RPs) or health-based guidance values (HBGVs) (Table 6) for the undesirable impurities potentially present in E 412.

TABLE 6 Reference points/health-based guidance values for impurities potentially present in guar gum (E 412).

Impurity HBGV/RP	Basis/reference
Lead (Pb)/0.5 μg/kg bw per day ($BMDL_{01}$)	The reference point is based on a study demonstrating perturbation of intellectual development in children with the critical response size of 1 point reduction in IQ. The EFSA CONTAM Panel mentioned that a 1 point reduction in IQ is related to a 4.5% increase in the risk of failure to graduate from high school and that a 1 point reduction in IQ in children can be associated with a decrease of later productivity of about 2%. A risk cannot be excluded if the exposure exceeds the $BMDL_{01}$ (MOE lower than 1). EFSA CONTAM Panel (2010)
Mercury (Hg)/4 μg/kg bw per week (TWI)	The HBGV was set using kidney weight changes in male rats as the pivotal effect. Based on the $BMDL_{10}$ of 0.06 mg/kg bw per day, expressed as mercury, and an uncertainty factor of 100 to account for inter and intra species differences, with conversion to a weekly basis and rounding to one significant figure, a TWI for inorganic mercury of 4 μg/kg bw per week, expressed as mercury was established. EFSA CONTAM Panel (2012)
Cadmium (Cd)/2.5 μg/kg bw per week (TWI)	The derivation of the reference point is based on a meta-analysis to evaluate the dose–response relationship between selected urinary cadmium and urinary beta-2-microglobulin as the biomarker of tubular damage recognised as the most useful biomarker in relation to tubular effects. A group-based $BMDL_5$ of 4 μg Cd/g creatinine for humans was derived. A chemical-specific adjustment factor of 3.9 was applied to account for human variability in urinary cadmium within each dose-subgroup in the analysis resulting in a reference point of 1.0 μg Cd per g creatinine. In order to remain below 1 μg Cd/g creatinine in urine in 95% of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 μg Cd/kg bw, corresponding to a weekly dietary intake of 2.5 μg Cd/kg bw. EFSA (2009)
Inorganic arsenic (iAs)/0.06 μg/kg bw per day ($BMDL_{05}$)	The reference point is based on a benchmark dose lower confidence limit (BMDL05) of 0.06 μg/kg bw per day identified for skin cancer. The reference point is considered to cover lung cancer, bladder cancer, skin lesions, ischaemic heart disease, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects. An MOE of 1 would correspond to the exposure level that is associated with a 5% increase relative to the background incidence for skin cancer, based on the available data'. An MOE of 1 raises a health concern Because there are no precedents in EFSA for identification of an MOE of low concern, when using a BMDL derived from human cancer data the CONTAM Panel decided not to determine a value for an MOE of low concern EFSA CONTAM Panel (2024)

Abbreviations: $BMDL_{01}$, benchmark dose (lower confidence limit); HBGV, Health-based guidance value; MOE, margin of exposure; IQ, intelligence quotient; TWI, Tolerable Weekly Intake; RP, Reference point.

The risk assessment of undesirable impurities helps to determine whether there could be a possible health concern if these impurities would be present at the limit values in the food additive. The assessment is performed by calculating the MOE (margin of exposure) by dividing the reference point (e.g. BMDL) by the exposure estimate (this opinion and EFSA ANS Panel, 2017), or by estimating the contribution of the use of guar gum (E 412) to the HBGV (expressed as a percentage of the HBGV).

3.6.1 | Toxic elements

The Panel noted that the occurrence data on toxic elements submitted by the IBO (Documentation provided to EFSA n. 1 and 2) are substantially lower than the current limits in the EU specifications for E 412.

Quantified results for the analysed commercial samples of E 412 were only reported for Pb with the highest level of 0.5 mg/kg. As, Cd and Hg were reported as below LOD or LOQ values and the reported LOQ was in the range of 0.02–0.1 mg/kg for each of these three elements. The IBO proposed lowest technologically achievable levels for Pb, Hg, Cd and As (see Table 2) identical with the current limits in the EU specifications of E 412.

In the absence of the information regarding the specification requirements for identity and purity of guar gum when used as E 412 in infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of

that age under special medical conditions (FC 13.1.5.1) and in Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC (FC 13.1.5.2) Panel assumed that the general specifications for guar gum (Table 1) apply also to these three food categories.

The Panel performed the risk assessment that would result if these toxic elements were present in E 412, at (i) the current maximum limit for toxic elements in the EU specifications that are identical to the proposed lowest technologically achievable levels by the IBO and (ii) at the highest measured value (for Pb 0.5 mg/kg) or, in the absence of any measured value(s), at the lowest reported LOQ (i.e. 0.02 mg/kg for Hg, Cd and As) modulated by the Panel by applying a factor of 10, to allow for a need for flexibility with respect to representativeness, homogeneity and differing analytical methods. It is considered that any mercury or arsenic in the samples correspond to the elements in the inorganic rather than organic form. Consequently, for the comparison, the HBGV for inorganic mercury and the RP for inorganic arsenic are used (Table 6).

The Panel emphasised that the choice of the maximum limits for toxic elements in the specifications is in the remit of risk management. The numbers used here are merely taken to support the risk assessment of these toxic elements as presented below.

The outcome of the risk assessment of the FAF Panel (Table 7) illustrates the health impact that would result if these toxic elements would be present in the food additive at the current maximum limit in the EU specification, and if they would be present in the food additive at the modulated levels.

TABLE 7 Risk assessment for toxic elements.

	(i) Based on the current EU specifications limits for toxic elements in E 412 for use in food for all age groups			
Exposure to E 412 (mg/kg bw per day)	**MOE for Pb at 2 mg/kg**	**% of the TWI for Hg at 1 mg/kg**	**% of the TWI for Cd at 1 mg/kg**	**MOE for As at 3 mg/kg**
2000[a]	0.13	350%	560%	0.01
2600[b]	0.10	455%	728%	0.008
200[c]	0.013	35%	56%	0.1
260[d]	0.1	45%	73%	0.08
1103[e]	0.23	193%	309%	0.18
1386[f]	0.18	242%	388%	0.14
498[g]	0.5	87%	139%	0.04
548[h]	0.46	95.9%	153%	0.036
449[i]	0.56	79%	126%	0.045
865[j]	0.29	151%	243%	0.023
	(ii) Based on the highest measured value for Pb and at the lowest reported LOQ for Hg, Cd and As (i.e. 0.02 mg/kg) modulated by the Panel by applying a factor of 10 (Documentation provided to EFSA n. 1)			
Exposure to E 412 (mg/kg bw per day)	**MOE for Pb at 0.5 mg/kg**	**% of the TWI for Hg at 0.2 mg/kg**	**% of the TWI for Cd at 0.2 mg/kg**	**MOE for As at 0.2 mg/kg**
2000[a]	0.50	70%	112%	0.15
2600[b]	0.38	91%	146%	0.12
200[c]	0.05	7%	11.2%	1.5
260[d]	0.38	9.1%	14.6%	1.2
1103[e]	0.91	39%	62%	0.27
1386[f]	0.72	49%	78%	0.22
498[g]	2.01	17%	28%	0.60
548[h]	1.82	19%	30%	0.55
449[i]	2.23	16%	25%	0.67
865[j]	1.16	30%	48%	0.35

[a]Mean exposure level for the population below 16 weeks of age (Regulatory maximum level exposure assessment scenario using the maximum permitted use level (10,000 mg/kg) in infant FSMP (FC 13.1.5.1)).

