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# Re-evaluation of xanthan gum (E 415) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as a food additive for uses in foods for all population groups

EFSA Panel on Food Additives and Flavourings (FAF),
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## Abstract

Xanthan gum (E 415) was re-evaluated in 2017 by the former EFSA Panel on Food Additives and Nutrient sources added to Food. As a follow-up to that assessment, the Panel on Food Additives and Flavourings (FAF) was requested to assess the safety of xanthan gum (E 415) for its uses as a food additive in food for infants below 16 weeks of age belonging to food category (FC) 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. The Panel concluded that the technical data provided by the interested business operators support an amendment of the specifications for E 415 laid down in Commission Regulation (EU) No 231/2012. Due to the low validity of the available clinical studies, the Panel concluded that a reference point could not be derived from them but the results of the available studies on neonatal piglets could serve to derive a reference point. The Panel calculated the margin of exposure for infants below 16 weeks of age consuming food for special medical purposes (FC 13.1.5.1) for the highest xanthan gum exposure and concluded that there are no safety concerns for the use of xanthan gum (E 415) as a food additive in FC 13.1.5.1.



**Keywords:** xanthan gum, E 415, food additive, 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 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 xanthan gum (E 415) as a food additive and the safety in the special sub-population of infants below 16 weeks of age.

The process followed involved the publication of a dedicated call for data allowing all interested business operators (IBOs) to provide the requested information for completing the assessment and to confirm that the additive is used in the food category 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 xanthan gum (E 415) comprised technical information, literature studies (including clinical studies), post marketing surveillance reports and use levels.

Xanthan gum (E 415) is a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with strains of *Xanthomonas campestris*, purified by recovery with ethanol or propan-2-ol, dried and milled. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and pyruvic acid, and is prepared as the sodium, potassium or calcium salt. Its solutions are neutral. Specifications for xanthan gum (E 415) have been defined in Commission Regulation (EU) No 231/2012.

*X. campestris* is a species which is recommended for the qualified presumption of safety (QPS) approach for safety assessment with the qualifications of 'absence of acquired resistances to antimicrobials' and 'for production purposes only'. The later qualification involves that no viable cells remain in the product. None of the production strains reported by the IBOs carried genes conferring acquired resistance to antimicrobials. However, based on the information provided by the IBOs, the absence of viable cells in 1 g of the final product was not demonstrated for the products obtained from some strains. The Panel noted that all strains used to produce xanthan gum (E 415) should meet the requirements of the QPS status, including demonstration of the absence of viable cells.

Upon EFSA request, no data on the particle size distribution were provided by the IBOs for the current assessment. One IBO provided information on the water solubility of E 415 determined by applying OECD Test Guideline (TG) 105 with several modifications needed due to the thickening properties of the food additive. The Panel considers that the outcome of testing for water solubility of E 415 is inconclusive. The Panel noted that in the absence of data no conclusion can be drawn on the presence of small particles including nanoparticles, which cannot be confirmed or excluded in the pristine food additive E 415. The Panel noted that currently no standardised methods are available to measure the particle size distribution or water solubility for the polysaccharide thickening and gelling agents used as food additives and that further research for method development is needed. The Panel noted, however, 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 xanthan gum (E 415). Based on these considerations the FAF Panel concluded that xanthan gum will not be present in the GI-tract in the pristine form taking into account the capacity of xanthan gum to absorb and swell in water, and the volume of fluid in the stomach and GI-tract. Therefore, a conventional risk assessment can be carried out for xanthan gum (E 415).

Dietary exposure to xanthan gum (E 415) for infants below 16 weeks of age from its use as a food additive was assessed based on (1) maximum permitted levels (MPLs) set out in the EU legislation (defined as the regulatory maximum level exposure assessment scenario) and (2) the reported use

levels (defined as the refined exposure assessment scenario). For infants below 16 weeks of age consuming special infant formulae (FC 13.1.5.1), exposure to xanthan gum (E 415) in the regulatory maximum level exposure assessment scenario was estimated at 240 mg/kg body weight (bw) per day for mean consumption while at the high-level consumption was estimated at 312 mg/kg bw per day. Exposure estimates are the same in the refined scenario using the maximum use level reported by industry as this maximum equals the MPL. In the refined estimated exposure assessment scenario using the mean of the reported use levels from industry, exposure estimates for xanthan gum (E 415) were 183 mg/kg bw per day at the mean and 238 mg/kg bw per day at the high level of consumption.

In response to the call for data, analytical data for levels of toxic elements (namely arsenic, lead, cadmium, mercury) in commercial samples of xanthan gum (E 415) were provided by IBOs. Most of the samples were reported as below the limit of determination of the analytical methods used. The highest quantified values reported were lead (Pb) at 0.11, cadmium (Cd) at 0.01, mercury (Hg) at 0.007 and arsenic (As) at 0.1 mg/kg. The Panel agreed that the lowest technologically achievable levels proposed by the IBOs (0.5 mg/kg for each of the 4 elements) were consistent with the occurrence data on these toxic elements, although the distance between the highest limit of quantitation (LOQ) and proposed lowest technologically achievable level for Hg is rather high.

The Panel assessed the risk that would result if the toxic elements were present in E 415, at (i) the current maximum limit in the EU specification and (ii) at the lowest technologically achievable levels proposed by the IBOs for xanthan gum E 415. For the general population, the Panel considered the refined non-brand-loyal exposure scenario to calculate the exposure to the toxic elements from the use of E 415 as calculated in the EFSA ANS Panel opinion from 2017. For infants < 16 weeks of age, the refined (brand loyal) exposure estimates based on the maximum and mean use levels of E 415 reported by industry as calculated in the current scientific opinion. The highest mean and 95th percentile exposure for the population above 16 weeks of age and toddlers (consumers only of food for special medical purposes (FSMP)) were considered as calculated in the EFSA ANS Panel opinion from 2017 at the maximum use level reported by the industry in refined brand loyal scenario.

The resulting figures show that the potential exposure to Pb, Hg and Cd from the consumption of E 415 would not be of concern if these toxic elements would be present in the food additive up to the lowest technologically achievable levels proposed by the IBO. The MOE values for arsenic are very low compared to the value of 1000 which would be considered sufficient. Using the existing EU specification for Pb in xanthan gum (E 415) (2 mg/kg) for these calculations the resulting MOE would not give rise to concern with exception of the highest exposure (95th percentile, maximum use level of E 415) of infants < 16 weeks of age, which shows a borderline MOE value of 0.8.

The Panel calculated the impact of the level of the toxic elements lead and cadmium in the food additive on the final product and compared that with the legal limits for elements in the final infant formula set by Reg. (EC) No 1881/2006. In all cases, the calculations indicate that the final product would comply with the maximum levels set out in Regulation EC No 1881/2006. However, for lead at the current max limit of 2 mg/kg in E 415, the fraction of the limit value in the formula approaches 100% which may lead to exceedance of the limit value considering that the food additive E 415 is not the only potential source of lead. Therefore, the Panel emphasises the need to reduce the specification limit value for lead in Regulation (EU) no 231/2012. The Panel further considers introducing specifications for cadmium, mercury and arsenic.

On the question of residual proteins, data were provided using the Kjeldahl method for total nitrogen and all gum samples were within the EU specification of not more than (NMT) 1.5% nitrogen. No data on levels of residual proteins measured as such in commercial samples of xanthan gum E 415 were submitted. The IBO proposed the continued use of the Kjeldahl method along with the existing 'EC limit value' on total nitrogen. The Panel concurs with this view. The Kjeldahl method should be indicated to be used for the determination of the nitrogen content in E 415.

On the question on the fate and any reaction products of xanthan gum (E 415) in infant formulae, it was stated that the gum has excellent heat stability and is stable in acid, alkaline and high concentration salt solutions. Therefore, no reaction products are to be expected to be present in infant formulae at any significant level. The Panel concurs with this view.

Acceptable data were provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii* in eight samples of xanthan gum E 415. The Panel noted that xanthan gum (E 415) may be prone to microbiological contamination and therefore microbiological specifications set for E 415 should also include Cronobacter (Enterobacter) sakazakii, based on the basis of the information provided.

Furthermore, the Panel noted that no analytical data were provided on the enzymes. The Panel recommends that during the manufacturing process any enzymes potentially present in xanthan gum

E 415 should be inactivated. Therefore, the Panel is of the view that the specifications of E 415 should ensure that the final product must not show any residual enzyme activity.

No new data were provided concerning ADME, acute toxicity, short-term and subchronic toxicity, genotoxicity, chronic toxicity and carcinogenicity and reproductive and developmental toxicity. In the EFSA opinion on 'Re-evaluation of xanthan gum (E 415) as a food additive', special studies in neonatal piglets were described and a no-observed-adverse-effect-level (NOAEL) of 750 mg/kg bw per day was identified based on histopathological changes in the intestine in the high dose group.

For the present evaluation clinical studies in infants below the age of 6 months were submitted. Due to the low validity of the clinical studies, the Panel concluded that a reference point could not be derived from them.

From the available piglet studies a NOAEL of 750 mg/kg bw per day could be derived which could be used for calculation of a MOE. Taking the exposure scenario with the highest exposure of 312 mg/kg bw per day the MOE resulted as 2.4. Given that xanthan gum is not absorbed the toxicokinetic inter- and intraspecies default uncertainty factor can be replaced by a substance specific factor of 1, and given the fact that an infant specific animal model was used the toxicodynamic interspecies default uncertainty factor can be replaced by a specific factor of 1, the Panel considered a MOE of 2.4 as sufficient.

Furthermore, the Panel considered that no concerns were raised by the data from clinical studies of infants from 12 weeks of age onwards and for young children during the re-evaluation of xanthan gum (E 415) and that in the post-marketing studies no adverse events with clinical significance were observed. Despite the absence of appropriate clinical studies, the Panel therefore, concluded that the use of xanthan gum in formulae for infants below 16 weeks of age up to a concentration of 1,200 mg/L, which results in an exposure of 312 mg/kg bw per day does not raise concerns.

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# 1. Introduction

The present opinion deals with:

- the risk assessment of xanthan gum (E 415) in food for infants below 16 weeks of age in the food category (FC) 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 xanthan gum (E 415) as a food additive (EFSA ANS Panel, 2017).

## 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

[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 programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.

[3] See Section 1.1.3.

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

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.

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).

This re-evaluation refers exclusively to the authorised uses of xanthan gum (E 415) as a food additive in food. It does not include a safety assessment of other uses of xanthan gum, such as for ad libitum addition of xanthan gum as a thickening agent to mother's milk or to infant formulae.

## 1.2. Previous evaluations of xanthan gum (E 415)

Xanthan gum (E 415) is authorised as a food additive in the EU according to Annexes II and III of Regulation (EC) No 1333/2008 on food additives and specific purity criteria on xanthan gum (E 415) have been defined in Commission Regulation (EU) No 231/2012.

Xanthan gum was evaluated by the SCF (1978)), when the acceptable daily intake (ADI) of 10 mg/kg body weight (bw) previously established by JECFA (1974)) was endorsed. The SCF did not report details on the toxicological data considered for the evaluation. In 1990, an ADI 'not specified' was allocated (SCF, 1992) 'as the highest possible feeding level was also the no-effect-level (NEL), the Committee considered it justified not to apply the 100-fold safety factor. The Committee was informed that levels in the range of 1–5 g/kg in foods and 0.5 g/L in beverages are usually adequate to obtain the desired technological effects. Based on this, the Committee decided to change the ADI to 'not specified'.

In 1997, the SCF evaluated the use of xanthan gum in foods for special medical purposes for infants and young children. The SCF was informed that xanthan gum may act in combination with guar gum to prevent sedimentation of components. The SCF considered that the use of xanthan gum in foods for special medical purposes for infants and young children is acceptable at levels up to 1.2 g/L (SCF, 1999). Accordingly, xanthan gum is also authorised as food for medical purposes (Annex II to Regulation (EC) No 1333/2008).

In 1986, JECFA reviewed xanthan gum and concluded on an ADI 'not specified' (JECFA, 1987a, 1987b) based on the lack of adverse effects in the available toxicity studies but requested an adequate long-term study in a second rodent species, because of the potential high exposure levels and the fact that xanthan gum is prepared from a microbial source not normally used in food (JECFA, 1987b). In 2016, the Committee concluded that the consumption of xanthan gum in infant formula or formula for special medical purposes intended for infants is of no safety concern at the maximum proposed use

[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.

level of 1,000 mg/L (JECFA, 2016a). According to the recent JECFA evaluation (JECFA, 2016b), a limit of 0.5 mg/kg for lead was introduced for xanthan gum for use in infant formula.

Xanthan gum was reviewed in TemaNord (2002)) who reported that there was no indication for toxic effects from xanthan gum, that there were no mutagenicity studies available and that JECFA requested an adequate long-term study in a second rodent species. TemaNord also indicated that no information on actual use levels was available.

