Opinion on the re-evaluation of sodium carboxy methyl cellulose (E 466) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as food additive for uses in foods for all population groups

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Opinion on the re-evaluation of sodium carboxy methyl cellulose (E 466) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as food additive for uses in foods for all population groups

EFSA Panel on Food Additives Flavourings (FAF),
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Abstract

Sodium carboxy methyl cellulose (E 466) was re-evaluated in 2018 by the former EFSA Panel on Food Additives and Nutrient sources added to Food (ANS). As a follow-up to this assessment, the Panel on Food Additives and Flavourings (FAF) was requested to assess the safety of E 466 for its uses as a food additive in food for infants below 16 weeks of age belonging to food categories (FC) 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants) in line with Regulation (EC) No 1333/2008. 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, including the safety assessment for FC 13.1.5.1 and 13.1.5.2 (Dietary foods for babies and young children for special medical purposes as defined in directive 1999/21/EC). The process involved the publication of a call for data. Based on the received data, the Panel concluded that the technical data provided by the interested business operator support an amendment of the specifications for sodium carboxy methyl cellulose (E 466) laid down in Commission Regulation (EU) No 231/2012. The interested business operators declared that E 466 is not used in food for infants below 16 weeks of age and in FC 13.1.5.1. Due to the lack of data, an assessment has not been performed for this FC and age group. The interested business operators did not provide biological and toxicological data to support the uses of E 466 in FC 13.1.5.2. Due to the almost unchanged database compared to the situation before the call for data, the FAF Panel confirmed the previous EFSA ANS Panel conclusion according to which the available data did not allow for an adequate assessment of the safety of use of sodium carboxy methyl cellulose (E 466) in infants and young children consuming foods belonging to the FC 13.1.5.2. ©2022 European Food Safety Authority. *EFSA Journal* published by John Wiley and Sons Ltd on behalf of European Food Safety Authority.

Keywords: sodium carboxy methyl cellulose, E 466, 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 additives 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 a follow-up to the above, this Opinion addresses the data gaps previously identified during the re-evaluation of sodium carboxy methyl cellulose (E 466) as a food additive and its 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 present in the food categories 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 sodium carboxy methyl cellulose (E 466) comprised technical information and literature studies.

According to Commission Regulation (EU) No 231/2012, sodium carboxy methyl cellulose (E 466) is the partial sodium salt of a carboxymethyl ether of cellulose, the cellulose being obtained directly from strains of fibrous plant material. Cellulose is a linear homopolymer consisting of repeating β-D-glucopyranosyl units linked via (1,4) glycosidic bonds. Sodium carboxy methyl cellulose contains substituted β-D-glucopyranosyl units with the following general formula: $C_6H_7O_2(OR_1)(OR_2)(OR_3)$, where R_1, R_2, R_3 each may be one of the following: -H; $-CH_2COONa$; $-CH_2COOH$. Sodium carboxy methyl cellulose is generally used as a food additive due to its emulsifying, stabilising and thickening properties. The substance has the CAS Registry Number 9004-32-4 and the EINECS number 618-378-6. Specifications for sodium carboxy methyl cellulose (E 466) have been defined in Commission Regulation (EU) No 231/2012.

In response to the EFSA call for data, analytical data on levels of toxic elements (arsenic, lead, cadmium, mercury) in commercial samples of E 466 were provided by one IBO for the additive intended for use in food for the general population. The Panel noted that the occurrence data on toxic elements submitted by the IBO are substantially lower than the current limits in the EU specifications. The potential exposure to toxic elements from the use of the food additive E 466 was calculated by assuming that they may be present in the food additive up to a certain limit value and then by calculation pro-rata to the estimates of exposure to the food additive itself. The Panel performed the calculations for three scenarios assuming the presence of As, Pb, Cd and Hg in E 466 at (i) the maximum current limit in the EU specification; (ii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher; and (iii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher and applied a factor of 5 in order to account for representativeness and analytical measurement uncertainty. The potential exposure to the toxic elements was compared against the available health-based guidance values (HBGV) and reference points (RPs). For scenarios (i) and (iii), the exposure to the toxic elements from the consumption of E 466 is substantial and this gives rise to concern.

The Panel concluded that the technical data provided by the IBO support an amendment of the specifications for sodium carboxy methyl cellulose (E 466) laid down in Commission Regulation (EU) No 231/2012.

Sodium carboxy methyl cellulose (E 466) is an additive authorised 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). The IBOs declared that E 466 is not used in food for infants below 16 weeks of age and in FC 13.1.5.1.

Considering the above dietary exposure to sodium carboxy methyl cellulose (E 466) from its use as a food additive for infants below 16 weeks of age and in FC 13.1.5.1 was not estimated. Dietary exposure to sodium carboxy methyl cellulose (E 466) was estimated for FC 13.1.5.2 for the consumers only of food for special medical purposes (FSMP) for infants above 16 weeks and toddlers (age 1–3 years).

Due to the lack of data, a safety assessment has not been performed for FC 13.1.5.1.

Due to the almost unchanged database compared to the situation before the call for data, the FAF Panel confirmed the previous EFSA ANS Panel conclusion according to which the available data did not allow for an adequate assessment of the safety of use of sodium carboxy methyl cellulose (E 466) in infants and young children consuming foods belonging to the category 13.1.5.2.

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1. Introduction

The present opinion deals with the follow-up on issues that have been expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of celluloses as food additives applicable to sodium carboxy methyl cellulose (E 466) (EFSA ANS Panel, 2018) and including the risk assessment of sodium carboxy methyl cellulose (E 466) for the use as food additive in food according to food category (FC) 13.1.5.1 (dietary foods for infants for special medical purposes and special formulae for infants) and FC 13.1.5.2 (dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC[1]) for infants above 16 weeks of age and young children up to 3 years.

The Panel noted that information to address the safety of sodium carboxy methyl cellulose (E 466) for uses in food for infants below 16 weeks of age according to FC 13.1.5.1 was not provided by the IBOs. A trade association representing food grade cellulose manufacturers declared that sodium carboxy methyl cellulose (E 466) is not used in food for infants below 16 weeks of age and consequently data to address these uses were not submitted (Documentation provided to EFSA n.1). This was confirmed by a trade association representing the EU specialised nutrition industry (Documentation provided to EFSA n.4). However, use levels for FC 13.1.5.2 were provided (see Sections 3.3.1 and 3.3.2; Documentation provided to EFSA n.4).

The Panel noted that the IBOs did not provide biological and toxicological data even on further request for the uses under FC 13.1.5.1 and FC 13.1.5.2 in infants above 16 weeks of age and young children up to 3 years.

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,[2] 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,[3] 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.[4] Now EFSA is expected to launch dedicated calls for data to be able to perform such risk assessments.

[1] Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. OJ L 91, 7.4.1999, p. 29–36.

[2] 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.

[3] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a program for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.

[4] See Section 1.1.3.

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[5] on food additives and additional (missing) information would then be provided by interested business operators to the EC.

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

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

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

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.[4]

1.1.2. Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[6] 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,[4] 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 these 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 was intended to 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).

According to the information received in the context of the EFSA call for data,[7] sodium carboxy methyl cellulose (E 466) is not used in food for infants below 16 weeks of age. Consequently, data to address the safety of the uses of sodium carboxy methyl cellulose (E 466) in food for infants below 16 weeks of age were not provided by any interested business operator (IBO) in response to the specific questions of the EFSA call for data. The present assessment will, therefore, cover only the follow-up on issues that have been expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of celluloses as food additives, applicable to sodium carboxy methyl cellulose (E 466) (EFSA ANS Panel, 2018).

The present assessment refers exclusively to the currently permitted uses of E 466 as a food additive and does not include a safety assessment of other uses of carboxymethyl celluloses.

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

[6] 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.

[7] Call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 18 July 2018. Available from: https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-sodium.

1.2. Previous evaluations of sodium carboxy methyl cellulose (E 466) for use in foods for infants

The Scientific Committee on Food (SCF) considered the use of sodium carboxy methyl cellulose (E 466) acceptable in foods for special medical purposes (FSMP) for infants and young children at levels up to 10 g/L (liquid foods) and up at 10 g/kg (solid foods). The same Committee reserved its opinion on a request to use E 466 in weaning foods pending on the finalisation of its assessment on persorption of macromolecular additives but noted that otherwise the toxicological data did not indicate any effects likely to be of concern for infants and young children over weaning age. However, the Committee has since been informed that sodium carboxy methyl cellulose in water is in colloidal form and hence is not likely to be persorbed (SCF, 1998; EFSA ANS Panel, 2018).