[b]95th percentile exposure level for the population below 16 weeks of age (Regulatory maximum level exposure assessment scenario using the maximum permitted use level (10,000 mg/kg) in infant FSMP (FC 13.1.5.1)).

[c]Mean exposure level for the population below 16 weeks of age (Regulatory maximum level exposure assessment scenario using the maximum permitted use level (1000 mg/kg) in infant FSMP (FC 13.1.1)).

[d]95th percentile exposure level for the population below 16 weeks of age (Regulatory maximum level exposure assessment scenario using the maximum permitted use level (1000 mg/kg) in infant FSMP (FC 13.1.1)).

[e]Highest mean exposure level for infants above 12 weeks up to 1 year of age consuming FSMP (FC 13.1.5.1 and 13.1.5.2) (Refined estimated exposure assessment scenario using maximum permitted use levels (10,000 mg/L for categories 13.1.5.1 and 10,000 mg/L for 13.1.5.2)).

[f]Highest 95th percentile exposure level for infants above 12 weeks up to 1 year of age consuming FSMP (FC 13.1.5.1 and 13.1.5.2) (Refined estimated exposure assessment scenario using the maximum permitted use levels (10,000 mg/L for categories 13.1.5.1 and 10,000 mg/L for 13.1.5.2)).

[g]Highest mean exposure level for toddlers consuming FSMP (FC 13.1.5.2) (Refined estimated exposure assessment scenario using maximum use levels reported by industry [See Section 3.5.3]).

[h]Highest 95th percentile exposure level toddlers consuming FSMP (13.1.5.2) (Refined estimated exposure assessment scenario using the maximum use levels reported by industry [See Section 3.5.3]).

[i]Highest mean exposure level for the general population (Refined Brand-Loyal Scenario -Toddlers), see Section 3.4.1, EFSA ANS Panel, 2017 on E 412.

[j]Highest 95th percentile exposure level for the general population (Refined Brand-Loyal Scenario -children 3–9 years). See Section 3.4.1, EFSA ANS Panel, 2017 on E 412.

The resulting figures indicate that, in the calculations carried out for infants aged < 16 weeks and those aged 12 weeks up to 1 year, in both scenarios (i) and (ii), the potential exposure to As, Pb, Hg and Cd from the use of E 412 in infant formulae and FSMP is substantial and raises concerns. This concern is especially notable for infants < 16 weeks of age.

Similarly, for all other population groups, the potential exposure to toxic elements from the use of E 412 considering the current maximum limit set in the EU specifications, and the values modulated by the Panel, is substantial and give raise to concern. The exception is Pb, for which the MOE is deemed sufficient when considering values modulated by the Panel.

The Panel noted that maximum levels for lead, cadmium and arsenic in infant formulae are set by Reg. (EC) No 2023/915 and therefore the Panel calculated the impact of the level of the toxic elements lead, cadmium and arsenic in the food additive on the final product and compared that with the maximum levels for the impurity to the product as placed on the market using MPL established for the use of E 412 in these products (see Appendix B).

Considering the results of these calculations and the fact that the food additive E 412 is not the only potential source of toxic elements, the Panel emphasises the need to reduce the specification limit value for toxic elements in Regulation (EU) No 231/2012. The Panel considered that maximum limits in the EU specifications for these toxic elements should be established based on actual levels in the commercial food additive. If the European Commission decides to revise the current limits in the EU specifications, the estimates of toxic elements intake as above could be taken into account.

3.6.2 | Other parameters

No data were provided on the level of furfural. The Panel calculated the exposure to furfural that could result if guar gum (E 412) contained furfural at the maximum concentration permitted in the specifications of 1 mg/kg. For infants below 16 week of age consuming infant formulae falling under FC 13.1.1 and FC 13.1.5.1, exposure to guar gum was calculated to be up to 2600 mg/kg bw per day, which would result in exposure to furfural at 2.6 μg/kg bw per day. This exposure is 0.5% of the ADI of 0–0.5 mg/kg bw per day established for furfural, furfuryl alcohol and other furfuryl derivatives' (EFSA, 2004a, 2004b). Therefore, the Panel considers that there is no need for changes of the maximum limit for furfural in the EU specifications of E 412.

The Panel noted that the IBO submitted information indicating the absence of borate in two samples of guar gum used as E 412, in accordance with the JECFA specifications (Table 1). Borate is not used at any stage of the guar gum manufacturing process, as described in the EFSA ANS Panel Opinion (EFSA ANS Panel, 2017). Consequently, the Panel does not find a need to include a limit value for borate in the EU specifications for this food additive.

Because of the polysaccharidic nature of E 412, it can be a substrate prone to microbiological contamination. Therefore, the Panel recommends including microbiological criteria in the EU specifications of E 412 in line with the JECFA (Total (aerobic) plate count: Not more than 5000 CFU/g, *E. coli*: Negative in 1 g, *Salmonella*: Negative in 25 g, Yeasts and moulds: Not more than 500 CFU/g). Since cases of infections with *Cronobacter* (*Enterobacter*) *sakazakii* were reported in the literature (Henry and Fouladkhah, 2019), the Panel is of the view that microbiological specifications set for E 412 should also include *Cronobacter* (*Enterobacter*) *sakazakii*; however, no data have been submitted.

The Panel further recommends that the Kjeldahl method should be indicated to be used for the determination of the nitrogen content in E 412 (see Subsection 3.2.2) as basis of the residual protein content determination.

The Panel noted that polysaccharide thickening and gelling agents used as food additives, to exert their technical function, in general, swell in liquid environments and are present as dispersed macromolecules. This also applies to guar gum (E 412). The Panel noted that E 412 is a hydrophilic macromolecule which in water forms a colloidal dispersion in which the macromolecules and/or polymolecular particles are dispersed throughout the liquids (liquid formulations, physiological fluids in the gastrointestinal (GI)-tract). They are not forming true solutions (molecular disperse systems) and are specific for their gelling properties. Based on the considerations above, the Panel also recommends changing the word 'soluble' to 'dispersible' in the EU specifications of E 412.

The Panel also considered that the CAS number 9000-30-0 corresponding to guar gum should be included in the existing EU specifications for E 412.

The EFSA ANS Panel in 2017 recommended to explore the need to separate the current EU specifications of E 412 to guar gum and clarified guar gum. However, one IBO, an association, stated that '*to the best of their knowledge clarified guar gum is not a commercial product and none of the members of the association have produced, marketed or been informed about commercial clarified guar gum*' (Documentation provided to EFSA n. 1). Consequently, no data have been reported for the clarified guar gum. The Panel further reviewed the ANS Panel recommendation and, considering toxicity data already assessed at the time of the re-evaluation and the information provided for current assessment, it did not find the need to separate specifications concerning the protein content in E 412. Therefore, the Panel considered single specifications for E 412 as appropriate.

3.6.3 | Summary of the proposed revisions to the EU specifications

Overall, based on the analytical data provided by the IBOs in response to the call for data,[17] further EFSA requests (Documentation provided to EFSA n. 1 and 2) and the above considerations, the Panel recommends the revisions of the existing EU specifications for guar gum as listed in Table 8.

TABLE 8 Proposal for a revised version of the existing EU Specifications for E 412.