EFSA provides qualified presumption of safety (QPS) assessments for a broad range of microorganisms as sources of food and feed additives, enzymes and plant protection products.[6] A notification referring to the taxonomic unit *Xanthomonas campestris*, only for the production of xanthan gum, was evaluated for QPS status, and recommended for the QPS list based on its long and broad history of safe use in the food industry, lack of implication in human or animal disease (apart from one record) and no indication of acquisition of resistance to antimicrobials in the literature (EFSA BIOHAZ Panel, 2015). *X. campestris*, when used for the production of xanthan gum, was added to the list of QPS recommended biological agents.[7]

In 2010, the EFSA NDA Panel issued an opinion on the scientific substantiation of health claims in relation to xanthan gum and increased satiety (interpreted in this opinion as the decrease in the motivation to eat after consumption of food, leading to a reduction in energy intake). The NDA Panel concluded that a cause and effect relationship had not been established between the consumption of xanthan gum and increased satiety (EFSA NDA Panel, 2010).

In 2011, the EFSA NDA Panel issued an opinion on the scientific substantiation of health claims in relation to xanthan gum and changes in bowel function (such as reduced transit time, more frequent bowel movements, increased faecal bulk or softer stools). The NDA Panel concluded that a cause and effect relationship has not been established between the consumption of xanthan gum and changes in bowel function (EFSA NDA Panel, 2011).

Jelly mini-cups are defined as 'jelly confectionery of a firm consistence, 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'. These jelly mini-cups may contain, among other gelling agents, xanthan gum (E 415). In the past, several EU member States expressed concerns about the safety of these mini-cups because they could pose a hazard for asphyxiation. Subsequently, in 2004, on a request from the European Commission, the EFSA the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC Panel) prepared a scientific opinion related to the use of certain food additives derived from seaweed or non-seaweed origin in jelly mini cups (EFSA AFC Panel, 2004). 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 AFC Panel, 2004). Following this opinion, jelly min-cups were suspended in 2004 by the European Commission to be placed on the market and imported into the EU (Commission Decision 2004/37/EC). The FAF Panel noted that the opinion of the AFC Panel does not question the safety of xanthan gum as an additive, but focusses strictly on the physical characteristics of the jelly min-cups. The use of these additives in jelly mini-cups is not authorised in the EU.

In 2017, the EFSA ANS Panel prepared a scientific opinion on the re-evaluation of xanthan gum (E 415) when used as a food additive in foods for all population groups including infants (EFSA ANS Panel, 2017).

In 2021, the EFSA FEEDAP Panel issued an opinion on the safety of a feed additive consisting of xanthan gum produced using four different strains of the species *X. campestris* (EFSA FEEDAP Panel, 2021). The identity of the strains evaluated at that time was not unambiguously established, data on 'antimicrobial susceptibility' were incomplete, and it was not possible to exclude the presence of viable cells/DNA of the production strains in the additive. The FEEDAP Panel noted that the four production strains did not meet the qualifications for the QPS approach.

[6] A Qualified Presumption of Safety (QPS) status is the result of a pre-assessment that covers safety concerns for humans, animals and the environment. If a microbial strain qualifies for the QPS approach, it is assumed that it does not raise concerns and the safety assessment can be simplified. (see also https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps).

[7] Updated list of QPS-recommended microorganisms for safety risk assessments carried out by EFSA: https://zenodo.org/record/7554079#.ZBA9KnbMKUk

## 1.3. Summary of the previous EFSA re-evaluation of xanthan gum (E 415) for uses in food for all population groups except for infants below 12 weeks of age[8]

Under the frame of Regulation (EC) No 257/2010, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) re-evaluated the safety of xanthan gum (E 415) when used as a food additive (EFSA ANS Panel, 2017).

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

- the available data were adequate for a refined exposure assessment for 25 out of 79 food categories;
- based on the reported use levels, a refined exposure (non-brand-loyal scenario) of up to 64 mg/kg bw per day in children (3–9 years) was estimated;
- a refined exposure assessment for consumers only of this food supplement was also calculated and was up to 38 mg/kg bw per day for children (3–9 years) considering high level exposure (95th percentile);
- xanthan gum is unlikely to be absorbed intact and is expected to be partially fermented by intestinal microbiota;
- adequate toxicity data were available;
- there was no concern with respect to genotoxicity;
- no adverse effects were reported in chronic studies in rats and dogs up to 1,000 mg/kg bw per day, the highest dose tested. In rats, the compound was not carcinogenic;
- repeated oral intake by adults of large amounts of xanthan gum up to 15,000 mg/person per day, corresponding to 214 mg/kg bw per day for at least 10 days was well tolerated, but some individuals experienced abdominal discomfort, which was considered by the Panel as undesirable but not adverse.

The ANS Panel concluded that there is no need for a numerical ADI for xanthan gum (E 415), and that there is no safety concern at the refined exposure assessment for the reported uses and use levels of xanthan gum (E 415) as a food additive.

Concerning the use of xanthan gum (E 415) in 'dietary foods for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and in 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2), and given that:

- for populations consuming foods for special medical purposes and special formulae, the highest refined exposure estimates (P95) on the maximum reported use data from food industry (750 mg/L for categories 13.1.5.1 and 250 mg/L for 13.1.5.2) were up to 115 mg/kg bw per day for infants (12 weeks–11 months, brand loyal scenario);
- in a number of clinical studies, consumption of xanthan gum in infant formula or formula for special medical purposes in infant was well tolerated up to concentration of 1,500 mg/L (232 mg/kg bw per day);
- no cases of adverse effects were reported from post-marketing surveillance with formulae containing xanthan gum at a concentration of approximately of 750 mg/L of reconstituted formula which supported the results of the clinical studies.The ANS Panel concluded, that there is no safety concern from the use of xanthan gum (E 415) in foods for special medical purposes consumed by infants and young children at concentrations reported by the food industry.

In addition, the following recommendation relevant for this evaluation was issued by the ANS Panel:

- the European Commission to consider revising the current limit for toxic element lead in the European Commission specification for xanthan gum (E 415) and adding limits for the impurities of the other toxic elements mercury, cadmium and arsenic in order to ensure that xanthan gum (E 415) as a food additive will not be a significant source of exposure to these toxic elements in food.

[8] According to the EFSA Scientific Committee Guidance (EFSA Scientific Committee, 2017) this opinion will include infants up to 16 weeks of age.

# 2. Data and methodologies

## 2.1. Data

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

- information submitted in response to the EFSA public call for data[9] and the conclusions and recommendations from previous evaluations.
- information from the Mintel Global New Products Database (GNPD) to identify the use of the food additive xanthan gum (E 415) 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 xanthan gum (E 415) for all population groups and to address the data gaps identified during the re-evaluation, the FAF Panel assessed the information provided:

- the risk assessment of xanthan gum (E 415) in food for infants below 16 weeks of age in the food category (FC) 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 xanthan gum (E 415) as a food additive (EFSA ANS Panel, 2017).

Dietary exposure to xanthan gum (E 415) 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 (200 and 260 mL/kg bw per day; EFSA Scientific Committee, 2017; see Section 3.3.3.1), respectively, with the maximum levels according to Annex II and reported use levels submitted to EFSA following a call for data. Different scenarios were used to calculate exposure (see Section 3.3.1). Uncertainties on the exposure assessment were identified and discussed (see Section 3.4.2).

# 3. Assessment

## 3.1. Identity and specifications of E 415

Xanthan gum is a polysaccharide consisting of a backbone of β-(1→4) linked D-glucose molecules, as also found in cellulose. Every second glucose molecule is substituted at C3 with a trisaccharide side chain consisting of β-D-mannose-(1→4)-β-D-glucuronic acid-(1→2)-α-D-mannose. In the side chains, the terminal mannose moiety is partially substituted with a pyruvate residue linked as an acetal to the 4- and 6-positions; the internal mannose unit is acetylated at C-6. The degree of pyruvate substitution varies between 30% and 50%, whereas 60–70% of the internal mannose molecules are acetylated. The pyruvyl and acetyl content depends on the fermentation conditions and the bacterial strain (Sworn, 2009; Draeger et al., 2011; Voragen et al., 2012). Average reported composition of polysaccharides in xanthan gum produced by *X. campestris* bacteria is 30.1% D-glucose, 27.3% D-mannose, 14.9% D-glucuronic acid, 7.1% pyruvate and 6.5% acetate (Garcıa-Ochoa et al., 2000).

Synonyms of xanthan gum are xanthan, polysaccharide B 1459, corn sugar gum.

The structural formula of xanthan gum is presented in Figure 1.

[9] Call for technical and toxicological data on xanthan gum (E 415) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. Available online: https://www.efsa.europa.eu/en/consultations/call/180718-5

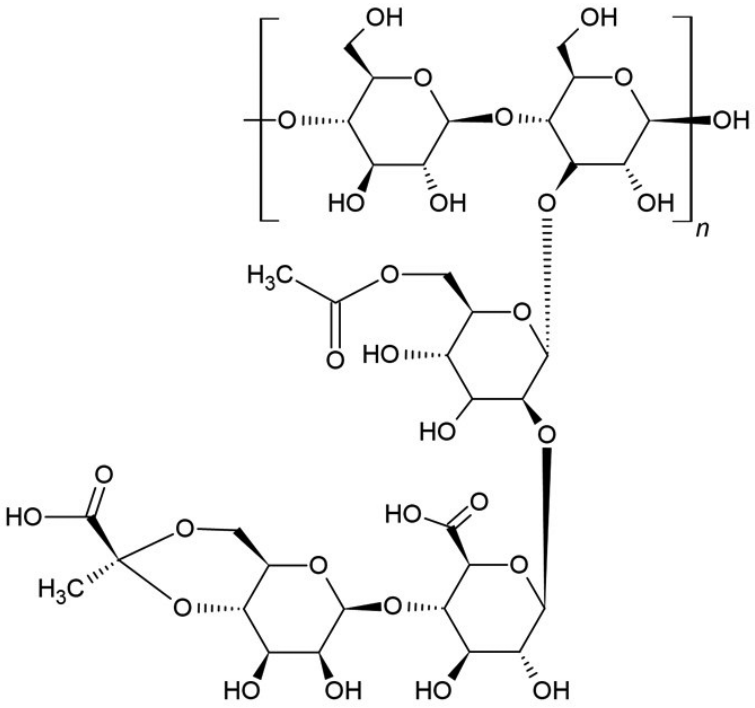

**Figure 1:** Xanthan gum: a polysaccharide composed of glucose, glucuronic acid, 6-acetylmannose and 4,6-pyruvylated mannose (Belsito et al., 2012; EFSA ANS Panel, 2017)

The specifications for xanthan gum (E 415) as defined in the Commission Regulation (EU) No 231/2012 and as proposed by JECFA (2016b) are listed in Table 1.

The Panel noted that the method for nitrogen content determination is provided in the JECFA specifications but not in the EU specifications of E 415.

**Table 1:** Specifications for xanthan gum (E 415) according to Commission Regulation (EU) No 231/2012 and proposed by JECFA (2016b)

| | **Commission Regulation (EU) No 231/2012** | **JECFA (2016b)** |
|---|---|---|
| Definition | Xanthan gum is a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with strains of *Xanthomonas campestris*, purified by recovery with ethanol or propan-2-ol, dried and milled. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and pyruvic acid, and is prepared as the sodium, potassium or calcium salt. Its solutions are neutral. | Xanthan gum is a polysaccharide gum with high molecular weight (of the order of 1,000 kDa) containing D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and pyruvic acid. It is produced by fermentation of a carbohydrate in a pure-culture of *Xanthomonas campestris*, recovered from the fermentation broth by precipitation with ethanol or isopropanol, dried and milled. The final product is manufactured in the form of a sodium, potassium or calcium salt and its solutions are neutral. |
| EINECS | 234-394-2 | |
| CAS number | – | 11138-66-2 |
| Molecular weight | Approximately 1,000,000 | – |
| Assay | Yields, on dried basis, not less than 4.2% and not more than 5% of $CO_2$ corresponding to between 91% and 108% of xanthan gum | Yields, on the dried basis, not less than 4.2% and not more than 5.4% of carbon dioxide ($CO_2$), corresponding to between 91% and 117%, respectively, of xanthan gum. |

| | Commission Regulation (EU) No 231/2012 | JECFA (2016b) |
|---|---|---|
| Description | Cream-coloured powder | Cream-coloured powder |
| Functional uses | – | Thickener, stabiliser, emulsifier, foaming agent |
| **Identification** | | |
| Solubility | Soluble in water. Insoluble in ethanol | Soluble in water. Insoluble in ethanol |
| Gel formation | – | To 300 mL of water, previously heated to 80° and stirred rapidly with mechanical stirrer in a 400-mL beaker, add, at the point of maximum agitation, a dry blend of 1.5 g of the sample and 1.5 g of carob bean gum. Stir until the mixture goes into solution, and then continue stirring for 30 min longer. Do not allow the water temperature to drop below 60° during stirring. Discontinue stirring, and allow the mixture to cool at room temperature for at least 2 h. A firm rubbery gel forms after the temperature drops below 40°, but no such gel forms in a 1% control solution of the sample prepared in the same manner but omitting the carob bean gum. |
| **Purity** | | |
| Loss on drying | Not more than 15% (105°C, 2.5 hours) | Not more than 15% (105°, 2.5 h) |
| Total ash | Not more than 16% on the anhydrous basis determined at 650°C after drying at 105°C for four hours | Not more than 16% after drying |
| Pyruvic acid | Not less than 1.5% | Not less than 1.5%[(a)] |
| Nitrogen | Not more than 1.5% | Not more than 1.5% (Kjeldahl)[(a)] |
| Ethanol and propan-2-ol | Not more than 500 mg/kg singly or in combination | Not more than 500 mg/kg of ethanol and isopropanol either singly or in combination[(a)] |
| Lead | Not more than 2 mg/kg | Not more than 2 mg/kg[(a)] Not more than 0.5 mg/kg for use in infant formula and formula for special medical purposes intended for infants. |
| **Microbiological criteria** | | |
| Total plate count | Not more than 5,000 colonies per gram | Not more than 5,000 CFU/g[(a)] |
| Yeast and moulds | Not more than 300 colonies per gram | Not more than 500 CFU/g[(a)] |
| *Escherichia coli* (*E. coli*) | Absent in 5 g | Negative by test[(a)] |
| *Salmonella* spp. | Absent in 10 g | Negative by test[(a)] |
| *Xanthomonas campestris* | Viable cells absent in 1 g | – |

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

(a): Note: 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, 2004, 2016a,b). These method details are omitted here for reasons of brevity and clarity.