1.3. Summary of the previous EFSA re-evaluation of sodium carboxy methyl cellulose (E 466) 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) has re-evaluated the safety of celluloses used as food additives. That assessment also covered sodium carboxy methyl cellulose (E 466) (EFSA ANS Panel, 2018).

The ANS Panel concluded that modified celluloses, including sodium carboxy methyl cellulose (E 466), are not absorbed intact, not fermented and are excreted intact via the faeces.

Data on acute oral toxicity were available to the ANS Panel for sodium carboxy methyl cellulose (E 466). These data indicated low oral acute toxicity. Short-term and subchronic toxicity studies performed with several modified celluloses were available to the ANS Panel. In the majority of the studies, animals were dosed via diet at levels up to 10%. Effects on body weight at the highest dose tested (10%) were reported in some, but not all studies, and were considered a consequence of nutritional constraints rather than toxicity. No adverse effects were reported with most of the tested celluloses, except for local effects on caecal size due to the presence of undigested fibre. The ANS Panel concluded that sodium carboxy methyl cellulose (E 466) does not raise concern for genotoxicity.

In the available chronic toxicity studies performed with sodium carboxy methyl cellulose (E 466), there were some inconsistencies in the data, however, the main effects seen were decreases in body weight gain at the highest dose probably due to nutritional imbalance. Adverse effects on reproductive performance or developmental effects were not observed in the available studies in rats and mice. The ANS Panel noted that sodium carboxy methyl cellulose (E 466) was frequently used in the vehicle used for gavage administration of other food additives/chemicals/drugs at concentrations up to 2% in chronic, reproductive and developmental toxicity and carcinogenicity studies. The absence of reported adverse effects in the vehicle control groups in the toxicity studies provided additional evidence of the lack of safety concern for modified celluloses at levels up to 2%.

Overall, the Panel considered that based on the animal data, the toxicity of celluloses was low; NOAELs were generally the highest doses tested (up to at least 9,000 mg/kg bw per day). The available data in humans indicated that daily doses of up to 6,000 mg for around 8 months were not associated with adverse effects. Nevertheless, as with other dietary fibres, large bolus intakes of celluloses were occasionally associated with laxation though a dose–response effect was not clearly observed. Overall, there were no indications that humans would be more sensitive than laboratory animals.

Carboxy methyl cellulose was one of the food additives reported to alter gut microbiota, promote gut inflammation, promote obesity and impair glycaemic control in a publication by Chassaing et al. (2015). Similar effects were reported for other emulsifiers (Swidsinski et al., 2009a,b; Renz et al., 2012; Merga et al., 2014; Cani and Everard, 2015; Chassaing et al., 2015; Romano-Keeler and Weitkamp, 2015; Lecomte et al., 2016; Shah et al., 2017). The ANS Panel noted that some of the effects associated with emulsifiers are not systematically studied as specific endpoints in toxicity studies performed according to the available toxicity test guidelines. However, the ANS Panel noted that the histopathological findings reported in some of those studies are not seen in long-term studies at high doses of celluloses.

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

The ANS Panel concluded that there was no need for a numerical ADI for the general population and that there would be no safety concern at the reported uses and use levels for all the celluloses re-evaluated as food additives, including E 466. The ANS Panel considered that it would be useful if risk managers had an indicative daily consumption/total exposure value for celluloses used as food additives which would not pose a safety concern and uses up to this value would not require a further risk assessment. The ANS Panel considered that an indicative total exposure (daily consumption value from food additive use) of around 660–900 mg/kg bw per day could be identified.

Regarding the use of sodium carboxy methyl cellulose (E 466) in foods belonging to the categories 13.1.5.1 'dietary foods for special medical purposes and special formulae for infants' and 13.1.5.2, 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC', the ANS Panel concluded that the available data did not allow for an adequate assessment of the safety of those uses. The ANS Panel, however, noted that E 466 seemed not to be used in these food categories as no use or use levels were submitted by the IBOs and very few foods belonging to these categories appeared to be labelled with 'E 466'.

The ANS Panel recommended that the European Commission considers lowering the maximum limits for the toxic elements arsenic, lead, mercury and cadmium present as impurities in the EU specifications for unmodified and modified celluloses (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468, E 469) to ensure that these food additives will not be a significant source of exposure to these toxic elements in food.

2. Data and methodologies

2.1. Data

The Panel based its assessment on information submitted following the EFSA public call for data[7] to collect relevant information from IBOs, and the conclusions and recommendations from previous evaluations.

To verify the use of sodium carboxy methyl cellulose (E 466) in food products the Mintel's GNPD was used.

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 sodium carboxy methyl cellulose (E 466) for all population groups and to address the data gaps identified during the re-evaluation, the FAF Panel assessed the information provided:

- For the follow-up on issues that have been expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of celluloses as food additives, applicable to sodium carboxy methyl cellulose (E 466) (EFSA ANS Panel, 2018); and
- For the risk assessment of sodium carboxy methyl cellulose (E 466) for the use as food additive in food according to FC 13.1.5.1 (dietary foods for infants for special medical purposes) and FC 13.1.5.2 (dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC) in infants above 16 weeks of age and young children up to 3 years.

The Panel noted that information to address the safety of sodium carboxy methyl cellulose (E 466) for uses in food for infants below 16 weeks of age according to FC 13.1.5.1 was not provided by any of the IBOs. A trade association representing food grade cellulose manufacturers declared that sodium carboxy methyl cellulose (E 466) is not used in food for infants below 16 weeks of age and consequently data to address these uses were not submitted (Documentation provided to EFSA n.1). This was confirmed by the trade association representing the EU specialised nutrition industry (Documentation provided to EFSA n.4).

Furthermore, the Panel noted that the IBOs did not provide biological and toxicological data even on further request for the uses under 13.1.5.1 and FC 13.1.5.2 in infants above 16 weeks of age and

young children up to 3 years. However, use levels for FC 13.1.5.2 were provided (see Section 3.3.1 and 3.3.2; Documentation provided to EFSA n.4).

3. Assessment

3.1. Identity and specifications of E 466

According to Commission Regulation (EU) No 231/2012[9], the food additive E 466 is named as sodium carboxy methyl cellulose. Cellulose is a linear homopolymer consisting of repeating β-D-glucopyranosyl units linked via (1,4) glycosidic bonds. Sodium carboxy methyl cellulose (E 466) is the partial sodium salt of a carboxymethyl ether of cellulose.

For more information on the physical properties and the chemical composition and structure of sodium carboxy methyl cellulose (E 466), the reader is referred to the ANS Panel opinion (EFSA ANS Panel, 2018) and Figure 1.

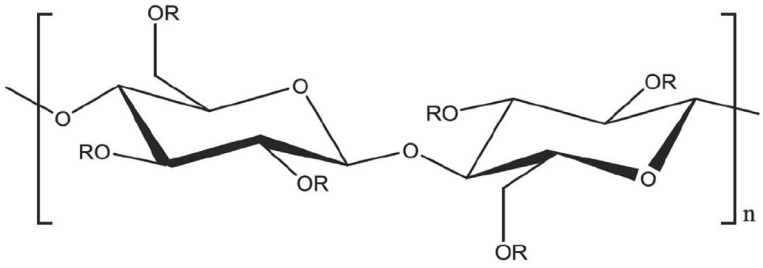

Figure 1: Chemical structure of sodium carboxy methyl cellulose E 466, where R = H or -CH_2COONa or -CH_2COOH. In this structure, 'n' represents the number of anhydrocellobiose repeating units (adapted from EFSA ANS Panel, 2018).

The specifications for sodium carboxy methyl cellulose (E 466) as defined in the Commission Regulation (EU) No 231/2012 are listed in Table 1.