	Commission regulation (EU) No 231/2012	Comment/justification for revision
Definition	Guar gum is the ground endosperm of the seeds of strains of the guar plant, *Cyamopsis tetragonolobus* (L.) Taub. (family *Leguminosae*). Consists mainly of a high molecular weight hydrocolloidal polysaccharide composed of galactopyranose and mannopyranose units combined through glycosidic linkages, which may be described chemically as galactomannan. The gum may be partially hydrolysed by either heat treatment, mild acid or alcaline oxidative treatment for viscosity adjustment	Unchanged
Einecs	232-536-0	Unchanged
CAS number	–	Cas Number to be included 9000-30-0
Molecular weight	50,000–8,000,000	Unchanged
Assay	Galactomannan content not less than 75%	Unchanged
Description	A white to yellowish-white, nearly odourless powder	Unchanged
Functional uses	–	Unchanged
Identification		
Test for galactose	Passes test	Unchanged
Test for mannose	Passes test	Unchanged
Solubility	Soluble in cold water	Dispersible in cold water
Purity		
Loss on drying	Not more than 15% (105°C, 5 h)	Unchanged
Total ash	Not more than 5.5% determined at 800°C	Unchanged
Acid-insoluble matter	Not more than 7%	Unchanged
Protein	Not more than 10% (factor N × 6.25)	Not more than 10% (factor N × 6.25) (Kjeldahl method)
Microbiological criteria	–	Microbiological criteria on: *Total plate count TAMC* *Yeast and Moulds TYMC* *Escherichia coli* *Salmonella* spp. S should be included in line with JECFA specifications. Microbiological criteria should be included for *Cronobacter sakazakii*
Starch	Not detectable by the following method: to a 1 in 10 solution of the sample add a few drops of iodine solution. (No blue colour is produced)	Not detectable by the following method: to a 1 in 10 dispersion of the sample add a few drops of iodine solution. (No blue colour is produced)
Organic peroxides	Not more than 0.7 mg active oxygen/kg sample	Unchanged
Furfural	Not more than 1 mg/kg	Unchanged
Pentachlorophenol	Not more than 0.01 mg/kg	Unchanged
Arsenic	Not more than 3 mg/kg	Lowered on the basis of the information provided and on the considerations of the Panel
Lead (Vol. 4)	Not more than 2 mg/kg	Lowered on the basis of the information provided and on the considerations of the Panel
Mercury	Not more than 1 mg/kg	Lowered on the basis of the information provided and on the considerations of the Panel
Cadmium	Not more than 1 mg/kg	Lowered on the basis of the information provided and on the considerations of the Panel

[17]Call for technical and toxicological data on guar gum (E 412) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-guar-gum-e-412-uses-foods

3.7 | Biological and toxicological data

3.7.1 | Previous evaluation by ANS Panel (2017)

A summary of the main conclusions for the biological and toxicological data from the assessment of the ANS Panel during the re-evaluation of E 412 (EFSA ANS Panel, 2017) is presented below. New information and assessments related to the specific age group below 16 weeks of age are reported in Section 3.7.2.

Absorption, distribution, metabolism, excretion

The in vitro *degradation and the* in vivo *digestibility of guar gum have been investigated in animals and humans. These studies demonstrated that guar gum would not be absorbed intact and would not be metabolised by enzymes present in the gastrointestinal tract. However, it would be partially fermented to SCFAs during its passage through the large intestine by the action of the intestinal tract microflora. The rate of hydrolysis in the gastrointestinal tract in humans is unknown; however, it is expected that fermentation of guar gum would lead to the production of products such as SCFAs which were considered of no concern by the Panel.*

Toxicological studies

Guar gum is regarded as not acutely toxic, based on the results of acute oral toxicity studies.

Short-term and subchronic studies on guar gum have not shown major adverse effects under the conditions of the tests.

Repeated oral administration of guar gum caused some growth reduction in rats, mice and rabbits at high doses, but these effects can partially be attributed to the bulk properties of guar gum when in contact with water or intestinal juices and have not been considered as adverse effects. Increased caecum weight in animals fed high amounts (2%–5% of the diet) of guar gum was also reported. NOAELs identified in short-term and subchronic studies correspond to the highest dose tested of approximately 18,000 mg guar gum/kg bw per day for rats and of approximately 15,000 mg/kg bw per day for mice (Graham et al.*, 1981; NTP, 1982). The Panel considered the available genotoxicity data on guar gum (E 412) to be sufficient to conclude that there is no concern with respect to genotoxicity. Guar gum has been tested in several species in long-term chronic and carcinogenicity studies up to doses of 7500 mg/kg bw per day in mice and 2500 mg/kg bw per day in rats (NTP, 1982). In female rats, statistically significant increased incidences of benign phaeochromocytomas of the adrenal gland were reported. However, no changes in the incidences of malignant phaeochromocytomas were observed, and the combined incidences of benign and malignant phaeochromocytomas in these animals were not statistically significant different. Male rats did not show any statistically significant difference on the incidence of phaeochromocytomas of the adrenal gland (NTP, 1982). The Panel considered that incidences of phaeochromocytomas and pituitary gland tumours occurring in the carcinogenicity study with F344 rats on guar gum, carried out in the early 1980s, are not relevant for human risk assessment. Only non-malignant proliferations were increased in that rat study not leading to an increase incidence of carcinomas. The Panel considered guar gum as not carcinogenic. The Panel could derive a NOAEL of 2500 mg/kg bw per day, the highest dose tested, from this study. The carcinogenicity study with guar gum in mice did not show carcinogenicity potential either. The Panel could derive a NOAEL of 7500 mg/kg bw per day, the highest dose tested, from this study. Guar gum did not show reproductive effects (fertility) or developmental toxicity effects in the available studies (FDRL, 1972, 1973).*

From a combined fertility/developmental study in rats (Collinset al., 1987), the Panel could identify a NOAEL of 5200 mg/kg bw per day for reproductive effects based on decreased number of corpora lutea and a NOAEL for developmental toxicity of 11,800 mg/kg bw per day the highest dose tested.

Allergenicity

The Panel noted that most of the reported cases of allergic reaction to guar gum were after inhalation in occupational settings. In addition, there was no indication that the guar gum used under these conditions complied with the requirement of the specifications of the food additive. Very few cases were reported after consumption of foods containing guar gum. Thus, it is clear that guar gum may induce allergic reactions, likely due to the proteins that are present in the gum. Therefore, the Panel considered that the allergenic potential of guar gum used as a food additive should be reduced as much as possible, e.g. *by decreasing the presence of proteins in the guar gum used as a food additive (E 412), which can be achieved by clarification of the gum.*

Human data

Human undesirable effects, such as flatulence, regurgitation, abdominal pain (cramps), bowel obstruction, constipation or on the contrary soft stools and diarrhoea, have also been reported upon consumption of guar gum as preparations (bolus dose) (Todd et al.*, 1980; Lewis, 1992; Aronson, 2009). Oral intake of large amount of guar gum (9000–30,000 mg/person corresponding to 128–429 mg/kg bw per day) was well tolerated in humans. In general, in most studies after consumption of around 15,000 mg per day corresponding to 214 mg/kg bw per day, some individuals experienced abdominal discomfort (Pittler and Ernst, 2001). In one interventional study with diabetic children, abdominal discomforts were reported in 5 out of 22 children given 13,500 mg guar gum per day corresponding to 314 mg/kg bw per day (Paganus* et al.*, 1987). The Panel considered the abdominal discomfort as undesirable but not adverse.*

3.7.2 | Data submitted

The following was requested in the EFSA call for data:

- A repeated dose study with direct oral administration of guar gum (E 412) to neonatal animals, which includes analysis of possible local effects on the gastrointestinal tract and its microbiota and on a possible reduction in the bioavailability of nutrients (vitamins and minerals, such as calcium, iron and zinc), that are normally contained in food for infants. The study shall be performed in piglets unless justification for the relevance of a study in another species is given;
- Clinical data focusing on gastrointestinal effects when used in dietary foods for special medical purposes in infants below 16 weeks of age (FC 13.1.5.1);
- Post-marketing surveillance reports on undesired and adverse reactions (including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions), indicating the ages and other relevant data of the exposed infants and young children and the use level of guar gum (E 412) in the marketed products, where guar gum is already in use;
- Published and unpublished case reports (e.g. available nutrivigilance data) on undesired and adverse effects, including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions, associated with the oral administration of guar gum in any form to infants and young children;
- Literature searches.