The revisions of the existing EU specifications proposed by the Panel are provided under Section 3.4.

## 3.2. Technical data submitted

In the response to the call for data, IBOs submitted data on the level of toxic elements and residual proteins in commercial samples of xanthan gum (E 415) (Documentation provided to EFSA n. 1–5). Further on a request of EFSA one IBO provided information on the solubility of the xanthan gum E 415 (Documentation provided to EFSA n. 11) and further IBOs provided information on the strains of *X. campestris* used in the production process of xanthan gum used as a food additive E 415 (Documentation provided to EFSA n. 5–10). The IBOs provided also additional information required in the call for data for the risk assessment of xanthan gum (E 415) for uses in foods for infants below 16 weeks of age.

### 3.2.1. Characterisation of the production strains

The production organisms for xanthan gum are all identified as *X. campestris*, a species which is recommended for the QPS status with the qualifications 'should not harbour any acquired antimicrobial resistance genes to clinically relevant antimicrobials' and 'for production purposes only', which implies the absence of viable cells in the product (EFSA BIOHAZ Panel, 2023).

The following strains were declared by the IBOs and none of them are genetically modified:

*X. campestris* [redacted]

The microorganism strain used in the production of xanthan gum (production strain) *X. campestris* [redacted] was obtained from [redacted]. No proof was provided that *X. campestris* [redacted] is deposited in an internationally recognised public culture collection. No analysis was provided on the identity of the production strain at the species level. The whole genome sequence (WGS) of the strain was interrogated for the presence of acquired antimicrobial resistance genes using one maintained database with thresholds of 80% identity and 60% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

The Panel noted that as no proof was provided that *X. campestris* [redacted] is deposited in an internationally recognised public culture collection, a verification of the strain independently from the IBO would not be possible.

*X. campestris* [redacted]

The production strain [redacted] was obtained from strain [redacted]. The production strain was deposited in an official microorganism culture collection ([redacted]). The strain was identified as *X. campestris* by WGS sequence analysis, with an average nucleotide identity (ANI) of 98.64% with respect to the type strain *X. campestris* [redacted]. The WGS of the strain was interrogated for the presence of virulence and acquired antimicrobial resistance genes using several maintained databases with thresholds of 80% identity and 80% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted], was obtained from [redacted]. The production strain was deposited in an official microorganism culture collection ([redacted]). The strain was identified as *X. campestris* by WGS sequence analysis, with an ANI of 98.68% with respect to the type strain *X. campestris* [redacted]. The WGS of the strain was interrogated for the presence of virulence and acquired antimicrobial resistance genes using several maintained databases with thresholds of 80% identity and 80% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] is deposited in an official microorganism culture collection ([redacted]). The strain was identified as *X. campestris* by WGS sequence analysis, with an ANI of 97.3% with respect to the reference strain *X. campestris* [redacted]. The WGS of the strain was interrogated for the presence of acquired antimicrobial resistance genes using two maintained

databases with thresholds of 80% identity and 60% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] is deposited in an official microorganism culture collection ([redacted]). It was obtained [redacted] from the parental strain *X. campestris* [redacted] The strain was identified as *X. campestris* by phylogenomic analysis. The WGS of the strain was interrogated for the presence of acquired antimicrobial resistance genes using two maintained databases with thresholds of 80% identity and 60% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] is deposited in an official microorganism culture collection [redacted]. It was obtained [redacted] from the parental strain *X. campestris* [redacted]. The strain was identified as *X. campestris* by phylogenomic analysis. Given its phylogenetic proximity with the production strain [redacted] as demonstrated by phylogenomic analysis, the results of the search for acquired antimicrobial resistance genes provided for strain [redacted] can be extended to strain [redacted] (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] is deposited in an official microorganism culture collection ([redacted]). The strain was identified as *X. campestris* by phylogenomic analysis. The WGS of the strain was interrogated for the presence of acquired antimicrobial resistance genes using two maintained databases with thresholds of 80% identity and 60% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] was obtained from *X. campestris* [redacted]. The strain is deposited in an official microorganism culture collection ([redacted]). *X. campestris* [redacted] was identified as *X. campestris* by WGS analysis, showing an ANI of 94% and a digital DNA–DNA hybridisation (dDDH) identity of 88% with respect to the type strain *X. campestris* [redacted]. The WGS of the strain was interrogated for the presence of acquired antimicrobial resistance genes using two maintained databases with thresholds of 30% identity and 50% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris* [redacted]

The production strain [redacted] was obtained from *X. campestris* [redacted]. The strain is deposited in an official microorganism culture collection ([redacted]). *X. campestris* [redacted] was identified as *X. campestris* by WGS analysis, showing an ANI of 91.7% and a dDDH identity of 87.6% with respect to the type strain [redacted]. The WGS of the strain was interrogated for the presence of acquired antimicrobial resistance genes using two maintained databases with thresholds of 30% identity and 50% length and no match was found (Documentation provided to EFSA n. 5, 8 and 9).

*X. campestris BX12*

The production strain BX12 is [redacted] deposited in an official microorganism culture collection [redacted] The strain was identified as *X. campestris* by WGS analysis, showing an ANI value of 98.9% with respect to the type strain *X. campestris* ATCC 33913. The WGS of the strain was interrogated for the presence of virulence and acquired antimicrobial resistance genes using several maintained databases with thresholds of 80% identity and 80% length and no match was found (Documentation provided to EFSA n. 6, 7 and 10).

*X. campestris BX32*

The production strain BX32 was obtained from strain BX12 described above [redacted] and selection [redacted]. *X. campestris* BX32 is deposited in an official culture collection ([redacted]). The strain was identified as *X. campestris* by WGS analysis, showing an ANI value of 98.9% with respect to the type strain *X. campestris* ATCC 33913. The WGS of the strain was interrogated for the presence of virulence and acquired antimicrobial resistance genes using several maintained databases with thresholds of 80% identity and 80% length and no match was found (Documentation provided to EFSA n. 6, 7 and 10).

Based on the information provided by the IBOs, the Panel noted that the requirement for absence of viable cells in the final product tested in 1 g according to the most recent version of the appropriate EFSA Guidance (currently the EFSA CEP Panel, 2021) was not proved for the products obtained from the strains [redacted].

### 3.2.2. 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.

One IBO provided information on the content of lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) in 26 batches of E 415 produced by five member companies (Documentation provided to EFSA n. 1 and 4). No information was provided on the production dates of the different batches. A number of analytical methods/variations were used, mainly based on inductively coupled plasma mass spectrometry (ICP-MS) but some using atomic absorption spectroscopy (AAS). The methods were briefly described, and their respective LOQ were provided. For Pb, the LOQs were reported in the range of 0.004 to 0.5 mg/kg; 20 of the 26 analysed batches were reported to be < LOQ and the remaining six batches were reported to be 0.06, 0.06, 0.07, 0.08, 0.09 and 0.11 mg/kg. For Cd, the LOQs were reported in the range of 0.004–0.3 mg/kg; 18 of the analysed batches were reported as < LOQ and the remaining 8 batches were reported to be 0.005, 0.007, 0.008, and 5 batches at 0.01 mg/kg. For Hg, the LOQ were reported in the range of 0.004 to 0.01 mg/kg, 25 batches were reported as < LOQ and the remaining 1 batch was at 0.007 mg/kg. For As, the LOQs were reported in the range of 0.004 to 0.1 mg/kg; 24 of the batches were reported as < LOQ and the remaining 2 batches were both at 0.1 mg/kg. (Documentation provided to EFSA n. 1 and 4).

The Panel noted that, due in part to the variety of analytical methods used, there were wide differences in the LOQ values reported by the different member companies of the association of IBOs. This was especially the case for Pb and Cd (being about a 100-fold range in LOQ values), still marked for As (being 25-fold) and less so for Hg (being a 2.5-fold range).

One IBO reported that the xanthan gum intended for use as a food additive E 415, is also supplied for pharmaceutical use and as such it must meet specifications in the European Pharmacopoeia (EP). The EP stipulates the methods to be used for analysis for toxic elements which are based on AAS which has higher (inferior) detection limits compared to ICP-MS. The IBO further states that for AAS based methods the LOQs for Pb, Cd, Hg and As by AAS are typically 1, 0.1, 0.1 and 1 mg/kg, respectively. The IBO stated that producers of E 415 test according to the EP method (Documentation provided to EFSA n. 4).

The IBO further stated that the lowest technological achievable levels of toxic elements in E 415 depends on their content in the raw materials and the process aids that are used in the manufacturing process. Currently, there is no specific step in the production process of xanthan gum to actively reduce levels of any toxic elements. The IBO proposed the lowest achievable levels for Pb, Cd, Hg and As to be each at 0.5 mg/kg (Table 2) for E 415 intended for use in all foods (i.e. including formulae) and for all age groups (i.e. including infants).

**Table 2:** Lowest technologically achievable levels for the toxic elements lead, mercury, cadmium and arsenic in commercial E 415 for all population groups including infants below 16 weeks of age, as proposed by an IBO (Documentation provided to EFSA n. 4)

| Lead | Mercury | Cadmium | Arsenic |
|---|---|---|---|
| 0.5 mg/kg | 0.5 mg/kg | 0.5 mg/kg | 0.5 mg/kg |

Another IBO stated that Reg. (EC) No 1881/2006 sets a maximum limit on lead at 0.01 mg/kg in liquid infant formula. At a use level of xanthan gum of 1,200 mg/L (this being the MPL) and at 0.5 mg/kg specification value proposed for lead in xanthan gum E 415, lead would contribute at 6% of the Pb maximum limit in the final product as sold (Documentation provided to EFSA n. 4).

### 3.2.3. Residual proteins

The following was requested in the EFSA call for data:

- analytical data on current levels of residual proteins in commercial samples of the food additive;
- the lowest technologically achievable level for residual proteins in order to adequately define their maximum limits in the specifications.

No data on levels of residual proteins measured as such in commercial samples of xanthan gum (E 415) were submitted.

One IBO stated that the nitrogen content of xanthan gum is typically ca. 1% and batches tested over time (not specified) were in the range of 0.26–1.5% of total nitrogen (Documentation provided to EFSA n. 1).

The IBO explained that the Kjeldahl method is used by producers to test for compliance with the EU specifications for total nitrogen in xanthan gum (i.e. not more than 1.5%, see Table 1) and that no member of the IBO association has methods in-house allowing a more specific protein/amino acid analysis. The IBO reported that 26 samples of xanthan gum had been sent to external laboratories for protein determination based on total amino acid analysis, after hydrolysis. For the 26 samples analysed, the sum of amino acids in the xanthan gum was in the range 0.5 to 7.1% w/w. Seven of these 26 samples were also analysed by the Kjeldahl method for total nitrogen and the protein content was calculated by multiplying the Kjeldahl total-N results by the conventional factor of 6.25 (to convert total nitrogen w/w to protein equivalents w/w). For the seven samples analysed using both methods, the sum of amino acids was in the range 52 to 84% (mean of 64%) of the 'Kjeldahl protein' results, suggesting that proteins contributed approximately two-thirds of the total nitrogen present in the xanthan gum samples (Documentation provided to EFSA n. 4). Additionally, the IBO reported that a further four samples were tested for total Kjeldahl nitrogen alone. These four samples along with the aforementioned seven samples (tested by Kjeldahl and for amino acids) were in the range of 0.6 to 1.3% total nitrogen, so all 11 samples were within the EU specifications of not more than (NMT) 1.5% nitrogen when analysed using the Kjeldahl method (Documentation provided to EFSA n. 4).

The Panel noted that the sample with the highest result (i.e. 7.1% w/w total amino acid content) was one of the seven batches analysed by the Kjeldahl method and the total-N content was 1.34%, which complies with the EU specifications for total nitrogen at NMT 1.5% established for xanthan gum (E 415).

Regarding enzymes (being proteins) the IBO stated that there is no evidence of oxidases or peroxidases in xanthan gum. During the fermentation process, the bacteria produce enzymes (i.e. amylases, cellulases or protease). However, according to the IBO, producers reduce the presence of enzymes as much as possible or deactivate them through the manufacturing process. The IBO further stated that any residual enzyme activities would not impact the properties of xanthan gum as such and its safety (Documentation provided to EFSA n. 1). The Panel noted that the IBO did not provide any data to support this statement.

No information was provided by the IBOs with regard to the lowest technologically achievable level for residual proteins requested in the call.