Table 1: Specifications for sodium carboxy methyl cellulose (E 466) according to Commission Regulation (EU) No 231/2012

	Commission Regulation (EU) No 231/2012
Synonyms	CMC; NaCMC; Sodium CMC,
Definition	Carboxy methyl cellulose is the partial sodium salt of a carboxymethyl ether of cellulose, the cellulose being obtained directly from strains of fibrous plant material
Chemical name	Sodium salt of the carboxymethyl ether of cellulose
Chemical formula	The polymers contain substituted anhydroglucose units with the following general formula: $C_6H_7O_2(OR_1)(OR_2)(OR_3)$, where R_1, R_2, R_3 each may be one of the following: – H – CH_2COONa – CH_2COOH
Molecular weight	Higher than approximately 17,000 (degree of polymerisation approximately 100)
Assay	Content on the anhydrous basis not less than 99.5%
Description	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder
Identification	
Solubility	Yields a viscous colloidal solution with water. Insoluble in ethanol
Foam test	A 0.1% solution of the sample is shaken vigorously. No layer of foam appears. (This test permits the distinction of sodium carboxy methyl cellulose from other cellulose ethers)

[9] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance. OJ L 83, 22.3.2012, p. 1–295.

	Commission Regulation (EU) No 231/2012
Precipitate formation	To 5 mL of a 0.5% solution of the sample, add 5 mL of 5% solution of copper sulfate or of aluminium sulfate. A precipitate appears. (This test permits the distinction of sodium carboxymethyl cellulose from other cellulose ethers and from gelatine, locust bean gum and tragacanth)
Colour reaction	Add 0.5 g powdered carboxy methyl cellulose sodium to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring until a clear solution is produced, and use the solution for the following test: To 1 mg of the sample, diluted with an equal volume of water, in a small test tube, add 5 drops of 1-naphthol solution. Incline the test tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer. A red-purple colour develops at the interface
pH	Not less than 5.0 and not more than 8.5 (1% colloidal solution)
Purity	
Degree of substitution	Not less than 0.2 and not more than 1.5 carboxymethyl groups (–CH_2COOH) per anhydroglucose unit
Loss on drying	Not more than 12% (105°C to constant weight)
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total glycolate	Not more than 0.4%, calculated as sodium glycolate on the anhydrous basis
Sodium	Not more than 12.4% on the anhydrous basis

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

3.2. Technical data submitted

3.2.1. Toxic elements

The following was requested in the EFSA call for data:

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

Analytical data were provided by one IBO, a trade association representing several manufacturers, (Documentation provided to EFSA n.1,2,3) for levels of lead, mercury, cadmium and arsenic in 42 samples of E 466. The samples were described by the IBOs '*as comprising various grades of E 466, Cellulose Gum*'. It was clarified by the data provider that these samples were manufactured as the food additive and described as 'grades' since E 466 can consist of different grades within the specifications defined by the EU, varying in degree of substitution, viscosity and particle size.

The data for the 42 samples were collected from four manufacturers, identified as A, B, C and D: Manufacturer A provided data for five samples covering 3 years (2018–2020); Manufacturer B provided data for five samples covering 1 year (2020); Manufacturer C provided data for five samples covering 3 years (2015–2017); and Manufacturer D provided data for 27 samples covering 1 year (2018).

The majority of the samples were analysed using acid digestion of the sample followed by inductively coupled plasma mass spectrometry (ICP-MS) analysis for lead, mercury, cadmium and arsenic. The exceptions were that the samples from Manufacturer B were analysed by cold vapour atomic absorption spectrometry (CV-AAS) for mercury. Also, for Manufacturer B, the method for the sample preparation was not given. Lastly, the samples from Manufacturer C used high-resolution mass spectrometry (ICP-HR-MS) as opposed to nominal mass resolution MS.

The reporting of the results was not consistent between the four data subsets with some manufacturers reporting against limit of detection (LOD) values and some reporting against limit of quantification (LOQ) values.

For lead, three samples were at 0.05, 0.06 and 0.09 mg/kg and all other values (39/42; range < 0.02 mg/kg to < 0.1 mg/kg) were less than the LOD or LOQ. The Panel noted that based on

this data set, all samples would be below a value of 0.1 mg/kg i.e. 20-fold lower than the current EU specification limit for lead at 2 mg/kg.

For mercury, all values (42/42; range < 0.0025 mg/kg to < 0.1 mg/kg) were less than LOD or LOQ. The Panel noted that based on this data set, all samples would be ≤ a value of 0.1 mg/kg i.e. 10-fold lower than the current EU specification limits for mercury at 1 mg/kg.

For cadmium, one sample was at 0.05 mg/kg and all other values (41/42, range < 0.001 mg/kg to < 0.05 mg/kg) were less than LOD or LOQ. The Panel noted that based on this data set, all samples would be ≤ a value of 0.05 mg/kg i.e. 20-fold lower than the current EU specification limits for cadmium of 1 mg/kg.

For arsenic, one sample was at 0.06 mg/kg and all other values (41/42, range < 0.015 mg/kg to < 0.05 mg/kg) were less than LOD or LOQ. The Panel noted that based on this data set, all samples would be below a rounded up value of 0.1 mg/kg i.e. 30-fold lower than current EU specification limits value for arsenic of 3 mg/kg.

All results above the LOQ were reported only for the five numerical data reported by one manufacturer.

The IBO did not provide a proposal on the lowest technologically achievable level for lead, mercury, cadmium and arsenic and recommended not to lower the limits for heavy metals in the specifications for E 466 (Documentation provided to EFSA n.3). The Panel was not in agreement with the arguments by the IBO that lowering the specifications would result in technical hurdles and that analytical laboratories could not achieve low LOQs/LODs with sufficient accuracy. Exposure to heavy metals from all sources should be reduced to the extent possible. The Panel was, therefore, of the opinion, that the specifications for heavy metals should be based on the lowest technologically achievable levels.

3.2.2. Information on particular specification requirements for the additive

The following information was requested in the EFSA call for data:

- The usage levels of use of sodium carboxy methyl cellulose (E 466) alone or in combination with other thickening agents (indication of food additive name and level of use) in the special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1).
- The fate and the reaction products of sodium carboxy methyl cellulose (E 466) in special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1).
- Particular specification requirements for identity and purity of sodium carboxy methyl cellulose (E 466) (e.g. content of toxic elements, sodium, total glycolate, isopropanol) in special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1). Analytical data on impurities in the final special formulae for infants below 16 weeks of age need to be provided when no legal limit has been established.
- In addition, data should be provided demonstrating the absence of *Cronobacter* (*Enterobacter*) *sakazakii*.

One IBO, a trade association representing producers of food grade cellulose, declared that E 466 is not applied as an additive in foods for infants below 16 weeks of age. No technical information was therefore provided for this part of the call for data (Documentation provided to EFSA n.1).

Another IBO, the trade association representing the EU specialised nutrition industry, declared that the E 466 is only used by its members: '*in liquid FSMPs for babies and young children from 6 months to 3 years of age (cat 13.1.5.2). We would want, if possible, the use of the additive to continue being permitted in this category for inborn errors of metabolism and other specialised diets such as renal and ketogenics*' (Documentation provided to EFSA n.4). The Panel considered that E 466 is not used in FC 13.1.5.1.

The reactions and fate in food of E 466 were reviewed by the EFSA ANS Panel as part of their re-evaluation of the whole class of celluloses (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469) as food additives (EFSA ANS, 2018). No specific concerns were raised in that re-evaluation, for any of the celluloses when used as additives in foods intended for the general population. Information on the fate and the reaction products of sodium carboxy methyl cellulose (E 466) in special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1) was not provided.

3.2.3. Particle size distribution

Upon request from EFSA, information on the particle size distribution was provided (Documentation provided to EFSA n.5,6,7). One IBO provided information on particle size distribution of 14 batches of five E 466 products from three manufacturers, determined by laser diffraction (LD) (Documentation provided to EFSA n.7). The analysed five E 466 products differ in the degree of substitution ranging from 0.65 to 0.95. The calculated 10th percentile of E 466 particles size ranged from 14 to 58 μm. The batches were analysed on different LD instruments and methods were not adequately described. The IBO stated that dynamic image analysis revealed that 90% of the particles are bigger than 20 μm.

The Panel noted that LD analysis is not considered a proper method to investigate the presence of nanosized particle as it does not provide information on the size of the constituent particles as required by the Guidance-TR and is prone to bias for polydisperse materials (Rauscher et al., 2019; Mech et al., 2020a,b).