One IBO indicated that based on their knowledge '*Clinical data focusing on gastrointestinal effects when used in dietary foods in infant formulae and for dietary foods for special medical purposes in infants below 16 weeks age*' and '*repeated dose study with direct oral administration to neonatal animals*' are not available and that no publication relevant for the safety evaluation of guar gum when used in foods for infant below 16 weeks age has been found (Documentation provided to EFSA n. 1).

3.7.2.1 | *Repeated dose study in neonatal piglets*

A 21-day repeated dose toxicity study on E 412 in neonatal piglets with 2-week recovery period was provided by one IBO (Documentation provided to EFSA n. 5). The design of this study followed the EMA (2009) and ICH (2010) guidelines, and the EFSA guidance (2017). The study was performed according to good laboratory practice (GLP); the analysis of ornithine decarboxylase, vitamins and minerals (performed in another laboratory) was excluded from the GLP compliance statement.

This study in neonatal piglets was assessed by means of a risk of bias (RoB) scoring scheme and was allocated to Tier 3 (high risk of bias), the scores for each risk of bias element are reported in Table 9.

TABLE 9 Outcome of the risk of bias assessment for the repeated dose study of Guar Gum in neonatal piglets.

	Selection (randomisation)	Selection (allocation and concealment)	Performance (experimental conditions)	Performance (blinding)	Attrition/exclusion	Detection (exposure characterisation)	Detection (confidence in the outcome)	Selective reporting	Other sources of bias
Score	–	+	+	+	– –	–	–	–	+

This repeated dose toxicity study evaluated the toxicity of guar gum (Batch Z1, Lot 456A, Galactomannan content 85%). The test item was administered orally via feeding bottles to piglets for a minimum period of 21 consecutive days followed by a 14-day recovery period. Six groups of male and female piglets (domestic pig, strain: Large White Yorkshire; six animals per sex and group) were given the vehicle (artificial milk replacer) or a guar gum formulation (450, 2250, or 4500 mg/kg per day) in eight divided doses daily at 3-h intervals. The study included an extra control and a recovery group which received the high dose of the test item for 21 consecutive days and a recovery period of 14 days. Animals received artificial milk replacer during the recovery period. The dose volume was 450 mL/kg bw. The piglets were obtained from 7 sows, which were acclimatised for 2–5 days at the test facility. Piglets were housed as group with the respective sow till postnatal day (PND) 3. On PND 3, the piglets were allocated to the six groups but information on the randomisation of the allocation to the dose groups was not provided. From PND 3 until 24, piglets received test formulations which were prepared daily in HPLC water along with the artificial milk replacer, freshly before administration. The homogeneity of the dose suspensions was maintained by constant stirring using a magnetic stirrer prior to (10 min) and while dosing. However, the homogeneity of the test solutions was not analysed. The Panel noted that calculations taking into account body weight and dose volume administration suggest that some animals most probably did not empty the bottle. The Panel also noted that, due to the rapid growth of the animals, they should be weighed daily for proper adjustment of the dosing.

Mortalities were observed for males: 2, 2, 2, 2 and 1 of the control, low-, mid-, high- and high-dose recovery groups, respectively, and for females: 1, 1, 2 and 1 of the low-, mid-, high- and high-dose recovery groups, respectively. The animals which were found dead showed hypoactivity on the last day; no other clinical signs were reported during the study. Unexpectedly, dead animals did not reveal any macroscopic or microscopic lesions. The Panel noted that due to the premature deaths particularly in males the number of remaining animals in most groups was low (i.e. 4 animals per group).

Animals were weighed on PND 3, 10, 17, 23 and at termination on PND 24. In addition, animals of the recovery groups were weighed on PND 30, 37 and at termination on PND 38. On PND 23, a statistically significant decrease in body weight was observed in the male animals of the high dose group of the main study. The Panel considered this effect as adverse. No statistically significant changes in body weight were observed in the female animals.

No treatment-related adverse effects on formula consumption, haematology, coagulation parameters and urinalysis were observed.

On PND 24, a statistically significant increase in triglycerides in high-dose male animals was observed along with higher levels of total cholesterol and LDL cholesterol. In addition, on PND 24, similar changes were reported for female animals. No other treatment-related adverse changes were reported.

There were no treatment-related differences in blood vitamin and mineral levels between the treated and control groups.

Statistically significant increases in the concentrations of ghrelin in the low- and high-dose group in male animals were not considered toxicologically relevant due to the absence of a dose–response and the high variance of the values within the groups.

There were no treatment-related changes in the microflora measured as colony forming units/g faecal matter and the transit time (charcoal). No data were reported on the consistency of the faeces.

No adverse morphological changes were reported for the macroscopic and microscopic examinations of organs and tissues collected at the scheduled termination.

A reduction of body weights in high-dose group in males was noted by the Panel. This was considered adverse. However, because of the high risk of bias, the study could not be used to identify a reference point for an HBGV.

3.8 | Discussion

In the response to EFSA requests one IBO stated that E 412 is not used in food categories 13.1.1 and 13.1.5.1, but it is present in products under food category 13.1.5.2. Specifically, the IBO clarified that E 412 is used in FC 13.1.5.2 products for toddlers aged 1–3 years, excluding infants under 16 weeks. It is employed in liquid products containing amino acids designed for children diagnosed with specific medical conditions.

In the 2017 opinion, the ANS Panel recommended to consider separate specifications in the EU regulation for guar gum and clarified guar gum differing significantly in the protein content.

The Panel noted that one IBO stated that '*to the best of their knowledge clarified guar gum is not a commercial product and none of the members of the association have produced, marketed or been informed about commercial clarified guar gum*' and consequently, no data have been reported for the clarified guar gum.

For the present opinion, the Panel further reviewed the ANS Panel recommendation and considering toxicity data already assessed at the time of the re-evaluation and the information provided for current assessment did not find the need to separate specifications concerning the protein content in E 412. Therefore, the Panel considered single specifications for E 412 as appropriate. In response to the call for data, analytical data for levels of toxic elements (Pb, Hg, Cd and As) in commercial samples of guar gum (E 412) were provided by one IBO. The quantified results for the analysed commercial samples of E 412 were only reported for Pb with the highest level of 0.5 mg/kg. As, Cd and Hg were reported as below LOD or LOQ values and the reported LOQ was in the range 0.02–0.1 mg/kg for each of these three elements. The IBO proposed the lowest technologically achievable levels for Pb, Hg, Cd and As identical with the current limits in the EU specifications of E 412.

The Panel noted that the occurrence data on toxic elements submitted by the IBO are substantially lower than the current limits in the EU specifications for E 412.

The Panel performed the risk assessment that would result if these toxic elements were present in E 412, at (i) the current maximum limit for toxic elements in the EU specifications that are identical to the proposed lowest technologically achievable levels by the IBO and (ii) at the highest measured value (for Pb 0.5 mg/kg) or, in the absence of any measured value(s), at the lowest reported LOQ (i.e. 0.02 mg/kg for Hg, Cd and As) modulated by the Panel by applying a factor of 10, to allow for a need for flexibility with respect to representativeness, homogeneity and differing analytical methods.