The IBO proposed the continued use of the Kjeldahl method along with the existing limit value on total nitrogen (i.e. NMT 1.5%, Table 1) arguing that alternative methods (for proteins) validated for xanthan gum are not generally available and are not needed, since no evidence of sensitivity to xanthan gum has been reported that would necessitate a more specific test for proteinaceous material

(Documentation provided to EFSA n. 4). The Panel acknowledges that using the Kjeldahl method is appropriate.

### 3.2.4. Solubility

On a request from EFSA, one IBO provided results of the determination of water solubility of E 415 at 30°C. The analysis was performed following the OECD Test Guideline (TG) 105 (shake flask) method with some modifications resulting necessary due to the thickening properties of the xanthan gum. Four concentrations 1%, 2%, 3.3%, 4% of xanthan gum E 415 were tested on 24 h, 48 h and 72 h. During the visual inspection no particles were identified, and the samples were opaque (higher opacity was observed for higher concentrations tested). Centrifugation was applied on these samples. Speed rotation was set at the highest value allowed by the centrifuge 13,000 rpm (16,060 g). No significant changes were observed on aliquots after centrifugation. The aliquots were further diluted to reach the concentration until 0.05% required by the internal method of analysis, these dilutions were filtered with a syringe filter 0.45 μm to prepare vials for injection. The concentration of the recovered xanthan gum was determined by size-exclusion chromatography (SEC). As stated by the IBO the recovery average of the 3 days, based on the results at the highest concentration tested at 4%, 87.9% of xanthan gum powder i.e. 92.8% of dry xanthan gum was solubilised (Documentation provided to EFSA n. 11).

The same IBO provided further information on the relationship between the concentration of xanthan gum (E 415) and its viscosity in water (Documentation provided to EFSA n. 11). The analysis was performed on three E 415 batches at different concentrations from 15 up to 33.3 g/L at 23–25°C demonstrating a linear relationship between concentration and viscosity of E 415.

The Panel considers that the reported results do not allow conclusion on the water solubility of E 415. The Panel acknowledges the IBOs' difficulty in testing, and stresses that currently no standardised methods are available for the polysaccharide thickening and gelling agents used as food additives, such as xanthan gum (E 415) to measure the water solubility.

The Panel notes that E 415 is a hydrophilic macromolecule which in water forms a colloidal dispersion in which the macromolecules and/or polymolecular particles are dispersed throughout the liquids (e.g. 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.

### 3.2.5. Particle size distribution

No data on the particle size distribution were submitted in response to the EFSA request. The IBOs stated that they encountered serious technical challenges with identifying a suitable method for the particle size characterisation of E 415 according to the requirements of the EFSA SC Guidance – TR (Documentation provided to EFSA n. 12).

The Panel acknowledges the IBOs' difficulty and stresses that currently no standardised methods are available for the polysaccharide thickening and gelling agents used as food additives, such as xanthan gum (E 415) to measure the particle size distribution.

### 3.2.6. Information required for the risk assessment of xanthan gum (E 415) for uses in foods for infants below 16 weeks of age

The following was requested in the EFSA call for data:

- information on the fate and the reaction products of xanthan gum (E 415) in special formulae used for infants below 16 weeks of age under special medical conditions;
- information on particular specification requirements for identity and the purity of xanthan gum (E 415) (e.g. with respect to levels of protein residues; content of toxic elements, propan-2-ol/ ethanol) for special formulae used for infants below 16 weeks of age under special medical conditions. 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* in the food additive.

Three IBOs provided information requested in the call for data.

The IBOs did not provide data on the fate and the reaction products of xanthan gum (E 415) in special formulae used for infants below 16 weeks of age under special medical conditions. One IBO

reported that xanthan gum has good heat stability, is stable in acid, alkaline and high concentration salt solutions, and does not react with ingredients that are typically found in foods. The IBO stated that, based on these characteristics, there are no reaction products expected to be present in infant formulae at any significant level. The Panel noted that no evidence was provided to support the IBO statement (Documentation provided to EFSA n. 3).

Regarding the specifications for xanthan gum used for special formulae intended for infants below 16 weeks of age under special medical conditions, one IBO stated that there are no special requirements on purity criteria for xanthan gum E 415 intended for infant formulae/food (Documentation provided to EFSA n. 4).

One IBO provided data of the analysis for *Cronobacter (Enterobacter) sakazakii* in eight samples of xanthan gum E 415. All eight samples were negative (Documentation provided to EFSA n. 3). Three samples were tested by the ISO TS 22964 method (results: not detected in 1 g). Three samples were tested by the FDA BAM Chapter 29 method (results: negative in 25 g). Two samples tested by ISO 22964:2017 – enrichment method (results: absent in 10 g).

One IBO provided analytical data on lead and cadmium on 29 batches of infant formula powder (food category 13.1.5.1) formulated using E 415 (Documentation provided to EFSA n. 2). Lead and cadmium were reported as below the LOD of < 0.01 mg/kg for each element of the method used. The Panel noted that, based on these results the formula powder containing xanthan gum would meet the maximum limits for lead and cadmium set in Reg. (EC) No 1881/2006. The IBO did not provide any information on other impurities for which no legal limits have been established.

The IBO further stated that various products (FC 13.1.5.1) 'commercialised and/or clinically tested' contained xanthan gum up to 1,200 mg/L in the formula as consumed.

## 3.3. Exposure assessment

### 3.3.1. Authorised uses and use levels

Maximum levels of xanthan gum (E 415) 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, xanthan gum (E 415) is authorised in foods for infants below 16 weeks of age in 'Dietary foods for infants for special medical purposes and special formulae for infants' (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), see Table 3. Xanthan gum (E 415) is not authorised in FCs 13.1.1 and 13.1.2.

**Table 3:** MPLs of xanthan gum (E 415) 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) |
|---|---|---|---|---|
| 13.1.5.1 | Dietary foods for infants for special medical purposes and special formulae for infants | E 415 | From birth onwards for use in products based on amino acids or peptides for use with patients who have problems with impairment of the gastrointestinal tract, protein mal-absorption or inborn errors of metabolism | 1,200 |
| 13.1.5.2 | Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC | E 415 | From birth onwards for use in products based on amino acids or peptides for use with patients who have problems with impairment of the gastrointestinal tract, protein mal-absorption or inborn errors of metabolism | 1,200 |

MPL: maximum permitted level.

Xanthan gum (E 415) is not authorised to be added in nutrients intended to be used in foodstuffs for infants and young children according to Annex III, Part 5, Section B to Regulation No 1333/2008, except in nutrients preparations for the food categories 'Processed cereal based foods and baby foods for infants and young children as defined by Directive 2006/125/EC' (FC 13.1.3), under the conditions that the maximum level in foods mentioned in point 13.1.3 of Part E of Annex II is not exceeded.

### 3.3.2. Exposure data

Some food additives are authorised in the EU in infants' 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 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[10] for technical and toxicological data on xanthan gum (E 415) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. In response to this public call, information on the actual use levels of xanthan gum (E 415) in foods was made available to EFSA by industry. No analytical data on the concentration of xanthan gum (E 415) in foods were made available by the Member States.

#### 3.3.2.1. Reported use levels in food category 13.1.5.1

Two IBOs provided EFSA with 4 use levels of xanthan gum (E 415) in the food category 13.1.5.1 'Dietary foods for infants for special medical purposes and special formulae for infants' (Documentation provided to EFSA n. 2, 14). According to these IBOs, xanthan gum (E 415) is used at levels up to the MPL of 1,200 mg/L for FC 13.1.5.1 (as consumed). The four examples of special formulae (e.g. for infants suffering from cow's milk protein allergy) containing xanthan gum (E 415) were also reported to contain another thickener (pectins (E 440) or starch sodium octenyl succinate (E 1450)).

#### 3.3.2.2. Summarised data extracted from the Mintel Global New Products Database

The Mintel GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 4.0 million food and beverage products of which more than 1,200,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 24 out of its 27 member countries, and Norway presented in the Mintel GNPD.[11]

For the purpose of this Scientific Opinion, the Mintel GNPD[12] was used for checking the labelling of food and beverage products and food supplements for xanthan gum (E 415) within the EU's food market as the database contains the compulsory ingredient information on the label.

No products were found in the Mintel GNPD as labelled with xanthan gum (E 415) between January 2018 and January 2023. The additive is authorised for direct use (Annex II) in food for special medical purposes (FSMP) for infants below 16 weeks (FC 13.1.5.1) and for babies and young children above 16 weeks of age (FC 13.1.5.2) which products are most probably available from specialised outlets (e.g. pharmacy) not covered by the Mintel GNPD.

### 3.3.3. Exposure estimates

#### 3.3.3.1. Exposure estimates for infants below 16 weeks from FSMP formulae

Exposure to xanthan gum (E 415) from its uses as a food additive in FSMP formulae (FC 13.1.5.1) for infants below 16 weeks was estimated. 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[13]/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

[10] Call for technical and toxicological data on xanthan gum (E 415) as a food additive for uses in foods for all population groups including infants below 16 weeks of age.Available online: https://www.efsa.europa.eu/sites/default/files/consultation/callsfordata/180718_xanthan.pdf

[11] Missing Cyprus, Luxembourg and Malta.

[12] https://www.gnpd.com/sinatra/home/ accessed on 17 January 2023.

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

in food intended for infants below 16 weeks of age'. These recommended consumption levels correspond to 14–27 days old infants consumption. For the regulatory maximum level exposure assessment scenario, MPLs for FSMP (1,200 mg/kg for FC 13.1.5.1) were used. For the refined scenario, reported use levels (maximum and mean) were considered.

Table 4 summarises the estimated exposure to xanthan gum (E 415) from its use as a food additive in FC 13.1.5.1 for infants below 16 weeks of age.

**Table 4:** Dietary exposure to xanthan gum (E 415) in infant formulae (FC 13.1.5.1) for infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008 (in mg/kg bw per day)

| | **Infants (< 16 weeks of age)** |
|---|---|
| **Regulatory maximum level exposure assessment scenario (1,200 mg/kg)** | |
| • Mean consumption (200 mL formula/kg bw per day) | 240 |
| • High-level consumption (95th percentile, 260 mL formula/kg bw per day) | 312 |
| **Refined estimated exposure assessment scenario** | |
| **Scenario using maximum use level reported by industry (1,200 mg/kg)** | |
| • Mean consumption (200 mL formula/kg bw per day) | 240 |
| • High-level consumption (95th percentile, 260 mL formula/kg bw per day) | 312 |
| **Scenario using mean of use levels reported by industry (916 mg/kg)** | |
| • Mean consumption (200 mL formula/kg bw per day) | 183 |
| • High-level consumption (95th percentile, 260 mL formula/kg bw per day) | 238 |

bw: body weight.

### 3.3.4. Uncertainty analysis

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of 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: one reference point only to estimate exposure during the period of up to 16 weeks of age | +/– |
| **Regulatory maximum level exposure assessment scenario:** | |
| – exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008 | + |
| **Refined exposure assessment scenarios:** | |
| – exposure calculations based on the maximum level (reported use from industries) | + |
| – exposure calculations based on the mean level (reported use from industries) | +/– |

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

Xanthan gum (E 415) is authorised in food categories 13.1.5.1 and 13.1.5.2 according to Annex II to Regulation (EC) No 1333/2008.

There is uncertainty around the consumption values used and the typical and maximum levels reported by industry and used in the calculations, since the actual formula consumption and related additive use levels in that formula 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). In contrast, the levels used in the MPL scenario cannot legally be exceeded and this means that the uncertainty is one-sided. The actual use levels cannot legally be higher (so there is no uncertainty in that direction that could give rise to a potential for overestimation of exposure) but actual use levels (and so exposure) could be lower. The consequence of this one-sided uncertainty is that assuming use levels are all at the MPL has the potential to overestimate exposure (+, Table 5).

Irrespective of these uncertainties, based on the assumption that carers of children who have problems with impairment of the gastrointestinal tract, protein mal-absorption or inborn errors of metabolism would be brand-loyal to an infant formula for special medical purposes (FC 13.1.5.1) that suits this medical condition, the refined scenario using the maximum use level reported by industry (Table 4) would in general result in a reliable estimation of exposure for infants below 16 weeks of age.

## 3.4. Proposed revision to existing EU Specifications for xanthan gum E 415

The potential exposure to impurities from the use of the food additive E 415 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.

In the current opinion, the dietary exposure for infants below 16 weeks of age was estimated (see Section 3.3.3). The refined exposure estimates based on the maximum and mean use levels of E 415 reported by industry (Table 4) were considered. The mean and 95th percentile exposure estimates were 240 and 312 mg/kg bw per day for the maximum use level and 183 and 238 mg/kg bw per day for the mean use level reported.

For the infants above 16 weeks and toddlers, the dietary exposure to xanthan gum (E 415) for consumers only of FSMP was considered as calculated in the re-evaluation of the food additive (EFSA ANS Panel, 2017) at the maximum use level reported by the industry (750 mg/L for categories 13.1.5.1 and 250 mg/L for 13.1.5.2) and the highest mean and 95th percentile estimates were 41 and 115 mg/kg bw per day for toddlers and infants above 16 weeks to 1 year of age (in EFSA ANS Panel opinion as for 12 weeks to 1 year of age), respectively.