The IBO also provided results from scanning electron microscopy (SEM) analysis on 10 batches of four E 466 products previously analysed by LD (Documentation provided to EFSA n.7). The batches were analysed on different SEM instruments. The method and the measurands were not adequately described. The number-based size distributions and descriptive statistics were not presented. The IBO reported that in all analysed batches, the measured particles were of rod-like and sphere-like shapes. Furthermore, the IBO reported that no agglomerates and aggregates are present in the analysed E 466.

The Panel noted that the magnifications used for SEM analysis i.e. ×250, ×1000 and ×2500, and the resolution of the images estimate to be of order 20 nm does not allow to identify the constituent particles in the nano range.

Based on the data on particle size distribution submitted by the IBO and the criteria set in the relevant EFSA Scientific Committee Guidance (EFSA Scientific Committee, 2021), the Panel concluded that in this specific case, the presence of small particles, including nanoparticles, cannot be confirmed or excluded in the pristine food additive. The particle size distribution of pristine E 466 may also depend on other parameters such as the degree of substitution. EFSA received information provided by one IBO on the degree of substitution for 11 batches of five sodium carboxy methyl cellulose (E 466) products, which was ranging from 0.65 to 0.95 (Documentation provided to EFSA n.7). The Panel noted that these values are within the range of the EU specifications.

The Panel stresses that currently no standardised methods are available for the polysaccharide thickening and gelling agents used as food additives, such as sodium carboxy methyl cellulose (E 466) to measure the particle size distribution by number.

3.3. Exposure assessment

3.3.1. Authorised uses and use levels

Maximum levels of sodium carboxy methyl cellulose (E 466) in foods for infants 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 Annex II to Regulation (EC) No 1333/2008, sodium carboxy methyl cellulose (E 466) is authorised in dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1), from birth onwards in products for the dietary management of metabolic disorders, at a maximum level of 10,000 mg/kg (or mg/L as appropriate) 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) from birth onwards in products for the dietary management of metabolic disorders, at a maximum level (MPL) of 10,000 mg/kg (or mg/L as appropriate) (Table 2).

Sodium carboxy methyl cellulose (E 466) is also authorised according to Annex III, Part 5 to Regulation (EC) No 1333/2008. It can be added as a food additive in nutrient preparations intended to be used in dietary foods for infants and young children for special medical purposes as defined in Directive 1999/21/EC (FC 13.1.5) under the condition that the maximum level in foods mentioned in Annex II, Part E, point 13.1, is not exceeded (Table 3).

Table 2: MPLs of sodium carboxy methyl cellulose (E 466) in foods for infants and young children according to Annex II to Regulation (EC) No 1333/2008

Food category number	Food category name	E-number	Restrictions/exceptions	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 466	From birth onwards in products for the dietary management of metabolic disorders	10,000
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 466	From birth onwards in products for the dietary management of metabolic disorders	10,000

MPL: maximum permitted level.

Table 3: MPLs of sodium carboxy methyl cellulose (E 466) in foods for infants and young children according to Annex III to Regulation (EC) No 1333/2008

E number	Name of the food additive	Maximum permitted level	Nutrient to which the food additive may be added	Food category
E 466	Sodium carboxy methyl cellulose, Cellulose gum	For uses in nutrient preparations under the condition that the maximum level in foods mentioned in point 13.1 of Part E of Annex II is not exceeded	All nutrients	Dietary foods for infants and young children for special medical purposes as defined in Directive 1999/21/EC

All authorised uses of E 466 in foods can be seen in the 2018 opinion exposure section (EFSA ANS Panel, 2018; Table 13).

3.3.2. Exposure data

Some food additives are authorised in the EU in infant formulae as defined by Commission Directive 2006/141/EC (FC 13.1.1) and in dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1) at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, actual use levels are required for performing a more realistic exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a public call[10] for technical and toxicological data on sodium carboxy methyl cellulose (E 466) 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, no information on the actual use levels of sodium carboxy methyl cellulose (E 466) in foods was made available to EFSA by the IBOs. No analytical data on the concentration of sodium carboxy methyl cellulose (E 466) in foods were made available by the Member States.

3.3.2.1. Reported use levels in food category 13.1.5.1 and as a carry-over from the authorised use according to annex III, part 5, section B

The IBOs did not provide EFSA with data for FC 13.1.5.1. Therefore, for this food category, the exposure assessment was not performed.

[10] Call for technical and toxicological data sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Available at: https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-sodium.

3.3.2.2. Reported use levels in food category 13.1.5.2

One IBO indicated that E 466 is needed for technological reasons in liquid FSMPs for babies and young children from 6 months to 3 years of age. They provided levels for the FC 13.1.5.2 for liquid products for over 1 year of age in the range of 1,700–3,000 mg/L (Documentation provided to EFSA n.4). Therefore, dietary exposure was estimated for the population groups of infants above 16 weeks of age and for toddlers.

3.3.2.3. Summarised data extracted from the Mintel's global new products database

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 3.4 million food and beverage products of which more than 1,300,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 24 of its 27 Member Countries and Norway presented in the Mintel GNPD.[11]

For the purpose of this Scientific Opinion, Mintel's GNPD[12] was used for checking the labelling of food and beverage products and food supplements for sodium carboxy methyl cellulose (E 466) within the EU's food market as the database contains the compulsory ingredient information on the label.

No products intended for use in infants below 16 weeks were found in Mintel's GNPD as labelled with sodium carboxy methyl cellulose (E 466).

In the whole of category of baby foods (including fruit products, desserts and yoghurts, growing up milk 1–4 years, biscuits and rusks, cereals, formula, …), one product (growing up milk 1–4 years) was found in Mintel's GNPD as labelled with sodium carboxy methyl cellulose (E 466).

Considering all foods on the EU market, 4,848 products were labelled with sodium carboxy methyl cellulose (E 466) between 2017 and 2022 according to Mintel GNPD.

Appendix B lists the percentage of the food products labelled with sodium carboxy methyl cellulose (E 466) out of the total number of food products per food subcategory according to the Mintel GNPD food classification. The percentages ranged from less than 0.1% in many food subcategories up to 16% in the Mintel GNPD food subcategories 'Gum' and 'Flavoured drinks' for E 466. The average percentage of foods labelled to contain sodium carboxy methyl cellulose (E 466) was 1.2%.

3.3.3. Exposure estimates

3.3.3.1. Dietary exposure to sodium carboxy methyl cellulose (E 466) for babies and young children consuming FSMP, FC 13.1.5.2

Sodium carboxy methyl cellulose (E 466) is authorised in the food categories 13.1.5.1 and 13.1.5.2. Because the IBOs declared that they do not use E 466 in FC 13.1.5.1, an exposure assessment scenario considering only FC 13.1.5.2 was performed to estimate the exposure of infants (above 16 weeks) and toddlers (classified as young children in Commission Delegated Regulation (EU) 2016/127, age of 1–3 years) who may eat and drink these FSMPs. The consumption of these foods is not reported in the EFSA Comprehensive database. To consider potential exposure to sodium carboxy methyl cellulose (E 466) via these foods, the Panel assumed that the amount of FSMP consumed by infants and toddlers resembles that of comparable foods in infants and toddlers from the general population. Thus, the consumption of FSMP categorised as FC 13.1.5 was assumed equal to that of formulae and food products categorised as FCs 13.1.1, 13.1.2, 13.1.3 and 13.1.4. Use levels (range) for the FC 13.1.5.2 were received for sodium carboxy methyl cellulose (E 466) (Documentation provided to EFSA n.4). The maximum of this range was used in the following scenario:

- Infants (> 16 weeks to 1 year): consumers only of FSMP were assumed to be exposed to sodium carboxy methyl cellulose (E 466) present at the maximum permitted level on a daily basis via consumption of FC 13.1.5.2. For the remaining food categories, the mean of the typical reported use levels of any of the celluloses (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 469) was used.
- Toddlers (1–3 years): Consumers only of FSMP were assumed to be exposed to sodium carboxy methyl cellulose (E 466) present at the maximum reported use level on a daily basis via consumption of FC 13.1.5.2. For the remaining food categories, the mean of the typical reported

[11] Missing Cyprus, Luxembourg and Malta.
[12] http://www.gnpd.com/sinatra/home/ accessed on 24/10/2022.

use levels was used considering the levels of any celluloses (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 469).