One IBO confirmed that E 412 is not used in food categories FC 13.1.1 and FC 13.1.5.1. In FC 13.1.5.2, it is exclusively used for infants aged 1 year and above. However, considering that E 412 is permitted in FC 13.1.1 and 13.1.5.1 for infants < 16 weeks and in FC 13.1.5.2 for those above 12 weeks the Panel calculated potential exposure to toxic elements from dietary E 412 exposure (see Section 3.5), taking into account:

- Infants < 16 weeks: the mean and 95th percentile exposure estimates, calculated in two scenarios depending on the MPL applicable to specific FC, were 200 and 260 mg/kg bw per day and 2000 and 2600 mg/kg bw per day (see Section 3.5.1).
- Infants above 12 weeks of age up to 1 year (consumers of special infant formulae in FC 13.1.5.2): the highest mean and 95th percentile exposure estimates were 1103 and 1386 mg/kg bw per day (see Section 3.5.2).

Additionally, the Panel considered dietary exposure to E 412 for toddlers (consumers of FSMP (FC 13.1.5.2)) at the highest mean and 95th percentile exposure estimates calculated in this opinion, which were 498 and 548 mg/kg bw per day, respectively.

For the general population, the Panel referred to exposure calculations for E 412 from the re-evaluation of the food additive (EFSA ANS Panel, 2017). In the current risk assessment, the highest exposure levels in the brand-loyal refined scenario for the mean and 95th percentile among different population groups were considered: 449 mg/kg bw per day for toddlers and 865 mg/kg bw per day for children, respectively.

The Panel concluded that the potential exposure to toxic elements resulting from the exposure to E 412 could be substantial (see Section 3.6.1), this is particularly pronounced in the calculations conducted for infants below 16 weeks of age and those aged between 12 weeks and 11 months. For Pb, the MOE is insufficient in all cases, except for the general population and toddlers, consumers of FSMP only, where the MOE is deemed sufficient when considering values modulated by the Panel.

The Panel also calculated the impact of the potential level of the toxic elements Pb, Cd and As in the food additive (i.e. up to the specifications limit values) on the final product and compared that with the legal limits for these elements in the final formula for infants below 16 weeks of age set by Regulation (EC) 2023/915 (see Appendix B). Considering the results of these calculations and the fact that the food additive is not the only potential source of toxic elements in the infant formula the Panel emphasises the need to reduce the specification limits for Pb, Cd and As in Regulation (EU) no 231/2012.

The Panel noted that the maximum limits in the EU specifications for toxic elements should be established based on actual levels in the commercial food additive. Therefore, the Panel recommended that the maximum limits be lowered on the basis of the information provided by the IBO and on the considerations of the Panel (see Table 8).

On the question of residual proteins, data were provided using the Kjeldahl method and other not described methods for total nitrogen and all gum samples were within the EU specification of 10% (N content × 6.25). The Panel is of the view that for harmonisation the Kjeldahl method should be indicated to be used for the determination of the residual protein content in E 412.

Regarding the question on specifications for guar gum use in special formulae intended for infants below 16 weeks of age under special medical conditions, the IBO explained that E 412 is not used in the food categories FC 13.1.1 and FC 13.1.5.1, and in FC 13.1.5.2 is used only for children from 1 year of age onwards, and no information was provided. The IBO further stated that there are no special requirements on purity criteria for guar gum E 412 intended for infant formulae/food.

Regarding the possibility of using clarified guar gum to cover all technological needs of the food additive E 412, the IBO stated that: '*clarified guar gum is not commercialised by the member of the association*'.

On the question on the fate and any reaction products of guar gum (E 412) in infant formulae, it was stated by the IBO that the '*guar gum shows no reaction with other components of food formulae*' and '*is not metabolised in the gastrointestinal tract and is partially fermented by the intestinal micro flora*' and *is soluble in cold and hot water developing a large range of viscosity depending upon the grade'*. Although no data were submitted to support this statement, the Panel considered that due to the identity and chemical nature of guar gum (see Section 3.1), no reaction products are expected to be present in infant formulae at any significant level.

One IBO provided data showing the absence of *Salmonella* spp. (neg/25 or 375 g) and *Escherichia coli* (neg/1–12.5 g) in analysed samples of E 412. The levels of TAMC (including TBC) and TYMC determined for analysed samples were ranging for TAMC 140–7200 CFU/g and for TYMC < 10–50 CFU/g. The Panel noted that guar gum (E 412) may be prone to microbiological contamination and therefore microbiological specifications should be set for E 412 and should also include *Cronobacter (Enterobacter) sakazakii*; however, no data were provided.

The Panel noted that polysaccharide thickening and gelling agents used as food additives, to exert their technical function, in general, swell in liquid environments and are present as dispersed macromolecules. This also applies to guar gum (E 412). The Panel noted that E 412 is a hydrophilic macromolecule which in water forms a colloidal dispersion in which the macromolecules and/or polymolecular particles are dispersed throughout the liquids (liquid formulations, physiological fluids in the gastrointestinal (GI)-tract). They are not forming true solutions (molecular disperse systems) and are specific for their gelling properties.

Based on the considerations above the Panel also recommends changing the word 'soluble' to 'dispersible' in the EU specifications of E 412.

Taking all these aspects into consideration, the Panel has made proposals for an update of the EU specifications for guar (E 412) (see Table 8).

The toxicological studies evaluated in the ANS opinion (EFSA ANS Panel, 2017), in which NOAELs of up to 18,000 mg/kg bw per day were identified, are not fully appropriate for the assessment of the safety of guar gum when used in food for infants below and above 16 weeks of age and young children consumers of food under FCs 13.1.1, 13.1.5.1 and 13.1.5.2. Therefore, the conclusion of the ANS Panel on the safety of E 412 as food additive is not applicable for this population.

The IBOs did not provide clinical data, post-marketing surveillance reports on undesired and adverse reactions and published and unpublished case reports.

A repeated dose study of guar gum in neonatal piglets with 2-week recovery period was provided (Documentation provided to EFSA n. 5). The design of this study followed the EMA (2009) and ICH (2010) guidelines, and the EFSA guidance (2017). The study was performed according to good laboratory practice (GLP). The study was assessed by means of a risk of bias (RoB) scoring scheme (see above) and was allocated to tier 3 (high risk of bias) because of several flaws. In this study, a

statistically significant reduction of body weights in the high-dose group in males was noted by the Panel. In the ANS opinion (EFSA ANS Panel, 2017), effects on the body weight at high doses in rats, mice and rabbits were attributed to the bulk properties of guar gum when in contact with water or intestinal juices and have not been considered as adverse effects. In the context of the assessment of the piglet study, the observed statistically significant body weight reduction in male piglets (highest dose, nominally 4500 mg/kg bw per day) was considered adverse by the Panel taking into account that the piglet is a model for developing infants and weight reduction would indicate adverse effects in this population.

Whereas there are indications of adverse effects in male piglets because of the high risk of bias of this study, the available data are not adequate to support the derivation of a reference point. The high risk of bias of the piglet study precludes its use to assess the safety of guar gum (E 412) in food for infants below and above 16 weeks of age and young children (FC 13.1.1, 13.1.5.1 and 13.1.5.2). As reported above, industry declared that guar gum is used only in FC 13.1.5.2 in food for toddlers for which also no adequate toxicological/clinical data were submitted to support its use.