With regard to the dietary exposure to the food additive for the general population, the Panel considered also the exposure calculations for E 415 as presented in the re-evaluation of the food additive (EFSA ANS Panel, 2017). The ANS Panel did not identify brand loyalty to a specific food category and therefore the Panel considered that the non-brand-loyal scenario covering the general population was the more appropriate and realistic scenario for the use of xanthan gum (E 415) as a food additive. Therefore, for current assessment the Panel considered as the worst case for all age groups the highest mean and 95th percentile exposure which was calculated for toddlers to be 40 mg/kg bw per day and children 64 mg/kg bw per day, respectively (EFSA ANS Panel, 2017).

The level of the impurity in the food additive combined with the estimated or potential intakes of E 415, 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 415.

**Table 6:** Reference points/health-based guidance values for impurities potentially present in E 415

| Impurity<br>HBGV/RP (μg/kg bw) | Basis/Reference |
|---|---|
| Lead (Pb)/<br>0.5 ($BMDL_{01}$) | 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).<br>EFSA CONTAM Panel (2010) |
| Mercury (Hg)/<br>4 (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 intraspecies differences, with conversion to a weekly basis and rounding to one significant figure, a TWI for inorganic mercury of 4 μg/kg bw, expressed as mercury was established.<br>EFSA CONTAM Panel (2012) |
| Cadmium (Cd)/<br>2.5 (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 (B2M) as the biomarker of tubular damage recognised as the most |

| Impurity HBGV/RP (μg/kg bw) | Basis/Reference |
|---|---|
| | 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 CONTAM Panel (2009a) |
| Arsenic (As)/ 0.3–8 ($BMDL_{01}$) | The reference point is based on a range of benchmark dose lower confidence limit ($BMDL_{01}$) values between 0.3 and 8 μg/kg bw per day identified for cancers of the lung, skin and bladder, as well as skin lesions. In general, the MOE should be at least 10,000 if the reference point is based on carcinogenicity in animal studies. However, as the BMDL for As is derived from human studies, an interspecies extrapolation factor (i.e. 10) is not needed, i.e. a MOE of 1,000 would be sufficient. EFSA CONTAM Panel (2009b), EFSA Scientific Committee (2012) |

HBGV: health-based guidance value; RP: reference point; $BMDL_{01}$: benchmark dose (lower confidence limit); TWI: tolerable weekly intake; MOE: margin of exposure.

The risk assessment of undesirable impurities helps inform 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 Table 6) by the exposure estimate (Table 4 and EFSA ANS Panel, 2017), or by estimating the contribution of the use of E 415 to the HBGV (expressed as a percentage of the HBGV).

### 3.4.1. Toxic elements

The Panel noted that the occurrence data on lead submitted by the IBO (Documentation provided to EFSA n. 1,4) are substantially lower than the current limit of 2 mg/kg for Pb in the EU specifications. There are currently no limits for the content of Hg, Cd and As in the EU specifications E 415.

The highest quantified results for the 26 commercial batches of E 415 that were analysed and reported by IBO were; lead at 0.11, cadmium at 0.01, mercury at 0.007 and arsenic at 0.1 mg/kg (Section 3.2.2). The IBO proposed lowest technologically achievable levels for lead, mercury, cadmium and arsenic at 0.5 mg/kg for each (Table 2).

The Panel noted that the limit values of 0.5 mg/kg proposed by the IBO are consistent with the analytical data and LOQ values reported, although the lowest achievable level that was proposed by IND is way above (50 fold) the highest LOQ for Hg.

The Panel performed the risk assessment that would result if these toxic elements were present in E 415, at (i) the current maximum limit for Pb in the EU specifications and (ii) at the lowest technologically achievable levels proposed by the IBOs for xanthan gum E 415.

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 Pb would be present in the food additive at the current maximum limit in the EU specification, and if Pb, Hg, Cd and As would be present in the food additive at the lowest technologically achievable levels proposed by the IBO.

**Table 7:** Risk assessment for toxic elements

| Exposure to E 415 (mg/kg bw per day) | (i) Based on the current EU specifications limits for toxic elements in E 415 for use in food for all age groups | | | |
|---|---|---|---|---|
| | MOE for Pb at 2 mg/kg | % of the TWI for Hg[(a)] | % of the TWI for Cd[(a)] | MOE for As[(a)] |
| 240[(b)] | 1.04 | – | – | – |
| 312[(c)] | 0.8 | – | – | – |
| 183[(d)] | 1.37 | – | – | – |

| Exposure to E 415 (mg/kg bw per day) | (i) Based on the current EU specifications limits for toxic elements in E 415 for use in food for all age groups | | | |
|---|---|---|---|---|
| | MOE for Pb at 2 mg/kg | % of the TWI for Hg[(a)] | % of the TWI for Cd[(a)] | MOE for As[(a)] |
| 238[(e)] | 1.05 | – | – | – |
| 41[(f)] | 6.10 | – | – | – |
| 115[(g)] | 2.17 | – | – | – |
| 40[(h)] | 6.25 | – | – | – |
| 64[(i)] | 3.91 | – | – | – |
| **Exposure to E 415 (mg/kg bw per day)** | **(ii) Based on the lowest technologically achievable levels in E 415 for use in food for all age groups as proposed by the IBO (Documentation provided to EFSA n. 4)** | | | |
| | MOE for Pb at 0.5 mg/kg | % of the TWI for Hg at 0.5 mg/kg | % of the TWI for Cd at 0.5 mg/kg | MOE for As at 0.5 mg/kg |
| 240[(b)] | 4.2 | 21 | 34 | 2.5–67 |
| 312[(c)] | 3.2 | 27 | 44 | 1.9–51 |
| 183[(d)] | 5.5 | 6.0 | 26 | 3.3–87 |
| 238[(e)] | 4.2 | 21 | 33 | 2.5–67 |
| 41[(f)] | 24 | 3.6 | 5.7 | 15–390 |
| 115[(g)] | 8.7 | 10 | 16 | 5.2–139 |
| 40[(h)] | 25 | 3.5 | 5.6 | 15–400 |
| 64[(i)] | 16 | 5.6 | 9.6 | 9.4–250 |

MOE: margin of exposure; TWI: tolerable weekly intake.

(a): No maximum limit is set in the current EU specifications for E 415.

(b): Mean exposure level for the population below 16 weeks of age (Refined estimated exposure assessment scenario using the maximum use level reported by industry (1,200 mg/kg) in infant FSMP (FC 13.1.5.1).

(c): 95th percentile exposure level for the population below 16 weeks of age (Refined estimated exposure assessment scenario using the maximum use level reported by industry (1,200 mg/kg) in infant FSMP (FC 13.1.5.1)).

(d): Mean exposure level for the population below 16 weeks of age (Refined estimated exposure assessment scenario using the mean of use levels reported by industry (986 mg/kg) in infant FSMP (FC 13.1.5.1)).

(e): 95th percentile exposure level for the population below 16 weeks of age (Refined estimated exposure assessment scenario using the mean of use levels reported by industry (986 mg/kg) in infant FSMP (FC 13.1.5.1)).

(f): Highest exposure level for the population above 12 weeks age and toddlers (Refined estimated exposure assessment scenario using the maximum use levels reported by industry ((750 mg/L for categories 13.1.5.1 and 250 mg/L for 13.1.5.2)) in infant FSMP (FC 13.1.5.1 and 13.1.5.2) – toddlers, – mean) data Section 3.4.1.3, EFSA ANS Panel, 2017 on E 415.

(g): Highest exposure level for the population above 12 weeks age and toddlers (Refined estimated exposure assessment scenario using the maximum use levels reported by industry ((750 mg/L for categories 13.1.5.1 and 250 mg/L for 13.1.5.2)) in infant FSMP (FC 13.1.5.1 and 13.1.5.2) – infants above 12 weeks to 1 year – 95th percentile) data Section 3.4.1.3, EFSA ANS Panel (2017) on E 415.

(h): Highest exposure level for the general population (Refined Non-Brand-Loyal Scenario -Toddlers – mean (data from, Section 3.4.1.3, EFSA ANS Panel, 2017 on E 415).

(i): Highest exposure level for the general population (Refined Non Brand-Loyal Scenario -Children 3–9 years – 95th percentile (data Section 3.4.1.3, EFSA ANS Panel, 2017 on E 415).

The resulting figures show that the potential exposure to Pb, Hg and Cd from the use of E 415 would not be of concern if these toxic elements would be present in the food additive up to the lowest technologically achievable levels proposed by the IBO. The MOE values for arsenic are very low compared to the value of 1,000 which would be considered sufficient (see Table 6).

Considering that Pb could be present in xanthan gum (E 415) at the existing limit in the EU specifications (2 mg/kg), the resulting MOE would generally not give rise to concern with exception of the highest exposure (95th percentile, maximum use level of E 415) of infants < 16 weeks of age, which shows a borderline MOE value of 0.8.

The Panel noted that maximum levels for lead and cadmium in infant formula are set by Reg. (EC) No 1881/2006 and therefore the Panel calculated the impact of the level of the toxic elements lead and cadmium in the food additive on the final product and compared that with the legal limits for these elements in the final formula (see Appendix B).

Considering the results of these calculations and the fact that the food additive E 415 is not the only potential source of toxic elements, the Panel emphasises the need to reduce the specification limit

value for lead in Regulation (EU) No 231/2012 and consider introducing specifications for cadmium, mercury and arsenic. 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.

### 3.4.2. Other parameters

The Panel noted that all strains used to produce xanthan gum (E 415) should meet the requirements of the QPS status. Therefore, the Panel recommends to revise the definition of E 415 accordingly (see Table 8).

Because of the polysaccharidic nature of E 415, it can be a substrate prone to microbiological contamination. Since cases of infections with *Cronobacter (Enterobacter) sakazakii* were reported in the literature (Henry and Fouladkhah, 2019) the Panel is of the view that current microbiological specifications set for E 415 should also include *Cronobacter (Enterobacter) sakazakii*, established on the basis of the information provided.

Furthermore, the Panel noted that no specific data were provided on the presence of enzymes. The Panel recommends that during the manufacturing process any enzymes potentially present in xanthan gum E 415 should be inactivated.

The Panel further recommends that the Kjeldahl method should be indicated to be used for the determination of the nitrogen content in E 415 (see Section 3.2.3).

The Panel noted that E 415 is a hydrophilic macromolecule, which in water forms a colloidal dispersion in which the macromolecules and/or polymolecular particles are dispersed throughout the liquids (e.g. liquid formulations, physiological fluids in the gastrointestinal (GI)-tract). They are not forming true solutions (rather: molecular disperse systems) and are specific for their gelling properties. Therefore, the Panel recommends changing in the definition of E 415 'Its solutions are neutral' to 'Its dispersions in water are neutral'. Following these considerations, the Panel recommends changing the word 'soluble' to 'dispersible' in the EU specifications of E 415.

The Panel also considered that the CAS number 11138-66-2 corresponding to xanthan gum should be included in the existing EU specifications for E 415.

### 3.4.3. Summary of the proposed revisions to the EU specifications

Overall, based on the analytical data provided by the IBOs in response to the EFSA call for data[14] (Documentation provided to EFSA n. 1–12) and the above considerations, the Panel recommends the revisions of the existing EU specifications for xanthan gum as listed in Table 8.

**Table 8:** Proposal for a revised version of the existing EU Specifications for Xanthan gum (E 415)

| | **Commission Regulation (EU) No 231/2012** | **Comment/justification for revision** |
|---|---|---|
| Synonyms | – | |
| **Definition** | Xanthan gum is a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with strains of *Xanthomonas campestris*, purified by recovery with ethanol or propan-2-ol, dried and milled. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and pyruvic acid, and is prepared as the sodium, potassium or calcium salt. Its solutions are neutral. | Xanthan gum is a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with strains of *Xanthomonas campestris*, which are unequivocally identified and meet the criteria for qualification for QPS status (i.e. absence of acquired antimicrobial resistance genes), purified by recovery with ethanol or propan-2-ol, dried and milled. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, pyruvic acid and acetic acid, and is prepared as the sodium, potassium or calcium salt. Its dispersions in |

[14] Call for technical and toxicological data on locust bean gum (E 410) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. Available online: https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-locust-bean-gum-e-410-uses

| | Commission Regulation (EU) No 231/2012 | Comment/justification for revision |
|---|---|---|
| | | water are neutral. The final product must not show any residual enzyme activity. |
| EINECS | 234-394-2 | Unchanged |
| CAS | | Include CAS number: 11138-66-2 |
| Molecular weight | Approximately 1,000,000 | To update to 1,000,000 Da |
| Assay | Yields, on dried basis, not less than 4.2% and not more than 5% of $CO_2$ corresponding to between 91% and 108% of xanthan gum | Unchanged |
| Description | Cream-coloured powder | Unchanged |
| **Identification** | | |
| Solubility | Soluble in water. Insoluble in ethanol | Dispersible in water. Insoluble in ethanol. |
| **Purity** | | |
| Loss on drying | Not more than 15% (105°C, 2.5 hours) | Unchanged |
| Total ash | Not more than 16% on the anhydrous basis determined at 650°C after drying at 105°C for four hours | Unchanged |
| Pyruvic acid | Not less than 1.5% | Unchanged |
| Nitrogen | Not more than 1.5% | Not more than 1.5% (Kjeldahl method) |
| Ethanol and propan-2-ol | Not more than 500 mg/kg singly or in combination | Unchanged |
| Lead | Not more than 2 mg/kg | Maximum limit to be lowered on the basis of the information provided and on the considerations of the Panel |
| Cadmium | Not presently specified | Maximum limit to be included on the basis of the information provided and the considerations of the Panel |
| Mercury | Not presently specified | Maximum limit to be included on the basis of the information provided and the considerations of the Panel |
| Arsenic | Not presently specified | Maximum limit to be included on the basis of the information provided and the considerations of the Panel |
| **Microbiological criteria** | | |
| Total plate count | Not more than 5,000 colonies per gram | Unchanged |
| Yeast and moulds | Not more than 300 colonies per gram | Unchanged |
| *Escherichia coli* | Absent in 5 g | Unchanged |
| *Salmonella* spp. | Absent in 10 g | Unchanged |
| *Xanthomonas campestris* | Viable cells absent in 1 g | – |
| *Cronobacter sakazakii* | | Microbiological criteria should be included on the basis of the information provided |

EINECS: European Inventory of Existing Commercial Chemical Substances; CAS: Chemical Abstract Service.