Dietary exposure was calculated by multiplying concentrations of E 466 (for FC 13.1.5.2) or any of the celluloses (for the other food categories) per food category with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are considered as not adequate to assess repeated exposure. The exposure was estimated in this way for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group. Based on these distributions, the mean and 95th percentile of exposure was calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011).

Table 4: Dietary exposure for infants above 16 weeks of age and toddlers according to Annex II to Regulation (EC) No 1333/2008 (in mg/kg bw per day) with levels of E 466 for FSMP formulae (FC 13.1.5.2) and levels of celluloses (E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 469) for the remaining foods

	Infants (> 16 weeks to 1 year)[(a)] mg/kg bw per day	Infants (6 months to 1 year)[(a)] mg/kg bw per day	Toddlers (1–3 years)[(b)] mg/kg bw per day
FSMP consumers only scenario			
• Mean	14–911	12–911	13–156
• 95th percentile	28–987	29–987	46–243

(a): Using the MPL for the FC 13.1.5.2.
(b): Using the maximum reported use level (3,000 mg/kg) for the FC 13.1.5.2.

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: – Consumption data: different methodologies/representativeness/underreporting/misreporting/ no portion size standard for subjects above 16 weeks of age	+/–
Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days for subjects above 16 weeks of age	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Database: uncertainties to which types of food the levels refer	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Infants above 16 weeks of age: – Use levels from all celluloses considered for FCs other than FC 13.1.5.2 – Exposure calculations based on the MPL for FC 13.1.5.2; – Exposure calculations based on the average of the typical level was considered for the remaining FCs	 +/– + +/–
Toddlers: – Use levels from all celluloses considered for FCs other than FC 13.1.5.2 – Exposure calculations based on the maximum reported use from industry for FCs 13.1.5.2, for the remaining FC, the average of the typical level was considered	 +/– +/–

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

Sodium carboxy methyl cellulose (E 466) is authorised in dietary foods for infants and young children for special medical purposes as defined by Commission Directive 1999/21/EC and special formulae for infants (FC 13.1.5.1 and FC 13.1.5.2) according to Annexes II and III to Regulation (EC) No 1333/2008. No use levels were submitted for formulae intended for infants (i.e. below 1 year); therefore, for this population of infants, exposure assessment was performed for the consumers only of FSMP (FC 13.1.5.2) using the MPL. Exposure assessment for toddlers was performed using the maximum reported use level (see Table 4).

The exposure assessment for infants would in general result in an overestimation of the exposure to E 466. If E 466 is, indeed, only used in liquid follow-on formulae for toddlers (from 1 year) and based on the assumption that carers of children would be brand loyal to a special formula (FC 13.1.5.2), the exposure assessment would in general result in a reliable estimation of the exposure for toddlers.

It should be noted that the use according to Annex III to Regulation No 1333/2008 was taken into account in the regulatory maximum level exposure assessment scenario as the maximum level authorised according to the Annex III is '*For uses in nutrient preparations under the condition that the maximum level in foods mentioned in point 13.1 of Part E of Annex II is not exceeded*'.

3.4. Proposed revision to existing EU specifications for sodium carboxy methyl cellulose (E 466)

The potential exposure to impurities from the use of the food additive E 466 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 its 2018 re-evaluation of the celluloses used as food additives, in view of the interchangeability of the different celluloses added to foods along with the fact that for the large majority of applications/food categories, the MPLs are *quantum satis*, the ANS Panel took a group approach and estimated exposure to all celluloses (E 460–466, E 468 and E 469) as a group. The highest exposure was observed for toddlers in both of the refined exposure scenarios (non- and brand-loyal scenarios). The ANS Panel, at that time, identified brand loyalty to specific food categories in infants and toddlers (e.g. flavoured drinks). In that refined brand-loyal exposure scenario, the exposure of toddlers to the celluloses (E 460–466, E 468 and E 469) was calculated to be 190 and 506 mg/kg bw per day for the highest mean and 95th percentile values, respectively (EFSA ANS Panel, 2018). The Panel noted that using these exposure figures to calculate pro-rata exposure to toxic elements (as below) provides an overestimation since the previously estimated exposure to the group of cellulose additives (E 460–466, E 468 and E 469; EFSA ANS Panel, 2018), in the present assessment, is instead considered to come only from E 466.

In the current opinion, the dietary exposure for infants and toddlers (consumers only of FSMPs) was estimated (see Table 4). The highest mean for the refined exposure estimate was 911 mg/kg bw per day and the highest 95th percentile estimate was 987 mg/kg bw per day for both age groups. The Panel noted that using these exposure figures to calculate pro-rata exposure to toxic elements (as below) would in general result in an overestimation (see Section 3.3.4).

These calculations have been performed irrespective of the fact that toxicological and clinical data were not submitted for this use of E 466.

The Panel noted that the IBOs declared that E 466 is not used in food for infants below 16 weeks of age and, therefore, the exposure to toxic elements from the use of E 466 for this age group was not calculated. According to the IBOs, sodium carboxy methyl cellulose (E 466) is used in FC 13.1.5.2 (see Sections 3.2.2 and 3.3.2.2) for children from 6 months to 3 years of age. Therefore, the dietary exposure to toxic elements from the use of E 466 was estimated for this food category and population groups only (see Table 4).

The level of the impurity in the food additive combined with the estimated intakes of E 466, presented in Table 4, 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 and constituents potentially present in E 466.

Table 6: Reference points/health-based guidance values for impurities potentially present in E 466

Impurity/constituent/ HBGV/RP (μg /kg bw)	Basis/Reference
Lead (Pb)/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). EFSA CONTAM Panel (2010)
Mercury (Hg)/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 per week, expressed as mercury was established. EFSA CONTAM Panel (2012)
Cadmium (Cd)/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 as the biomarker of tubular damage recognised as the most useful biomarker in relation to tubular effects. A group-based $BMDL_5$ of 4 μg Cd/g creatinine for humans was derived. A chemical-specific adjustment factor of 3.9 was applied to account for human variability in urinary cadmium within each dose-subgroup in the analysis resulting in a reference point of 1.0 μg Cd per g creatinine. In order to remain below 1 μg Cd/g creatinine in urine in 95% of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 μg Cd/kg bw, corresponding to a weekly dietary intake of 2.5 μg Cd/kg bw. EFSA 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. an 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); bw: body weight; TWI: Tolerable Weekly Intake; MOE: margin of exposure.

The risk assessment of the 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 RP (e.g. BMDL Table 6) by the exposure estimate (Table 4), or by estimating the contribution of the use of E 466 to the HBGV (expressed as percentage of the HBGV).

3.4.1. Toxic elements

The Panel noted that the concentration data on toxic elements submitted by the IBO are substantially lower than the current limits in the EU specifications (Documentation provided to EFSA n.1,2,3). The Panel considered that the maximum limits in the EU specifications for toxic elements should be established based on actual levels measured 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 described below could be considered.

One IBO provided analytical data for As, Cd, Hg and Pb for the additive intended for use in food for the general population (Documentation provided to EFSA n.1,2,3). The data were for 42 samples and were provided by four different manufacturers of E 466 (Section 3.2.1). The Panel noted that for five samples, numerical data were reported: lead 0.05, 0.06, 0.09 mg/kg, arsenic 0.06 mg/kg and cadmium 0.05 mg/kg, which were reported above their respective LOQ. All other results for the four toxic elements were reported below their respective LOD or LOQ. Taking the few measured concentrations and the upper end of the ranges of LODs into account, the Panel decided to perform the risk assessment of the toxic elements considering the rounded up highest measured value of the

level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher, i.e. 0.1 mg/kg for arsenic, 0.05 mg/kg for cadmium, 0.1 mg/kg for mercury and 0.1 mg/kg for lead (see Section 3.2.1). The Panel used these values as a starting point to characterise the risk of potential exposure to toxic elements derived from the consumption of the food additive.