4 | CONCLUSIONS

The Panel concluded that the technical data provided by the IBO support further amendments of the specifications for E 412 laid down in Commission Regulation (EU) No 231/2012, as presented by the recommendations made in Table 8.

The submitted data are not sufficient to demonstrate that the use of guar gum (E 412) in food for infants (below and above 16 weeks of age) and young children consumers of food under FC 13.1.1, 13.1.5.1 and 13.1.5.2 is safe.

5 | DOCUMENTATION AS PROVIDED TO EFSA

1. ASSOCIATION FOR INTERNATIONAL PROMOTION OF GUMS (AIPG), 2019. Submission of data in response to the call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 17 December 2019.
2. ASSOCIATION FOR INTERNATIONAL PROMOTION OF GUMS (AIPG), 2022. Additional data and clarifications submitted following the call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 22 June 2022.
3. SPECIALISED NUTRITION EUROPE (SNE), 2023, Additional data and clarifications submitted following the call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age, (correspondence), Submitted on 4 September 2023
4. SPECIALISED NUTRITION EUROPE (SNE), 2023, Additional data and clarifications submitted following the call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age, Submitted on 24 November 2023.
5. SHEFEXIL, 2023. Submission of data in response to the call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 30 December 2023.

ABBREVIATIONS

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
ANS Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
APC	Aerobic Plate Count
bw	body weight
CAS	Chemical Abstract Service
CFU	Colony forming unit
FAF Panel	Panel on Food Additives and Flavourings
FAO/WHO	Food and Drug Organisation/World Health Organisation
FC	Food category
FSMP	Food for special medical purposes
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	lowest-observed-adverse-effect level
Mintel GNPD	Mintel's Global New Products Database
MOE	margin of exposure
MPL	maximum permitted levels
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PND	postnatal day
SC	Scientific Committee of EFSA
SCF	Scientific Committee on Food
TAMC	total aerobic microbial count

TYMC	total combined yeast and mould count
TWI	tolerable weekly intake
WG	Working Group

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBER

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APPENDIX A

Data requested in the call for data (Call for technical and toxicological data on guar gum (E 412) for uses as a food additive in foods for all population groups including infants below 16 weeks of age[18]

Kind of data	Data requested in the call for data	Responses from interested parties	Comment
A. Information regarding the follow-up of the conclusions and the recommendations of the EFSA ANS Panel opinion on the safety of guar gum (E 412) as food additive			
1. Technical data	• Analytical data on current levels of lead, mercury, cadmium and arsenic, in commercial samples of the food additive • The lowest technologically achievable level for lead, mercury, cadmium and arsenic in order to adequately define their maximum limits in the specifications • Current levels of residual proteins in clarified and unclarified preparations • The possibility to use clarified guar gum to cover all technological needs of the food additive E 412, especially for the use in 13.1.1 (infant formulae) and 13.1.5.2 (dietary foods for babies and young children for special medical purposes) where the additive is authorised only when the formulae contain partially hydrolysed proteins and peptides • The lowest technologically achievable level for residual proteins in clarified and unclarified preparations in order to adequately define their maximum limits in the specifications in view of case reports on hypersensitivity reactions associated with guar gum In addition, a proposal for separate specifications for clarified and unclarified guar gum (E 412) is requested • Because of both the botanical origin and the polysaccharidic nature of guar gum, it can be a substrate of microbiological contamination. Data should be provided demonstrating the absence of *Salmonella* spp. and *Escherichia coli* and on the lowest total aerobic microbial count (TAMC) and total combined yeast and mould count (TYMC) that can be reached	Data submitted	Assessed, see Sections 3.2 and 3.6
2. Toxicological data	According to the conclusions and recommendations in the Scientific opinion on the re-evaluation of guar gum (E 412) as a food additive by the EFSA ANS Panel published in 2017[3], the generation of additional data to assess the potential health effects of guar gum (E 412) 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 babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2) was recommended. These requirements will be addressed as outlined in Section B.2	No data provided	See Sections 3.7, 3.8 and 4
3. Literature searches	Literature searches should be conducted relevant for the safety evaluation of guar gum (E 412) for all uses in foods for all population groups from 12/10/2016[6] up to the date of the data submission, as described in the Guidance for submission for food additive evaluations (see its section 5.3)	Data provided	Assessed, see Section 3.7
B. Information required for the risk assessment of guar gum (E 412) as food additive for use in foods for infants below 16 weeks of age			
1. Technical data	• Information on the levels of use of guar gum (E 412), alone or in combination with other thickening agents (indication of food additive name and level of use in the infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of that age under special medical conditions (FC 13.1.5.1) • Information on the fate and the reaction products of guar gum (E 412) in the infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of that age under special medical conditions (FC 13.1.5.1) • Information on particular specification requirements for identity and the purity of guar gum (E 412) (e.g. with respect to levels of protein residues; use of clarified guar gum or content of toxic elements, furfural, pentachlorophenol, isopropanol, borate) when used in the infant formulae for infants below 16 weeks of age (FC 13.1.1), as well as in special formulae for infants of that age under special medical conditions (FC 13.1.5.1). Analytical data on impurities in the final special formulae for infants below 16 weeks of age need to be provided when no legal limit has been established In addition, data should be provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii*	No data provided	See Section 1.1.3

[18] https://www.efsa.europa.eu/en/consultations/call/181010-4 and responses from interested parties.

(Continued)

Kind of data	Data requested in the call for data	Responses from interested parties	Comment
2. Toxicological data	Within the frame of the EFSA Guidance of the Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age[5] the following information on the toxicological properties of guar gum (E 412) and its adverse effects relevant for use in infant formulae in infants below 16 weeks of age, as well as for special formulae used for infants of that age under special medical conditions considering that the studies are of appropriate duration: • A repeated dose study with direct oral administration of guar gum (E 412) to neonatal animals, which includes analysis of possible local effects on the gastrointestinal tract and its microbiota and on a possible reduction in the bioavailability of nutrients (vitamins and minerals, such as calcium, iron and zinc), that are normally contained in food for infants. The study shall be performed in piglets unless justification for the relevance of a study in another species is given • Clinical data focusing on gastrointestinal effects when used in dietary foods for special medical purposes in infants below 16 weeks of age (FC 13.1.5.1) • Post-marketing surveillance reports on undesired and adverse reactions (including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions), indicating the ages and other relevant data of the exposed infants and young children and the use level of guar gum (E 412) in the marketed products, where guar gum is already in use • Published and unpublished case reports (e.g. available nutrivigilance data) on undesired and adverse effects, including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions, associated with the oral administration of guar gum in any form to infants and young children	Only repeated dose toxicity study on neonatal animals provided	See Sections 1.1.3, 3.7, 3.8, 4
3. Literature searches	Literature searches should be conducted relevant for the safety evaluation guar gum (E 412) when used in foods for infants below 16 weeks of age up to the date of the data submission, as described in the Guidance for submission for food additive evaluations (see its section 5.3)		

APPENDIX B

Estimation of the fraction of the levels of toxic elements in E 412 with respect to the regulatory maximum levels in the final food product for which the additive is used

The Panel estimated the fraction (%) of the levels of the toxic elements lead, cadmium and arsenic in E 412 with respect to the regulatory maximum levels in the final product (formulae) as sold as laid down in Regulation (EC) No **2023/915** considering:

- The current specification for lead, cadmium and arsenic in E 412 according to Regulation (EU) No 231/2012 at 2 mg/kg, 1 mg/kg and 3 mg/kg, respectively.
- The highest measured value for lead and for cadmium and arsenic at the lowest reported LOQ (i.e. 0.02 mg/kg) modulated by the Panel by applying a factor of 10.
- The maximum permitted use level of E 412 in the final food of 1000 mg/kg in FC 13.1.1 and 10,000 mg/kg in FC 13.1.5.1.
- The range of maximum levels (ML) for lead (0.01–0.02 mg/kg), cadmium (0.005–0.02 mg/kg) and arsenic (0.01–0.02 mg/kg) in formulae for infants as laid down in Regulation (EC) No 2023/915.