## 3.5. Biological and toxicological data

### 3.5.1. Previous evaluation by ANS Panel (2017)

The following text (in italics) is from the opinion published in 2017 (EFSA ANS Panel, 2017). New information and assessments related to the specific age group below 16 weeks of age are added in the following subsection.

*The toxicokinetic studies demonstrated that xanthan gum would not be absorbed intact and would not be metabolised by enzymes present in the gastrointestinal tract. The limited extent of fermentation*

*of xanthan gum would lead to the production of fermentation products such as SCFAs. The Panel considered that their formation as fermentation products from xanthan gum does not raise a safety concern*.

*From short-term and subchronic toxicity studies no toxicological relevant changes were reported apart from a decrease in red blood cell count and haemoglobin concentration in dogs receiving 2,000 mg/kg bw per day for 12 weeks*.

*Xanthan gum (E 415) does not give rise to concerns for genotoxicity*.

*No adverse effects were reported in chronic studies in rats and dogs up to 1,000 mg/kg bw per day, the highest dose tested. In rats, the compound was not carcinogenic*.

*Dietary feeding of xanthan gum at levels of 0 (control), 250 and 500 mg/kg bw per day to groups of albino rats of both sexes during a three-generation reproduction study had no adverse effect on parental, reproductive and developmental toxicity*.

***Studies in young animals***

***Piglets***

*Xanthan gum in ProNurse® milk replacer was administered to Domestic Yorkshire Crossbred Swine (farm piglets) (n = 6/sex per group) for 20 days from postnatal day (PND) 2 onwards at dose levels of 0, 750 or 7,500 mg/L (equivalent to 0, 375 or 3,750 mg/kg bw per day). In a follow-up study performed within 2-months in the same laboratory using the same protocol piglets were provided with 0 or 1,500 mg xanthan gum/L milk replacer (equivalent to 750 mg/kg bw per day) (Documentation provided to EFSA n. 4). The milk replacer was given to all groups orally, six times per day for 20 consecutive days, at a dose volume of 500 mL/kg bw per day (~ 83.33 mL/kg/dose)*. JECFA (2016a, 2016b) *considered the two studies together as a single study. The Panel agreed with this assumption*.

*All animals survived the daily administration until necropsy on PND 22. In the high-dose group, alteration in the faecal output (green, soft, watery, increased defaecation) was observed in all female piglets. These clinical observations were also observed in most animals of the mid-dose group, although the number of times these observations were made during the study were less. In the high-dose group, the male animals showed also the following additional pelage/skin aberrations; abrasion, scabbed areas and unkempt appearance and female animals unkempt appearance. The clinical observations in the low-dose group were comparable to the observations in the control group. Body weight gain and food consumption of the low- and mid-dose group were comparable to the control group. In the high-dose group, histopathological findings were observed in the large intestine (caecum, colon, rectum) and small intestine (duodenum). In the large intestines, goblet cell hypertrophy/hyperplasia, gland/lumen dilation, and/or increased foreign material were observed and mucosal atrophy was observed in the small intestine. These effects were observed in fewer animals in the lower dose groups and the severity was considered minimal. No test substance-related effects among haematological and clinical chemistry parameters in either sex at any interval were observed. The Panel considered the no-observed-effect-level (NOEL) for xanthan gum in neonatal piglets to be 375 mg/kg bw per day, based on the changes of the faeces (green, soft, watery, increased defaecation) in the mid-dose and high-dose group, and the NOAEL was 750 mg/kg bw per day based on histopathological changes in the intestine in the high dose*.

***Infants***

***Clinical studies***

*The study by Ross Products Division, Pediatric Nutrition Research and Development (1997) aimed to evaluate the effect of xanthan gum added to a casein hydrolysate formula on mineral calcium (Ca), phosphorous (P), magnesium (Mg), fat and nitrogen balance as primary variables in 6 term healthy infants of age ranging from 33 to 137 days at the initiation of the study (mean body weight of 6.553 kg) in a randomised crossover design. The intake of xanthan gum (1,500 mg/L of formula) was calculated to be 176 mg/kg bw per day, based on reported mean consumption of 771 mL formula/day. Secondary variables included the evaluation of zinc balance due to the decreased precision of this assessment. Formula intake, stool pattern and gastrointestinal transit time were also measured. Infants were fed a powdered hydrolysate without or with xanthan gum for the first 11–12 days and admitted to the metabolic unit for the 72-h balance. The results obtained did not show any consistent influence of xanthan gum on the nutrient balances of infants fed hydrolysate formula. No differences were observed in intakes or incidence of feeding-related spit-up and/or vomit. Positive effects on stool consistency and marked decrease of percent of stools which were watery were observed. Conversely,*

*total zinc absorption was lower in all infants fed hydrolysate formula with xanthan gum compared to the equivalent formula without xanthan gum. However, the differences observed in this study as well had no effect on the growth of infants*.

*In the study by Ross Products Division, Pediatric Nutrition Research and Development (1998), the tolerance of infants to four different powdered protein hydrolysate formulas, containing different levels of xanthan gum, was investigated. A number of 182 infants judged to be in good health, full term with a gestational age of 37–42 weeks, a birth weight greater than 2,500 g and age < 28 days was enrolled in the study. Infants were fed commercially labelled protein hydrolysate formula for 1 week, followed by a 1-week period in which they randomly received one of the four experimental protein hydrolysate formulas containing either 500, 1,000 or 1,500 mg xanthan gum/L. The main outcome indicators to test the hypothesis were stool number, mean stool rank consistency and incidence of spit up and vomiting. From the 182 children, 125 completed the study and 12 were non-completers due to formula intolerance (in the majority of cases taking the formula without xanthan gum) or parental dissatisfaction. The remaining 45 infants exited before the test period started. According to the authors, the xanthan gum-containing formula was better tolerated than the corresponding formula without xanthan gum, reduced the number of stools per day and significantly decreased the percent of watery stools*.

*In the study by Ross Products Division, Pediatric Nutrition Research and Development (2001), full-term infants were fed either with a reconstituted protein hydrolysate formula containing xanthan gum (750 mg/L, equivalent to 102 mg/kg bw per day) or an equivalent formula without xanthan gum from 14 up to 112 days of age. The primary objective of this study was to compare growth, measured by weight and weight gain per day. Secondary study variables included length, length gain, food intake, stool characteristic and incidence of feeding-related spit up and/or vomit. The results obtained indicated that the primary variables weight and weight gain per day did not differ for infant fed with the two formulas. Similarly, length, length gain as well as incidences of spit up or vomit associated with feedings did not differ. The volume of formula intake (mL/day and mL/kg per day) and number of stools per day were significantly greater in the infants fed with reconstituted protein hydrolysate formula without xanthan gum compared to the equivalent formula with xanthan gum*.

*The study by Abbott Nutrition Research and Development and Scientific Affairs (2007), was conducted to demonstrate that fractional absorption of zinc was similar when infants were fed a powdered hydrolysate-based formula containing xanthan gum compared to commercial powdered milk-based formula. A total of 22 healthy, full-term infants, between 60 and 105 days of age were enrolled. Fractional absorption of Zn was analysed as primary efficacy variable, while calcium absorption and zinc absorption and excretion were the secondary and supportive variables. The results obtained suggest that xanthan gum may affect mineral absorption. However, despite the presence of xanthan gum, calcium absorption appeared to be more than adequate to meet infant requirements. The effect on zinc was less clear, but the differences between groups observed for zinc intakes were not statistically significant*.

*The study by Abbott Nutrition Research and Development and Scientific Affairs (2011) aimed to evaluate the tolerance of infants fed infant formula containing different carbohydrate sources, stabilisers and/or emulsifier, infants were fed with casein hydrolysate formula with or without xanthan gum at concentration of 750 mg/L (dose 120–126 mg/kg bw per day) for 20–28 days. Overall, the results obtained indicated that no clinically relevant differences in adverse effects between the infant groups fed with formula containing or not xanthan gum were observed. In addition, the presence of xanthan gum in the casein hydrolysate formula decreased vomiting and induced significant reduction in the number of stools per day compared to the corresponding formula without xanthan gum. Growth characteristics were also not affected*.

*Post-marketing surveillance data were collected by Abbott Nutrition from June 2010 through May 2015, evaluating the use of formulae based on hydrolysed protein and containing approximately 750 mg xanthan gum/L of reconstituted formulae (…). A total of 131 million patient treatment days*[15] *were estimated by the manufacturer based on sales data. The data showed that consumption of formula containing xanthan gum was not associated with an increased rate of adverse events. The rate for any adverse event was less than one case report per 10,000 patient treatment days. Overall, the collected data indicated that consumption of formula containing xanthan gum was not associated with increase rate of adverse events*.

[15] One patient treatment day is equivalent to the consumption of 0.8 L of product by an infant in a 24-h period.

*Overall, based on the results obtained in these clinical studies, the Panel noted that consumption of xanthan gum in infant formula or formula for special medical purposes in infant was well tolerated, did not influence mineral (Ca, P, Mg), fat and nitrogen balance and did not affect growth characteristics up to concentration of 1,500 mg/L (232 mg/kg bw per day). These results were supported by the outcome of the post-marketing surveillance with formulae containing xanthan gum at a concentration of approximately 750 mg/L of reconstituted formula*.

### 3.5.2. Newly available data

No new data were submitted following the call for data with respect to ADME and animal toxicity.

#### 3.5.2.1. Clinical data

The IBOs submitted six clinical studies (Borschel et al., 2014; Vandenplas et al., 2014, 2016; Dupont et al., 2015, 2016; Sant'Anna and Mooney, 2018) (Documentation provided to EFSA n. 13 and 14). In addition, the IBOs submitted two studies dealing with necrotising enterocolitis (NEC) following use of xanthan gum (Beal et al., 2012; Woods et al., 2012) (Documentation provided to EFSA n. 13). From the clinical studies only the studies of Borschel et al. (2014), and Sant'Anna and Mooney (2018) contained information on the presence of xanthan gum. Because of lacking information concerning xanthan gum, the other studies do not contribute to the assessment of xanthan gum. Therefore, only the study of Borschel et al., and Sant'Anna and Mooney are described below.

The study of Borschel et al. (2014) was a masked, randomised, parallel growth study, conducted in 137 infants. The infants were randomised between birth and 9 days of age and were fed either a ready-to-feed (RTF) or reconstituted powdered (PWD) form of an extensively hydrolysed casein-based formula. The RTF contained 70.4 g/L carbohydrate blend consisting of 70% sucrose and 30% modified tapioca starch; the PWD contained 69.1 g/L carbohydrate blend consisting of 70% corn maltodextrin and 30% sucrose. Although no adverse effects were reported, because of lacking information on the content of xanthan gum the assessment of the study does not contribute to the assessment of the safety of xanthan gum.

The retrospective study of Sant'Anna and Mooney (2018) is published in the form of an abstract. The number of infants on xanthan gum containing formula was 14 and their age was given as < 1 year. Further information is rather sparse, no information on gender, weight, duration of treatment, outcome other than an overall percentage in comparison to a rice-base formula is given. No information on the content of xanthan gum is provided. Although no adverse effects were reported, because of lacking information this study does not contribute to the assessment of the safety of xanthan gum. The most recent (full) publication from this group (Abdulezer et al., 2002) does not give more information than this abstract on the content of xanthan gum.

**Assessment of xanthan gum in the feeding of preterm infants**

NEC is an important clinical problem in preterm infants. It is associated with significant morbidity and mortality. In high-income countries, the rate of NEC is between 2% and 7% among babies born < 32 weeks' gestation and between 5% and 22% among those born < 1,000 g (Battersby et al., 2018). The study of Beal et al. (2012) was described in the previous opinion: 'a report from the US FDA on infants who developed NEC after the use of a xanthan gum-containing thickening agent (SimplyThick (ST)). In total, 22 infants who developed NEC were included in this report. In all infants, the reason for ST use was gastroesophageal reflux or dysphagia. Twenty-one infants were preterm with a median gestational age (GA) of 30.5 weeks. Sixteen infants began ingesting xanthan gum after 37 weeks post-menstrual age. ST was consumed for a median of 13 days prior to NEC onset (range: 1–31 days). The daily intake of ST was not provided in the report. ST was added to a mix of breast milk and formula (n = 11), formula alone (n = 10), and breast milk alone (n = 1). It was ingested by bottle (n = 18), bottle and gavage (n = 3), or gavage alone (n = 1). Nineteen infants developed NEC at > 37 week post-menstrual age. Fourteen cases required surgery and 7 died'.