The Panel observed that if these values, i.e. 0.1 (As), 0.05 (Cd), 0.1 (Pb) and 0.1 (Hg) mg/kg, were to be considered as the maximum limits for the EU specifications, this would mean that the performance of the analytical method applied should guarantee a limit of quantification (LOQ) of two-fifths of the maximum limit, i.e. 0.04 (As), 0.02 (Cd), 0.04 (Pb) and 0.04 (Hg) mg/kg, in accordance with the provisions of Commission Regulation (EC) No 333 /2007[13] for toxic elements in food. These LOQ values, especially for cadmium, may be technically difficult to be achieved with the analytical techniques commonly applied for the measurement of toxic elements (e.g. ICP-MS). Of note, E 466 is a sodium-containing food additive and sodium can inhibit ionisation efficiency in the ICP-MS; thus, a lower sensitivity could be expected. Therefore, the Panel decided to perform also an estimate of the exposure to toxic elements, derived from the food additive, considering the above-mentioned values but now multiplied by a factor of 5 in order to account for representativeness and analytical measurement uncertainty. The resulting modulated values of toxic elements to calculate the exposure are 0.5 (As), 0.25 (Cd), 0.5 (Pb) and 0.5 (Hg) mg/kg.

The outcome of these considerations is that the Panel performed the risk assessment that would result if these toxic elements were present in E 466, using three scenarios: at (i) the maximum current limit in the EU specification; (ii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher; (iii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher and applied a factor of 5 (Table 7).

Table 7: Different scenarios for the calculation of the potential exposure to toxic elements from the use E 466

Source of the values (mg/kg) listed	Arsenic	Lead	Cadmium	Mercury
(i) Current limits in the EU specifications for E 466	3	2	1	1
(ii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher	0.1	0.1	0.05	0.1
(iii) Modulated values (as (ii) above with a factor of 5 applied)	0.5	0.5	0.25	0.5

The Panel emphasises that the choice of the factor, as well as other considerations such as on multiple sources of exposure, to conclude on 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 (see Table 8) illustrates the health impact that could result if revised maximum limits for toxic elements were to be used.

Table 8: Risk assessment for toxic elements

Exposure to E 466 (mg/kg bw/day)	Scenario (i) Based on the current EU specifications limits for toxic elements in E 466 for use in food for all age groups			
	MOE for As at 3 mg/kg	MOE for Pb at 2 mg/kg	of the TWI for Cd at 1 mg/kg %	% of the TWI for Hg at 1 mg/kg %
190[(a)]	0.53–14	1.3	53%	33%
506[(b)]	0.20-5.3	0.49	142%	89%
911[(c)]	0.11-2.9	0.27	255%	159%
987[(d)]	0.10-2.7	0.25	276%	173%

[13] Commission Regulation (EU) No 333/2007 of 28 March 2007 laying down the methods of sampling and analysis for the official control of the levels of lead, cadmium, mercury, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs. OJ L 88, 29.3.2007, p. 29–38.

Exposure to E 466 (mg/kg bw per day)	Scenario (ii) Based on the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher, in E 466 used in food for all age groups (Documentation provided to EFSA: 1,2,3).			
	MOE for As at 0.1 mg/kg	**MOE for Pb at 0.1 mg/kg**	**of the TWI for Cd at 0.05 mg/kg %**	**% of the TWI for Hg at 0.1 mg/kg %**
190[(a)]	16–421	26	3%	3%
506[(b)]	5.9-158	9.9	7%	9%
911[(c)]	3.3-88	5.5	13%	16%
987[(d)]	3.0-81	5.1	14%	17%
Exposure to E 466 (mg/kg bw per day)	**Scenario (iii) Based on the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher (Documentation provided to EFSA: 1,2,3) modulated by the Panel by applying factor 5 in E 466 used in food for all age groups.**			
	MOE for As at 0.5 mg/kg	**MOE for Pb at 0.5 mg/kg**	**of the TWI for Cd at 0.25 mg/kg %**	**% of the TWI for Hg at 0.5 mg/kg %**
190[(a)]	3.2–84	5.3	13%	17%
506[(b)]	1.2–32	2.0	35%	44%
911[(c)]	0.66–18	1.1	64%	80%
987[(d)]	0.61–16	1.0	69%	86%

(a): Highest exposure level among the different population groups (refined brand-loyal – toddlers – mean) (EFSA ANS Panel, 2018).
(b): Highest exposure level among the different population groups (refined brand-loyal – toddlers –95th percentile) (EFSA ANS Panel, 2018).
(c): Highest exposure level for infants on FSMP (refined brand-loyal – infants – mean) see Table 4, Section 3.3.1.
(d): Highest exposure level for infants on FSMP (refined brand-loyal – infants – 95th percentile) see Table 4, Section 3.3.1.

The resulting figures show, in scenarios (i) and (iii) as described above, that the exposure to toxic elements from the consumption of E 466 could be substantial.

Overall, based on the analytical data provided by the IBO in response to the EFSA call for data along with the considerations above, the Panel recommends the revisions of the existing EU specifications for sodium carboxy methyl cellulose (E 466) for toxic elements as listed in Table 9.

3.4.2. Additional revisions

The Panel noted that E 466 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. Therefore, the Panel recommends changing the word 'solution' to 'dispersion' in the EU specifications of E 466 (See Table 9).

The Panel also considered that the CAS number 9000-11-7 corresponding to sodium carboxy methyl cellulose should be included in the existing EU specifications for E 466.

Table 9: Proposal for a revised version of the existing EU specifications for sodium carboxy methyl cellulose (E 466)

	Commission Regulation (EU) No 231/2012	**Comment/justification for revision**
Synonyms	For brevity, see Table 1	Unchanged
Definition	See Table 1	Unchanged
Chemical name	See Table 1	Unchanged
CAS number	–	CAS number to be added '9000-11-7'
Chemical formula	see Table 1	Unchanged

	Commission Regulation (EU) No 231/2012	Comment/justification for revision
Molecular weight	see Table 1	Unchanged
Assay	see Table 1	Unchanged
Description	see Table 1	Unchanged
Identification		
Solubility	Yields a viscous colloidal solution with water. Insoluble in ethanol	Proposed revision: 'Yields a viscous colloidal dispersion in water. Insoluble in ethanol'
Foam test	see Table 1	Unchanged
Precipitate formation	see Table 1	Unchanged
Colour reaction	see Table 1	Unchanged
pH	Not less than 5.0 and not more than 8.5 (1% colloidal solution)	Proposed revision: 'Not less than 5.0 and not more than 8.5 (1% colloidal dispersion)'
Purity		
Degree of substitution	see Table 1	Unchanged
Loss on drying	see Table 1	Unchanged
Arsenic	Not more than 3 mg/kg	Lowered on the basis of the information provided and based on the considerations of the Panel
Lead	Not more than 2 mg/kg	Lowered on the basis of the information provided and based on the considerations of the Panel
Mercury	Not more than 1 mg/kg	Lowered on the basis of the information provided and based on the considerations of the Panel
Cadmium	Not more than 1 mg/kg	Lowered on the basis of the information provided and based on the considerations of the Panel
Total glycolate	see Table 1	Unchanged
Sodium	see Table 1	Unchanged

3.5. Biological and toxicological data

As a follow-up and in line with the conclusions and recommendations in the Scientific opinion on the re-evaluation of celluloses used as food additives (EFSA ANS Panel, 2018), the generation of additional data to assess the potential health effects of sodium carboxy methyl cellulose (E 466) when used as a food additive in 'dietary foods for infants for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and in 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2) was recommended. No data were submitted by the IBOs to address this data gap.

Furthermore, the following information on the toxicological properties of sodium carboxy methyl cellulose (E 466) and its adverse effects relevant for the safety of its use as a food additive in FSMPs for infants below 16 weeks was requested:

- A repeated dose study with direct oral administration of sodium carboxy methyl cellulose (E 466) to neonatal animals.
- Clinical data focusing on gastrointestinal effects to assess the safety of sodium carboxy methyl cellulose (E466) when used in dietary foods for special medical purposes in infants below 16 weeks of age (FC 13.1.5.1).
- Post-marketing surveillance reports on undesired and adverse reactions.
- Published and unpublished case reports as well as results from literature searches.

This information was also considered relevant for the risk assessment of the use of the food additive in FSMP for older infants and young children considering that the studies are of appropriate duration.

These data were not submitted by the IBOs. The Panel noted, however, that, as previously reported, a trade association representing producers of food grade cellulose declared that sodium carboxy methyl cellulose (E 466) is not used in food for infants below 16 weeks of age and

consequently data to address these uses were not submitted (Documentation provided to EFSA n.1). This was confirmed by the trade association representing the EU specialised nutrition industry (Documentation provided to EFSA n.4). The latter declared that the E 466 is only used by its members: '*in liquid FSMPs for babies and young children from 6 months to 3 years of age (cat 13.1.5.2). We would want, if possible, the use of the additive to continue being permitted in this category for inborn errors of metabolism and other specialised diets such as renal and ketogenics*' (Documentation provided to EFSA n.4). The Panel considered that E 466 is not used in FC 13.1.5.1.