The results of the calculations can be found for Pb in Tables B.1 and B.2 for Cd in Tables B.3 and B.4 and for As in Tables B.5 and B.6.

TABLE B.1 Estimation of the fraction of the levels of lead in E 412 with respect to the regulatory maximum levels in the final product (liquid formulae for infants below 16 weeks of age).

Specification for toxic elements status	Lead (mg/kg)	Use level of food additive in final product (mg/kg)	Concentration of toxic element in final product (mg/kg)	Maximum level in Reg. 2023/915 (mg/kg)	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	2.0	10,000	0.0200	0.01	200
Current EU specification	2.0	1000	0.0020	0.01	20
Modulated by the Panel	0.5	10,000	0.0050	0.01	50
Modulated by the Panel	0.5	1000	0.0005	0.01	5

TABLE B.2 Estimation of the fraction of the levels of lead in E 415 with respect to the regulatory maximum levels in the final product (powder formulae for infants below 16 weeks of age).

Specification for toxic elements status	Lead (mg/kg)	Use level of food additive in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of toxic element in final product (mg/kg)	Maximum level in Reg. 2023/915 (mg/kg) as sold	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	2.0	10,000	80,000	0.16	0.05	320
Current EU specification	2.0	1000	8000	0.016	0.05	32
Modulated by the Panel	0.5	10,000	80,000	0.04	0.05	80
Modulated by the Panel	0.5	1000	8000	0.004	0.05	8

[a]The maximum levels of food additives set out in Annex II shall apply to the food as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted the maximum levels shall apply to the food as reconstituted according to the instructions on the label taking into account the minimum dilution factor.

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

TABLE B.3 Estimation of the fraction of the levels of cadmium in E 412 with respect to the regulatory maximum levels in the final product (liquid formulae for infants below 16 weeks of age, marketed as powder and manufactured from cow's milk proteins or from cow's milk protein hydrolysates).

Specification for toxic elements status	Cadmium (mg/kg)	Use level of food additive in final product (mg/kg) as reconstituted[a]	Concentration of toxic element in final product (mg/kg)[b]	Maximum level in Reg. 2023/915 (mg/kg)	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	1.0	10,000	0.01	0.005	200
Current EU specification	1.0	1000	0.001	0.005	20
Modulated by the Panel	0.2	10,000	0.002	0.005	40
Modulated by the Panel	0.2	1000	0.0002	0.005	4

[a]The maximum levels of food additives set out in Annex II shall apply to the food as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted the maximum levels shall apply to the food as reconstituted according to the instructions on the label taking into account the minimum dilution factor.

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, online: available at https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the maximum level of 0.01 mg/kg for infant formulae 'marketed as powder and manufactured from soya protein isolates, alone or in a mixture with cow's milk proteins protein', the fraction of toxic elements from the food additive on the ML of the final product would be half of the respective value in the last column.

TABLE B.4 Estimation of the fraction of the levels of cadmium in E 412 with respect to the regulatory maximum levels in the final product (powder formulae for infants below 16 weeks of age, marketed as powder and manufactured from cow's milk proteins or from cow's milk protein hydrolysates).

Specification for toxic elements status	Cadmium (mg/kg)	Use level of food additive in final product (mg/kg)[a]	Use level considering the dilution[b]	Concentration of toxic element in final product (mg/kg)	Maximum level in Reg. 2023/915 (mg/kg)	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	1.0	10,000	80,000	0.08	0.02	400
Current EU specification	1.0	1000	8000	0.008	0.02	40
Modulated by the Panel	0.2	10,000	80,000	0.016	0.02	80
Modulated by the Panel	0.2	1000	8000	0.002	0.02	8

[a]The maximum levels of food additives set out in Annex II shall apply to the food as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted the maximum levels shall apply to the food as reconstituted according to the instructions on the label taking into account the minimum dilution factor.

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, online: available at https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the maximum level of 0.02 mg/kg for 'infant formulae marketed as powder and manufactured from soya protein isolates, alone or in a mixture with cow's milk proteins protein', the fraction of toxic elements from the food additive on the ML of the final product would be half of the respective value in the last column.

TABLE B.5 Estimation of the fraction of the levels of arsenic in E 412 with respect to the regulatory maximum levels in the final product (liquid formulae for infants below 16 weeks of age, marketed as powder and manufactured from cow's milk proteins or from cow's milk protein hydrolysates).

Specification for toxic elements status	Arsenic (mg/kg)	Use level of food additive in final product (mg/kg) as reconstituted[a]	Concentration of toxic element in final product (mg/kg)[b]	Maximum level in Reg. 2023/915 (mg/kg)	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	3.0	10,000	0.03	0.01	300
Current EU specification	3.0	1000	0.003	0.01	30
Modulated by the Panel	0.2	10,000	0.002	0.01	20
Modulated by the Panel	0.2	1000	0.0002	0.01	2

[a]The maximum levels of food additives set out in Annex II shall apply to the food as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted the maximum levels shall apply to the food as reconstituted according to the instructions on the label taking into account the minimum dilution factor.

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, online: available at https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the maximum level of 0.01 mg/kg for infant formulae 'marketed as powder and manufactured from soya protein isolates, alone or in a mixture with cow's milk proteins protein', the fraction of toxic elements from the food additive on the ML of the final product would be half of the respective value in the last column.

TABLE B.6 Estimation of the fraction of the levels of arsenic in E 412 with respect to the regulatory maximum levels in the final product (powder formulae for infants below 16 weeks of age, marketed as powder and manufactured from cow's milk proteins or from cow's milk protein hydrolysates).

Specification for toxic elements status	Arsenic (mg/kg)	Use level of food additive in final product (mg/kg)[a]	Use level considering the dilution[b]	Concentration of toxic element in final product (mg/kg)	Maximum level in Reg. 2023/915 (mg/kg)	Fraction of toxic element from FA on ML of final product ML (%)
Current EU specification	3.0	10,000	80,000	0.24	0.02	1200
Current EU specification	3.0	1000	8000	0.024	0.02	120
Modulated by the Panel	0.2	10,000	80,000	0.016	0.02	80
Modulated by the Panel	0.2	1000	8000	0.0016	0.02	8

[a]The maximum levels of food additives set out in Annex II shall apply to the food as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted the maximum levels shall apply to the food as reconstituted according to the instructions on the label taking into account the minimum dilution factor.

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, online: available at https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the maximum level of 0.02 mg/kg for 'infant formulae marketed as powder and manufactured from soya protein isolates, alone or in a mixture with cow's milk proteins protein', the fraction of toxic elements from the food additive on the ML of the final product would be half of the respective value in the last column.

Considering the results of the above estimations and the fact that the food additive is not the only potential source of toxic elements, the Panel emphasises the need to reduce the specification limit values for lead, cadmium and arsenic in Regulation (EU) no 231/2012.

APPENDIX C

Risk of bias/internal validity for experimental animal studies (modified from to NTP, 2015, 2019) – Template

C.1 | DECISION RULES

The ratings of the key and non-key questions (++, +, –, – –) will be integrated to classify the studies in tiers from 1 to 3 corresponding to decreasing levels of internal validity.