Woods et al. (2012) reported three extremely preterm infants who developed NEC after feeding with human milk or formula thickened with ST (one of them with ST and then another xanthan gum-containing thickening agent). GA ranged between $24^{3/7}$ and $28^{6/7}$ weeks. ST was started at, respectively, 53, 58, 108 days of age. NEC was diagnosed at, respectively, 60, 80, 117 days of age. No information on the intake of xanthan gum nor on the follow-up is provided in the paper.

The FAF Panel noted that the conclusions drawn in 2017 are still valid that 'the described cases of NEC are not related to the food additive use of xanthan gum in the manufacturing of infant formula

and that the dosages of xanthan gum associated with the cases of NEC are not known but are expected to be in gram amounts'.

#### 3.5.2.2. Post-marketing surveillance data

Post-marketing data were obtained from two IBOs in the form of summary tables of adverse events (Documentation provided to EFSA n. 2 and 14). The first IBO provided data collected during a two-year period [redacted] on xanthan gum containing formulae available on the market during which period a consumption corresponding to ~ [redacted] patient treatment days with a dose [redacted] and ~ [redacted] patient treatment days with a dose of [redacted] is reported. Only one adverse event is reported, the symptoms were vomiting and skin reaction (possibly urticaria) which needed treatment. The second IBO provided data collected during a one-year period [redacted] on commercial products containing xanthan gum that are available on the market worldwide. No information is given on the content of xanthan gum. During the data collection period the consumption of commercial products containing xanthan gum corresponded to ~ [redacted] patient treatment days and 1,036 adverse events are reported. Three case reports came from health care providers, one case report of elevated blood potassium, one case report of vomiting and one case report of a *Cronobacter (Enterobacter) sakazakii* infection in a premature infant receiving a commercial product containing xanthan gum at home. In the latter case, all tested batches associated with this report were negative for *Cronobacter (Enterobacter) sakazakii*. All other adverse case events are presented in a summarising table with reports on spitting, vomiting, flatulence, crying and irritability. One case of a confirmed allergic reaction was reported.

The Panel considered that the relationship between the events and the intake of xanthan gum is not confirmed, and that the post-marketing surveillance data do not show specific alerts except for the very rare symptoms of one allergic reaction. No additional cases of adverse reactions were found by a literature search submitted by the IBOs (Documentation provided to EFSA n. 2 and 14).

## 4. Discussion

The current assessment deals with the risk assessment of xanthan gum (E 415) when used in food for infants below 16 weeks of age in the food category (FC) 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). It also addresses as a follow-up the issues that were identified in the 2017 re-evaluation of xanthan gum E 415 (EFSA ANS Panel, 2017).

*X. campestris* is used for the production of xanthan gum, a species which is recommended for the QPS approach for safety assessment with the qualifications of 'absence of acquired resistances to antimicrobials' and 'for production purposes only'. The later qualification involves that no viable cells remain in the product. None of the production strains reported by the IBOs carried genes conferring acquired resistance to antimicrobials. However, based on the information provided by the IBOs, the absence of viable cells in 1 g of the final product, tested following the most recent appropriate EFSA Guidance (currently EFSA CEP Panel, 2021), was not demonstrated for the products obtained from the strains [redacted]. The Panel noted that all strains used to produce xanthan gum (E 415) should meet the requirements of the QPS status, including demonstration of the absence of viable cells.

In response to the call for data, analytical data for levels of toxic elements (namely arsenic, lead, cadmium, mercury) in commercial samples of xanthan gum (E 415) were provided by IBOs. Most of the samples were reported as below the limit of quantification of the analytical methods used. The Panel agreed that the lowest technologically achievable levels proposed by the IBOs (0.5 mg/kg for each of the four toxic elements) were consistent with the occurrence data on these toxic elements and the LOQ values reported, although the lowest achievable level that was proposed by IND is way above (50 fold) the highest LOQ for Hg.

The Panel performed the risk assessment that would result if these toxic elements were present in E 415 at (i) the current maximum limit for Pb in the EU specifications and (ii) at the lowest technologically achievable levels proposed by the IBOs for xanthan gum E 415.

The Panel considered the refined non-brand-loyal exposure scenario to calculate the exposure to the toxic elements from the use of E 415 for the general population. For the general population, the highest mean and the highest 95th percentile in the refined non-brand-loyal exposure scenario were calculated for toddlers to be 40 mg/kg bw per day and for children 3–9 years of age 64 mg/kg bw per day, respectively (EFSA ANS Panel, 2017). For infants < 16 weeks of age, the refined (brand loyal) exposure estimates based on the maximum and mean use levels of E 415 reported by industry

(Table 4) were considered. The mean and 95th percentile exposure estimates were 240 and 312 mg/kg bw per day for the maximum use level and 183 and 238 mg/kg bw per day for the mean use level reported. The highest mean and 95th percentile exposure for the population above 16 weeks of age and toddlers (consumers only of FSMP) were considered as calculated in the EFSA ANS Panel opinion from 2017 at the maximum use level reported by the industry in the refined brand loyal scenario as 41 and 115 mg/kg bw per day for toddlers and infants from 12 weeks to 1 year of age, respectively.

The resulting figures show that the potential exposure to Pb, Hg and Cd from the use of E 415 would not be of concern if these toxic elements would be present in the food additive up to the lowest technologically achievable levels proposed by the IBO. The MOE values for arsenic are very low compared to the 'requested' values i.e. 1,000 (see Table 6).

Considering that Pb could be present in xanthan gum (E 415) at the existing limit in the EU specifications (2 mg/kg), the resulting MOE would generally not give rise to concern with exception of the highest exposure (95th percentile, maximum use level of E 415) of infants < 16 weeks of age, which shows a borderline MOE value of 0.8.

The Panel calculated the impact of the level of the toxic elements lead and cadmium in the food additive on the final product and compared that with the legal limits for elements in the final infant formula set by Regulation (EC) No 1881/2006 (see Appendix B). In all cases the calculations indicate that the final product would comply with the maximum levels set out in Regulation (EC) No 1881/2006. However, for lead at the current max limit of 2 mg/kg in E 415 the fraction of the limit value in the formula approaches 100% (Appendix B, Table B.2) which may lead to exceedance of the limit value considering that the food additive E 415 is not the only potential source of lead. Therefore, the Panel emphasises the need to reduce the specification limit value for lead in Regulation (EU) no 231/2012. The Panel further considers introducing maximum limits for cadmium, mercury and arsenic in the EU specifications.

On the question of residual proteins, data were provided using the Kjeldahl method for total nitrogen and all gum samples were within the EU specification of NMT 1.5% nitrogen. No data on levels of residual proteins measured as such in commercial samples of xanthan gum E 415 were submitted. The IBO proposed the continued use of the Kjeldahl method along with the existing 'EC limit value' on total nitrogen (i.e. NMT 1.5%, Table 1) on the basis that validated method(s) for proteins in xanthan gum are not generally available and are not needed, since no evidence of sensitivity to xanthan gum has been reported that would necessitate a more specific test for proteinaceous material. The Panel concurs with this view. The Kjeldahl method should be indicated to be used for the determination of the nitrogen content in E 415.

Regarding the question on specifications for xanthan gum use in special formulae intended for infants below 16 weeks of age under special medical conditions, it was stated that there are no special requirements on purity criteria for xanthan gum E 415 intended for infant formulae/food. Therefore, the data provided by the IBOs and the specifications they have proposed, apply to the additive intended for all age groups, including infants < 16 weeks of age.

On the question on the fate and any reaction products of xanthan gum (E 415) in infant formulae, it was stated by the IBO that the gum has excellent heat stability and is stable in acid, alkaline and high concentration salt solutions. Therefore, no reaction products are to be expected to be present in infant formulae at any significant level. Although no data were submitted to support this statement, the Panel considered that due to the chemical nature and composition of xanthan gum (see Section 3.1) no reaction products are expected to be present in infant formulae at any significant level.

Acceptable data were provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii* in eight samples of xanthan gum E 415. The Panel noted that xanthan gum (E 415) may be prone to microbiological contamination and therefore microbiological specifications set for E 415 should also include *Cronobacter (Enterobacter) sakazakii*, based on the basis of the information provided.

Furthermore, the Panel noted that no analytical data were provided on the enzymes. The Panel recommends that during the manufacturing process any enzymes potentially present in xanthan gum E 415 should be inactivated. Therefore, the Panel is of the view that the specifications of E 415 should ensure that the final product must not show any residual enzyme activity.

The Panel noted that in the re-evaluation of xanthan gum E 415 in 2017 (EFSA ANS Panel, 2017) information regarding particle size was reported. In 2016, the IBO submitted data on SEM analyses conducted on 10 samples and stated that the smallest particulates (not free) were viewed on the surface of much larger particles and none of these particles was smaller than 150 nm.

Upon EFSA request no data on the particle size distribution were provided by the IBOs for the current assessment. One IBO provided information on the water solubility of E 415 determined by

applying OECD TG 105 (OECD, 1995) with several modifications needed due to the thickening properties of the food additive.

The Panel considers that the outcome of testing for water solubility of E 415 is inconclusive. The Panel noted that in the absence of data no conclusion can be drawn on the presence of small particles including nanoparticles, which cannot be confirmed or excluded in the pristine food additive E 415. The Panel noted that currently no standardised methods are available to measure the particle size distribution or water solubility for the polysaccharide thickening and gelling agents used as food additives and that further research for method development is needed. The Panel noted, however, 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 xanthan gum (E 415). The data provided by the IBO showing that the plot of viscosity versus concentration is increasing linearly with no inflection point or discontinuity is consistent with a dispersion of the macromolecules. Similarly, the phenomenon of viscosity synergy when xanthan gum (E 415) is added in combination with other gums (EFSA ANS Panel, 2017) indicates that there is an interaction between the dispersed gums at the molecular level.

The Panel noted that E 415 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 these considerations the FAF Panel concluded that xanthan gum will not be present in the GI tract in the pristine form taking into account the capacity to absorb and swell in water, and the volume of fluid in the stomach and GI-tract. Therefore, a conventional risk assessment can be carried out for xanthan gum (E 415) following the EFSA Guidance for submission for food additive evaluations (EFSA ANS Panel, 2012) and the Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017).

Based on the considerations above the Panel also recommends changing the word 'soluble' to 'dispersible' in the EU specifications of E 415.

Overall, on the basis of the information provided, the Panel has made recommendations for amendments to the existing EU specifications for xanthan gum E 415 in Table 8.

Dietary exposure to xanthan gum (E 415) for infants below 16 weeks of age from its use as a food additive was assessed based on (1) MPLs set out in the EU legislation (defined as the regulatory maximum level exposure assessment scenario) and (2) the reported use levels (defined as the refined exposure assessment scenario). Both scenarios are based on the recommended consumption levels from Scientific Committee Guidance (EFSA Scientific Committee, 2017) which recommends values of 200 and 260 mL formula/kg bw per day as conservative mean and high-level consumption values for 14- to 27-day-old infants.

For infants below 16 weeks of age consuming special infant formulae (FC 13.1.5.1), exposure to xanthan gum (E 415) in the regulatory maximum level exposure assessment scenario was estimated at 240 mg/kg bw per day for mean consumption while at the high-level consumption was estimated at 312 mg/kg bw per day. Exposure estimates are the same in the refined scenario using the maximum use level reported by industry as this maximum equals the MPL. In the refined estimated exposure assessment scenario using the mean of the reported use levels from industry, exposure estimates for xanthan gum (E 415) were of 183 mg/kg bw per day at the mean and 238 mg/kg bw per day at the high level of consumption.

Based on the assumption that carers of children would be brand-loyal to an infant formula for special medical purposes (FC 13.1.5.1), the refined scenario using the maximum use level reported by industry would in general result in a reliable estimation of exposure for infants below 16 weeks of age.

No new data were provided concerning ADME, acute toxicity, short-term and subchronic toxicity, genotoxicity, chronic toxicity and carcinogenicity and reproductive and developmental toxicity. In the EFSA opinion on Re-evaluation of xanthan gum (E 415) as a food additive (2017), special studies in neonatal piglets were described and a NOAEL of 750 mg/kg bw per day was identified based on histopathological changes in the intestine in the high dose group.

In the former re-evaluation the use of xanthan gum (E 415) in foods for infants from 12 weeks of age onwards and for young children was considered. For the present evaluation clinical studies in infants below the age of 6 months were submitted. However, as the information in the content of xanthan gum is lacking, their results cannot support the safe use in the age group below 12 weeks. From the post-marketing reports it can be concluded that the highest concentration used was 1,200 mg/L, which is the MPL.

There are reports on preterm infants who developed NEC after the use of a xanthan gum-containing thickening agent (SimplyThick (ST)) by direct addition to mother's milk or infant formulae. In May 2011, FDA warned parents and healthcare providers alike to avoid feeding ST to infants who were born before 37-week gestation because of a potential association with NEC. However, the present opinion only addresses the authorised uses as a food additive and does not include a safety assessment of other uses of xanthan gum, such as for ad libitum addition of xanthan gum as a thickening agent to mother's milk or to infant formulae.