A position paper dealing with the impact of emulsifiers on the gut microbiota was indicated as relevant by one IBO (Vo et al., 2019; Documentation provided to EFSA n.2). In addition, the Panel was made aware of a paper on the effects of carboxy methyl cellulose on zebrafish, i.e. lipid accumulation and expression of genes associated with obesity (Baran et al., 2020). The Panel considered that these studies do not add information which can be used for the safety assessment of sodium carboxy methyl cellulose (E 466) for its uses as food additive.

3.5.1. Other studies

The Panel was made aware of recent studies in which sodium carboxy methyl cellulose was investigated in mice and humans. These studies addressing the microbiota and a few toxicological endpoints showed changes in the microbiota composition in mice and also in humans (Arnold et al., 2022; Chassaing et al., 2022; Chassaing et al., 2015; Naimi et al., 2021; Sandall et al., 2020; Viennois et al., 2020; Viennois and Chassaing, 2021). However, the consequences and the meaning of these changes in the microbiota composition for relevant health outcomes are currently not clear.

In three studies, using the same mouse strain and the same dose of sodium carboxy methyl cellulose, additional health effects were investigated. Effects on endpoints such as fasting glucose and spleen weight were observed in some studies, however, not in other studies. In the studies with an effect, the effect size was small. For other endpoints using subjective measurements (colonic length, fat (pad) weight), effects were also not consistently observed in all studies. They had been obtained under non-blinded conditions which introduced a high risk of bias (Chassaing et al., 2015; Sandall et al., 2020; Viennois et al., 2020).

APC^{min} mice – which are predisposed to intestinal adenoma formation – showed an increased number of adenomas in the small intestine, but not in the colon when fed a diet containing carboxy methyl cellulose (Viennois and Chassaing, 2021). Mutations in the APC gene are known to lead to adenomas and later, carcinomas, in the colon in humans (Markowitz and Bertagnolli, 2009). The Panel therefore considered that in the absence of additional mechanistic information, the relevance of findings in the small intestine in mice exposed to carboxy methyl cellulose were uncertain and likely not relevant to humans.

Gene expression changes in certain brain regions in mice were not accompanied by histopathological or functional investigation so that the meaning of these findings remain open (Arnold et al., 2022).

In a preliminary study in humans, endpoints (oral glucose tolerance test, insulin sensitivity, six circulating cytokines, circulating anti-lipopolysaccharide IgG, anti-flagellin IgG, urinary metabolome, body weight) remained unchanged by 11-day administration of carboxy methyl cellulose (15 g/day) although profound changes in the microbiota diversity were reported (Chassaing et al., 2022).

The Panel agreed with the statement of the authors of the human study (Chassaing et al., 2022) that additional studies are required to assess the extent to which the observed changes in the microbiota composition would persist with prolonged exposure to sodium carboxy methyl cellulose and what the potential health consequences would be.

3.6. Discussion

The Panel noted that the IBOs declared that E 466 is not used in food for infants below 16 weeks of age and in FC 13.1.5.1 and did not provide toxicological data to support the uses in FC 13.1.5.2.

Analytical data on toxic elements were provided by one IBO for levels of As, Cd, Hg and Pb for the additive intended for use in food for the general population. The IBO did not submit any proposal for the lowest technologically achievable limits, however, recommended not to lower the currently existing limits for toxic elements in the EU specifications for E 466. The Panel noted that the concentration data on toxic elements submitted by the IBO are substantially lower than the current limits in the EU specifications.

The Panel considered the potential presence of As, Pb, Cd and Hg in E 466 at (i) the maximum current limit in the EU specification; (ii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher; (iii) the rounded up highest measured value of the level of toxic element or the highest LOD or LOQ, in the absence of any measured value(s) for that element whichever was reported higher and applied a factor of 5 (Table 7).

The Panel considered the refined brand-loyal exposure scenario to calculate the exposure to the toxic elements from the use of E 466. For the general population, the mean and the highest 95th percentile refined brand-loyal exposure scenario were 190 and 506 mg/kg bw per day in toddlers (EFSA ANS Panel, 2018). Considering the population of infants (above 16 weeks of age) and of toddlers (consumers only of FSMP), the highest mean and 95th percentile exposure were, respectively, calculated in this opinion at 911 and 987 mg/kg bw per day both for infants above 16 weeks of age.

For scenarios (i) and (iii), the exposure to the toxic elements from the consumption of E 466 is substantial and this gives rise to concern (see Table 8). The Panel noted that the exposure assessment would in general result in an overestimation of the exposure to E 466 (EFSA ANS Panel, 2018, Table 5).

The Panel noted that the maximum limits in the EU specifications for toxic elements should be established based on actual levels in the commercial food additive. Therefore, the Panel recommended that the maximum limits to be lowered on the basis of the information provided by the IBO and on the considerations of the Panel (see Table 9).

Based on the data on particle size distribution submitted by the IBOs and the criteria set in the relevant EFSA Scientific Committee Guidance (EFSA Scientific Committee, 2021), the Panel concluded that the presence of small particles, including nanoparticles, cannot be confirmed or excluded in the pristine food additive. The Panel noted that currently no standardised methods are available to measure the particle size distribution 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. This also applies to sodium carboxy methyl cellulose. The FAF Panel considers that sodium carboxy methyl cellulose 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.

The Panel is aware of recent studies on sodium carboxy methyl cellulose in mice and humans addressing changes in the microbiome and some toxicological endpoints. The Panel agreed with the statement of the authors of the human study (Chassaing et al., 2022) that additional studies are required to assess the extent to which the observed changes in the microbiota composition would persist with prolonged exposure and what the health consequences would be. The Panel considered that the preliminary results do not allow identifying specific health concerns and that the whole field needs further investigation on a large scale.

4. Conclusions

The Panel concluded that the technical data provided by the IBO support an amendment of the specifications for sodium carboxy methyl cellulose (E 466) laid down in Commission Regulation (EU) No 231/2012, as presented by the recommendations made in Table 9.

The IBOs declared that E 466 is not used in food for infants below 16 weeks of age and in FC 13.1.5.1. Due to the lack of data, an assessment has not been performed for this FC and age group.

The IBO did not provide biological and toxicological data to support the uses of E 466 in FC 13.1.5.2. Due to the almost unchanged database, the FAF Panel confirmed the previous EFSA ANS Panel conclusion according to which the available data did not allow for an adequate assessment of the safety of use of sodium carboxy methyl cellulose (E 466) in infants and young children consuming foods belonging to the category 13.1.5.2.

Documentation as provided to EFSA

1) Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA), 2019. Submission of data in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in January 2020.

2) Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA), 2020. Clarification on the data submitted in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in June 2020.
3) Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA), 2020. Clarification on the data submitted in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in September 2020.
4) Specialised Nutrition Europe (SNE), 2020. Clarifications on the uses and use levels in food categories 13.1.5.1 and 13.1.5.2. Submitted via email in October–November 2020.
5) Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA), 2020. Clarification on the data submitted in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in March 2021.
6) International Cellulosics Association (ICA) (former Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA)), 2022. Clarification on the data submitted in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in April 2021.
7) International Cellulosics Association (ICA) (former Organisation des Fabricants de produits Cellulosiques Alimentaires (OFCA)), 2022. Clarification on the data submitted in response to the call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted in July 2022.