Tier 1:

- All the key questions are scored +/++
  AND
- No more than one non-key question is scored –
  AND
- No non-key question is scored –

Tier 2:

- All the other combinations not falling under tier 1 or 3

Tier 3:

- Any question is scored – –

OR

- More than one key question is scored –

*Indicate the key questions: Q1, Q3, Q4, Q6, Q7.

Number	Question	Domain of bias	Rating (++, +, –, – –)
1*	**Was administered dose or exposure level adequately randomised? (please apply the question also on F1 and F2 generation)** **Key question**	Selection	++ if the method is described and it is adequate + if the authors only indicate that randomisation was done but do not describe the method – no mentioning of randomisation – – direct evidence of no randomisation
2	**Was allocation to study groups adequately concealed?**	Selection	++ properly concealed and described how concealment was performed + mentioning that concealment was performed; + is also appropriate if non-concealment does not influence the outcome – – if non-concealment does influence the outcome (measurements with a subjective part (e.g. preparation of fat pads, observation of behaviour) – – if non-concealment does influence the outcome to a very important part (subjective measurements)
3*	**Were experimental conditions identical across study groups?** **Key question**	Performance	++ experimental conditions described and identical across study groups (feeding, water supply, bedding, day/night cycle; temperature; humidity) + incomplete description of experimental conditions; + is also appropriate if lack of information does not influence the outcome – if lack of information does influence the outcome – – if factors clearly indicate that treatment conditions were different does influence the outcome to a very important part

(Continues)

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Number	Question	Domain of bias	Rating (++, +, –, – –)
4*	**Was the research personnel blinded to the study group? Key question**	Performance	++ if there is direct evidence that the research personnel did not know what group animals were allocated to, and it is unlikely that they could have broken the blinding of allocation
			+ if not reported and lack of adequate allocation concealment could not appreciably affect the handling/outcome of measurements of different study groups (e.g. methods used which do not have a subjective component)
			– if not reported and lack of adequate allocation concealment could appreciably affect the handling/measurement of different study groups (e.g. methods used which have a subjective component)
			– – if there is direct evidence that it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation
5	**Were outcome data complete without attrition or exclusion from analysis?**	Attrition/exclusion	++ There is direct evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study OR Missing data have been imputed using appropriate methods (ensuring that characteristics of animals are not significantly different from animals retained in the analysis)
			+ There is indirect evidence that loss of animals was adequately addressed, and reasons were documented when animals were removed from a study OR It is deemed that the proportion lost would not appreciably bias results. This would include reports of no statistical differences in characteristics of animals removed from the study from those remaining in the study OR There is insufficient information provided about loss of animals (record 'NR' as basis for answer) but it is considered that this does not have an impact on the validity of the study
			– There is indirect evidence that loss of animals was unacceptably large and not adequately addressed (e.g. if unexplained loss is equal or more than 25%) OR There is insufficient information provided about loss of animals (record 'NR' as basis for answer) and it is suspected that this would have an impact on the validity of the study Note: Unexplained inconsistencies between materials and methods and results sections (e.g. inconsistencies in the numbers of animals in different groups) could be an example of indirect evidence
			– – There is direct evidence that loss of animals was unacceptably large and not adequately addressed
6*	**Can we be confident in the exposure characterisation? Key question**	Detection	++ There is direct evidence that the substance was sufficiently described and consistently administered (e.g. with the same method and timeframe) across treatment groups
			+ There is indirect evidence that the substance was sufficiently described and consistently administered (i.e. with the same method and time-frame) across treatment groups OR There is insufficient information provided about description and administration of the substance (record 'NR' as basis for answer) but it is considered that this does not have an impact on the validity of the study
			– There is indirect evidence that the substance was not sufficiently described and was not consistently administered (e.g. with the same method and timeframes) across groups OR There is insufficient information provided about description and administration of the substance (record 'NR' as basis for answer) and it is suspected that this has an impact on the validity of the study

(Continued)

Number	Question	Domain of bias	Rating (++, +, –, – –)
			– – There is direct evidence that the substance was not sufficiently described and/or was not consistently administered (e.g. with the same method and timeframes) across groups
7*	**Can we be confident in the outcome assessment? Key question**	Detection	
		Element 1 Was the outcome assessed at the same length of time (i.e. day and/or time of day) after initial exposure in all study groups? (remember to take into consideration the endpoints assignments) **Element 2** Was a reliable and sensitive animal model used for investigating the test compound and selected endpoints? **Element 3** Was the number of animals per dose group appropriate? **Element 4** Was the number of animals per sex in each cage appropriate for the study type and animal model? **Element 5** Was the timing and duration of administration of the test compound appropriate? **Element 6** Were reliable and sensitive test methods used for investigating the selected endpoints? **Element 7** Were the measurements collected at suitable time points in order to generate sensitive, valid and reliable data?	++ There is direct evidence + It is deemed that deviation would not appreciably bias results. OR There is insufficient information provided, but it is considered that this does not have an impact on the validity of the study – There is insufficient information provided (record 'NR' as basis for answer) and it is suspected that this has an impact on the validity of the study. – – There is direct evidence for a deviation
8	**Were all outcomes measured according to the methodology section reported?**	Selective reporting	++ There is direct evidence that all of the study's measured outcomes (apical and intermediate) outlined in the protocol, methods, abstract and/or introduction that are relevant for the evaluation have been reported This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance
			+ There is indirect evidence that all of the study's measured outcomes (apical and intermediate) outlined in the protocol, methods, abstract and/or introduction that are relevant for the evaluation have been reported. This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not) OR Analyses that had not been planned in advance (i.e. retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the unplanned analyses were appropriate and selective reporting would not appreciably bias results (e.g. appropriate analyses of an unexpected effect) OR There is insufficient information provided about selective outcome reporting (record 'NR' as basis for answer) but it is considered that this does not have an impact on the validity of the study

(Continues)

(Continued)

Number	Question	Domain of bias	Rating (++, +, −, − −)
			− There is indirect evidence that all of the study's measured outcomes (apical and intermediate) outlined in the protocol, methods, abstract and/or introduction that are relevant for the evaluation have not been reported OR There is indirect evidence that unplanned analyses were included that may appreciably bias results OR There is insufficient information provided about selective outcome reporting (record 'NR' as basis for answer) and it is suspected that this has an impact on the validity of the study. Note: Unexplained inconsistencies between materials and methods and results/abstract or summary sections (e.g. inconsistencies in the numbers of animals in different groups) could be an example of indirect evidence
			− − There is direct evidence that not all of the study's measured outcomes (apical and intermediate) outlined in the protocol, methods, abstract and/or introduction that are relevant for the evaluation have not been reported In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data that were not prespecified or reporting outcomes not prespecified, or that unplanned analyses were included that would appreciably bias results
9	**Were statistical methods appropriate?**	Other sources of bias	++ There is direct evidence that the statistical methods seem appropriate and were clearly reported (adequate treatment of multiple testing)
			+ Statistical methods were not clearly reported, but it may be inferred from other information that they were appropriate OR There is insufficient information provided about statistical methods (record 'NR' as basis for answer) but it is considered that this does not have an impact on the validity of the study
			− Statistical methods were not clearly reported but it may be inferred from other information that they were not appropriate OR There is insufficient information provided about statistical methods (record 'NR' as basis for answer) and it is suspected that this has an impact on the validity of the study.
			− − There is direct evidence that the statistical methods applied were inappropriate