Therefore, the FAF Panel noted that the conclusions on the food additive drawn in 2017 are still valid that 'the described cases of NEC are not related to the food additive use of xanthan gum in the manufacturing of infant formula and that the dosages of xanthan gum associated with the cases of NEC are not known, but are expected to be in gram amounts'.

From the available piglet studies a NOAEL of 750 mg/kg bw per day could be derived which could be used for calculation of a MOE. Taking the scenario with the highest exposure of 312 mg/kg bw per day the MOE resulted as 2.4. Given that xanthan gum is not absorbed the toxicokinetic inter- and intraspecies default uncertainty factor can be replaced by a substance specific factor of 1, and given the fact that an infant specific animal model was used, the toxicodynamic interspecies default uncertainty factor can be replaced by a specific factor of 1, the Panel considered a MOE of 2.4 as sufficient.

Furthermore, the Panel considered that no concerns were raised by the data from clinical studies of infants from 12 weeks of age onwards and for young children (EFSA ANS Panel, 2017) and that in the post-marketing studies no adverse events with clinical significance were observed. Despite the absence of appropriate clinical studies, the Panel therefore, concluded that the use of xanthan gum in formulae for infants below 16 weeks of age up to a concentration of 1,200 mg/L, which results in an exposure of 312 mg/kg bw per day does not raise concerns.

## 5. Conclusions

The Panel concluded that the technical data provided by the IBO support an amendment of the specifications for E 415 laid down in Commission Regulation (EU) No 231/2012, as presented by the recommendations made in Table 8.

Due to the low validity of the clinical studies, the Panel concluded that a reference point could not be derived from them, but the results of the adequate piglet study could serve to derive a reference point (750 mg/kg bw per day). When calculating the MOE for infants < 16 weeks of age consuming FSMP (FC 13.1.5.1) for the highest xanthan gum exposure, this was 2.4. The Panel concluded that the MOE does not raise concerns.

## 6. Documentation as provided to EFSA

1) Biopolymer International, 2019. Submission of data in response to the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 3 January 2019.
2) United Pharmaceuticals, 2019. Submission of data in response to the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 3 January 2019.
3) Specialised Nutrition Europe (SNE), 2019. Submission of data in response to the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 4 January 2019.
4) Biopolymer International, 2020. Clarifications on heavy metals and residual proteins in commercial samples of the food additive xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 6 March 2020.
5) Biopolymer International, 2022. Additional data and clarifications submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 25 February 2022.
6) Cargill, 2021. Additional data and clarifications submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 4 January 2021.

7) Cargill, 2022. Additional data and clarifications submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 24 June 2022.
8) Biopolymer International, 2022. Clarifications on the production microorganism of the food additive xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 30 November 2022.
9) Biopolymer International, 2022. Clarifications on the production microorganism of the food additive xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 15 December 2022.
10) Cargill, 2022. Clarifications on the production microorganism of the food additive xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 15 December 2022.
11) Biopolymer International, 2022. Additional data submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 28 October 2022.
12) Biopolymer International, 2022. Additional data and clarifications submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 23 September 2022.
13) Specialised Nutrition Europe (SNE), 2021. Additional data and clarifications submitted following the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 17 June 2021.
14) Abbott Nutrition on behalf of the SNE Dossier Preparation Group on Xanthan Gum, 2019. Submission of data in response to the call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 11 February 2019.

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## Abbreviations

| | |
|---|---|
| AAS | atomic absorption spectroscopy |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, excretion |
| AFC | EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food |
| ANI | average nucleotide identity |
| ANS Panel | EFSA Panel on Food Additives and Nutrient Sources added to Food |
| ATCC | American Type Culture Collection |
| BMDL | benchmark dose (lower confidence limit) |
| bw | body weight |
| CAS | Chemical Abstract Service |
| CBS | Westerdijk Fungal Biodiversity Institute culture collection |
| CFBP | French Collection of Phytopathogenic Bacteria |
| CFU | colony forming unit |
| CNCM | National Microorganism Culture Collection of Institut Pasteur |
| dDDH | digital DNA–DNA hybridisation |
| DSMZ | German Collection of Microorganisms and Cell Cultures |
| EINECS | European Inventory of Existing Commercial Chemical Substances |
| FA | Food additive |
| FAF Panel | Panel on Food Additives and Flavourings |
| FAO/WHO | Food and Drug Organization/World Health Organization |
| FC | food category |
| FSMP | food for special medical purposes |

| | |
|---|---|
| GA | gestational age |
| GI | gastrointestinal |
| HBGV | health-based guidance value |
| IBO | interested business operator |
| ICP-MS | inductively-coupled plasma mass spectrometry |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| LOAEL | lowest-observed-adverse-effect level |
| Mintel GNPD | Mintel Global New Products Database |
| MOE | margin of exposure |
| MPL | maximum permitted levels |
| NDA | EFSA Panel on Nutrition, Novel Foods and Food Allergens |
| NEC | necrotising enterocolitis |
| NMT | not more than |
| NOAEL | no-observed-adverse-effect level |
| NOEL | no-observed-effect level |
| OECD | Organisation for Economic Co-operation and Development |
| PND | postnatal day |
| PWD | reconstituted powdered |
| QPS | qualified presumption of safety |
| RP | reference point |
| RTF | ready-to-feed |
| SEM | scanning electron microscopy |
| SC | Scientific Committee of EFSA |
| SCF | Scientific Committee on Food |
| ST | *SimplyThick* |
| TG | Test Guideline |
| TWI | tolerable weekly intake |
| WG | Working Group |
| WGS | whole genome sequence |

# Appendix A – Data requested in the call for data (Call for technical and toxicological data on xanthan gum (E 415) for uses as a food additive in foods for all population groups including infants below 16 weeks of age)[16]

| Kind of data | Data requested in the call for data | Responses from IBOs | Comment |
|---|---|---|---|
| **A. Information regarding the follow-up of the conclusions and the recommendations of the EFSA ANS Panel opinion on the safety of xanthan gum (E 415) as a food additive** | | | |
| **1. Technical data** | • analytical data on current levels of lead, mercury, cadmium and arsenic in commercial samples of the food additive;<br>• the lowest technologically achievable level for lead, mercury, cadmium, and arsenic in order to adequately define their maximum limits in the specifications;<br>• analytical data on current levels of residual proteins in commercial samples of the food additive;<br>• the lowest technologically achievable level for residual proteins in order to adequately define their maximum limits in the specifications.<br>The information should be supported by data from at least five different batches and the analyses should be performed with appropriate analytical methods. EFSA seeks specific data on the methods of analysis used. These include but are not limited to e.g. the principle of the method, the scope of the method (i.e. the range of sample types that the method is used for), the concentration units used to express the analytical result(s), validation of the method (in particular limit of detection (LOD) and (LOQ)).<br>Such methods should employ state of the art techniques. | Data submitted | Assessed, no further follow-up |
| **3. Literature searches** | Literature searches should be conducted relevant for the safety evaluation of xanthan gum (E 415) for all uses in foods for all population groups from 12/10/2016[17] up to the date of the data submission, as described in the Guidance for submission for food additive evaluations (see its Section 5.3)[18]. | Data submitted | Assessed, no further follow-up |
| **B. Information required for the risk assessment of xanthan gum (E 415) as a food additive for use in foods for infants below 16 weeks of age** | | | |
| **1. Technical data** | • information on the levels of use of xanthan gum (E 415), alone or in combination with other thickening agents (indication of food additive name and level of use) in the special formulae used for infants below 16 weeks of age under special medical conditions;<br>• information on the fate and the reaction products of xanthan gum (E 415) in special formulae used for infants below 16 weeks of age under special medical conditions;<br>• information on particular specification requirements for identity and the purity of xanthan gum (E 415) (e.g. with respect to levels | Data submitted | Assessed, no Further follow-up |

[16] Available online: https://www.efsa.europa.eu/en/consultations/call/180718-5 and responses from IBOs.
[17] Date of last literature search reported in the EFSA ANS opinion.
[18] Guidance for submission for food additive evaluations. EFSA ANS Panel, 2012. https://doi.org/10.2903/j.efsa.2012.2760

| Kind of data | Data requested in the call for data | Responses from IBOs | Comment |
|---|---|---|---|
| | of protein residues; content of toxic elements, propan-2-ol/ethanol) for special formulae used for infants below 16 weeks of age under special medical conditions. 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.<br>In addition, data should be provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii* in the food additive. | | |
| **2. Toxicological data** | • post-marketing surveillance reports on undesired and adverse reactions (including e.g. flatulences, 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 xanthan gum (E 415) in the marketed products, where the FSMPs are already in use;<br>• published and unpublished case reports (e.g. available nutrivigilance data) on undesired and adverse effects, including e.g. flatulences, gastrointestinal discomfort, changes of stool-frequencies and -consistency, diarrhoea and allergic reactions), associated with the oral administration of xanthan gum in any form to infants and young children.<br>No other studies will be required if the use levels of xanthan gum (E 415) in food for special medical purposes in infants (FC 13.1.5.1) do not exceed the maximum reported use levels of xanthan gum (E 415) as recently provided by industry (750 mg/L). | Data submitted | Assessed, no further follow-up |
| **3. Literature searches** | Literature searches should be conducted relevant for the safety evaluation of xanthan gum (E 415) 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 Section 5.3, EFSA ANS Panel, 2012). | Data submitted | Assessed, no further follow-up |

# Appendix B – Estimation of the fraction of the levels of toxic elements in E 415 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 and cadmium in E 415 with respect to the regulatory maximum levels in the final product (formulae) as sold as laid down in Regulation (EC) No 1881/2006[19] considering:

- The current specification for lead in E 415 according to Regulation (EU) No 231/2012, 2 mg/kg. There is currently no specification for cadmium in E 415.
- The lowest technically achievable levels of lead and cadmium in commercial E 415 products, 0.5 mg/kg for each, as proposed by one interested business operator (Documentation provided to EFSA n. 4), see also Section 3.2.2.
- The maximum permitted use level of E 415 in the final food of 1,200 mg/kg in FC 13.1.1 and the mean use level of 916 mg/kg reported by industry for the uses in food for infants below 16 weeks of age, see Section 3.3.1.
- The range of maximum levels (MLs) for lead (0.01–0.02 mg/kg) and cadmium (0.005–0.02 mg/kg) in formulae for infants as laid down in Regulation (EC) No 1881/2006.

The results of the calculations can be found in Tables B.1 and B.2 for lead and Tables B.3 and B.4 for cadmium.

**Table B.1:** Estimation of the fraction of the levels of lead in E 415 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. 1881/2006 (mg/kg) | Fraction of toxic element from FA on ML of final product ML (%) |
|---|---|---|---|---|---|
| Current EU specification | 2.0 | 1,200 | 0.0024 | 0.010 | 24 |
| Current EU specification | 2.0 | 916 | 0.0018 | 0.010 | 18 |
| Proposal IBO | 0.5 | 1,200 | 0.0006 | 0.010 | 6 |
| Proposal IBO | 0.5 | 916 | 0.00046 | 0.010 | 4.6 |

FA: food additiv IBO: interested business operator; ML: maximum level.

**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. 1881/2006 (mg/kg) as sold | Fraction of toxic element from FA on ML of final product ML (%) |
|---|---|---|---|---|---|---|
| Current EU specification | 2.0 | 1,200 | 9,600 | 0.0192 | 0.020 | 96 |
| Current EU specification | 2.0 | 916 | 7,328 | 0.0147 | 0.020 | 74 |
| Proposal IBO | 0.5 | 1,200 | 9,600 | 0.00480 | 0.020 | 24 |
| Proposal IBO | 0.5 | 916 | 7,328 | 0.00367 | 0.020 | 18 |

IBO: interested business operator; ML: maximum level.

(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, 2018, available at https://zenodo.org/record/1256085#.X89vU9hKiUk.

[19] Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs (Text with EEA relevance). OJ L 364, 20.12.2006, p. 5–24.

**Table B.3:** Estimation of the fraction of the levels of cadmium in E 415 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. 1881/2006 (mg/kg) | Fraction of toxic element from FA on ML of final product ML (%) |
|---|---|---|---|---|---|
| Current EU specification | n/a | | | | |
| Current EU specification | n/a | | | | |
| Proposal IBO | 0.5 | 1,200 | 0.0006 | 0.005 | 12 |
| Proposal IBO | 0.5 | 916 | 0.00046 | 0.005 | 9 |

IBO: interested business operator; ML: maximum level.

(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, 2018, 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 415 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. 1881/2006 (mg/kg) | Fraction of toxic element from FA on ML of final product ML (%) |
|---|---|---|---|---|---|---|
| Current EU specification | n/a | | | | | |
| Current EU specification | n/a | | | | | |
| Proposal IBO | 0.5 | 1,200 | 9,600 | 0.00480 | 0.010 | 48 |
| Proposal IBO | 0.5 | 916 | 7,328 | 0.00367 | 0.010 | 37 |

IBO: interested business operator; ML: maximum level.

(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 (2018). Available online: 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 value for lead and to introduce a maximum level for cadmium, in Regulation (EU) no 231/2012.