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Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
ANS Panel EFSA	Panel on Food Additives and Nutrient Sources added to Food
BMDL	benchmark dose (lower confidence limit)
bw	body weight
CAS	chemical abstract service
FAF Panel	Panel on Food Additives and Flavourings
FAO/WHO	Food and Drug Organisation/World Health Organisation
FC	food category
FSMP	food for special medical purposes
GI	gastrointestinal
HBGV	health-based guidance value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
LOQ	limit of quantification
Mintel GNPD	Mintel's Global New Products Database
MOE	margin of exposure
MPL	maximum permitted levels
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PND	postnatal day
RP	reference point
SC	Scientific Committee of EFSA
SCF	Scientific Committee on Food
TWI	Tolerable Weekly Intake
WG	Working Group

Appendix A – Data requested in the call for data (Call for technical and toxicological data on sodium carboxy methyl cellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age)[14]

Kind of data	Data requested in the call for data	Responses from interested business operators	Comment
A. Information regarding the follow-up of the conclusions and the recommendations of the EFSA ANS Panel opinion on the safety of sodium carboxy methyl cellulose (E 466) as food additive			
1.Technical data	• Analytical data on current levels of lead, mercury, cadmium and arsenic in commercial samples of the food additive; • The lowest technologically achievable level for lead, mercury, cadmium and arsenic in order to adequately define their maximum limits in the specifications	Data submitted	Assessed, no further follow-up
2.Toxicological data	According to the conclusions and recommendations in the Scientific opinion on the re-evaluation of sodium carboxy methyl cellulose (E 466) as a food additive by the EFSA ANS Panel published in 2017, the generation of additional data to assess the potential health effects of sodium carboxy methyl cellulose (E 466) when used as a food additive in 'dietary foods for infants for special medical purposes and special formulae for infants' (Food category 13.1.5.1) and in 'dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC' (Food category 13.1.5.2) was recommended. These requirements could be addressed as outlined in Section B.2	No data submitted	No data submitted, see Conclusions section.
3. Literature searches	Literature searches should be conducted relevant for the safety evaluation of sodium carboxymethylcellulose (E466) for all uses in foods for all population groups from 5 February 2017 up to the date of the data submission, as described in the Guidance for submission for food additive evaluation (see its Section 5.3)	Information provided	Assessed, no further follow-up
B. Information required for the risk assessment of sodium carboxy methyl cellulose (E 466) as food additive for use in foods for infants below 16 weeks of age			
1. Technical data	For the uses of sodium carboxymethylcellulose (E466) as a food additive in foods for infants below 16 weeks (FC 13.1.5.1) EFSA seeks information on: • The usage levels of use of sodium carboxymethylcellulose (E466) alone or in combination with other thickening agents (indication of food additive name and level of use) in the special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1);	No data submitted	No data submitted, see Conclusions section.

[14] Available from: https://www.efsa.europa.eu/en/consultations/call/call-technical-and-toxicological-data-sodium and responses from interested business operators.

Kind of data	Data requested in the call for data	Responses from interested business operators	Comment
	• The fate and the reaction products of sodium carboxy methyl cellulose (E 466) in special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1); • Particular specification requirements for identity and purity of sodium carboxy methyl cellulose (E 466) (e.g. content of toxic elements, sodium, total glycolate, isopropanol) in special formulae for infants below 16 weeks of age under special medical conditions (FC 13.1.5.1). Analytical data on impurities in the final special formulae for infants below 16 weeks of age need to be provided when no legal limit has been established. In addition, data should be provided demonstrating the absence of *Cronobacter (Enterobacter) sakazakii*.		
2. Toxicological data	• A repeated dose study with direct oral administration of sodium carboxy methyl cellulose (E 466) to neonatal animals, which includes gross and histopathological examination of gastrointestinal tract, influence on the microbiota and a possible modification in the bioavailability of nutrients, that are normally contained in food for infants. The study shall be performed in piglets unless justification for the relevance of a study in another species is given; • Clinical data focusing on gastrointestinal effects to assess the safety of sodium carboxy methyl cellulose (E 466) when used in dietary foods for special medical purposes in infants below 16 weeks of age (FC 13.1.5.1); • Post-marketing surveillance reports on undesired and adverse reactions (including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and consistency, diarrhoea and allergic reactions), indicating the ages and other relevant data of the exposed infants and young children and the use levels in the marketed products; • Published and unpublished case reports (e.g. available nutrivigilance data) on undesired and adverse effects, including e.g. flatulence, gastrointestinal discomfort, changes of stool-frequencies and - consistency, diarrhoea and allergic reactions, associated with the oral administration of sodium carboxy methyl cellulose (E 466) in any form, to infants and young children.	No data submitted	No data submitted, see Conclusions section.

Kind of data	Data requested in the call for data	Responses from interested business operators	Comment
3. Literature searches	Literature searches should be conducted relevant for the safety evaluation of sodium carboxy methyl cellulose (E 466) 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 evaluation (see its Section 5.3)	No data submitted	No data submitted, see Conclusions section.

Appendix B – Number and percentage of food products labelled with E 466 out of the total number of food products present in the Mintel GNPD per food subcategory between 2017 and 2022

Mintel subcategory(a)	Total number of products	Products labelled with food additive (E 466)	
		Number	%
Gum	886	146	16.5
Flavoured Milk	1,189	191	16.1
Artificial Sweeteners	147	18	12.2
Instant Noodles	823	93	11.3
Frozen Desserts	954	101	10.6
Nutritional & Meal Replacement Drinks	3,155	327	10.4
RTD (Iced) Coffee	1,101	92	8.4
Dairy Based Ice Cream & Frozen Yogurt	6,609	444	6.7
Meal Kits	972	56	5.8
Sandwiches/Wraps	1,306	75	5.7
Water Based Ice Lollies, Pops & Sorbets	956	49	5.1
Malt & Other Hot Beverages	1,075	51	4.7
Cakes, Pastries & Sweet Goods	12,079	533	4.4
Cream	1,403	60	4.3
Shelf-Stable Desserts	2,169	91	4.2
Plant Based Ice Cream & Frozen Yogurt (Dairy Alternatives)	657	27	4.1
Other Spirits	214	8	3.7
Bread & Bread Products	9,760	360	3.7
Beverage Mixes	761	28	3.7
Sports Drinks	869	31	3.6
Chilled Desserts	4,513	156	3.5
Mixed Assortments	189	6	3.2
Vitamins & Dietary Supplements	12,165	383	3.1
Cooking Sauces	4,472	120	2.7
Dessert Toppings	456	12	2.6
Fruit/Flavoured Still Drinks	1935	50	2.6
Pastilles, Gums, Jellies & Chews	3,495	88	2.5
Hors d'oeuvres/Canapes	3,350	83	2.5
Sandwich Fillers/Spreads	703	17	2.4
Beverage Concentrates	1,637	39	2.4
Pastry Dishes	1,175	24	2.0
Standard & Power Mints	452	9	2.0
Plant-Based Drinks (Dairy Alternatives)	3,178	60	1.9
Rice Snacks	533	10	1.9
Other Snacks	184	3	1.6
Other Natural Sweeteners	748	11	1.5
Creamers	140	2	1.4
Noodles	751	10	1.3
Baking Ingredients & Mixes	9,300	122	1.3
Dressings & Vinegar	2,692	34	1.3
Dips	1955	23	1.2
Fresh Cheese & Cream Cheese	2,359	24	1.0
Margarine & Other Blends	817	8	1.0
Soft Cheese Desserts	1,154	11	1.0

Mintel subcategory(a)	Total number of products	Products labelled with food additive (E 466)	
		Number	%
Prepared Meals	7,294	68	0.9
Poultry Products	8,063	67	0.8
Sweetened Condensed Milk	124	1	0.8
Medicated Confectionery	678	5	0.7
Mayonnaise	1,224	9	0.7
Wheat & Other Grain-Based Snacks	1776	12	0.7
Drinking Yogurt & Liquid Cultured Milk	2,567	17	0.7
Meat Pastes & Pates	2,450	16	0.7
Energy Drinks	1,477	8	0.5
Pizzas	3,743	20	0.5
Meat Products	21,001	104	0.5
Table Sauces	6,099	30	0.5
Sweet Biscuits/Cookies	17,346	82	0.5
Tequila	215	1	0.5
Flavoured Alcoholic Beverages	1,540	7	0.5
Corn-Based Snacks	2,225	10	0.4
Other Sugar Confectionery	1,124	5	0.4
Syrups	687	3	0.4
Toffees, Caramels & Nougat	1755	7	0.4
Wet Soup	3,340	13	0.4
Meat Substitutes	4,849	18	0.4
Dry Soup	1,085	4	0.4
Butter	1,642	6	0.4
Fish Products	13,697	45	0.3
Curd & Quark	923	3	0.3
Growing Up Milk (1–4 years)	312	1	0.3
White Rum	324	1	0.3
Nectars	2,718	8	0.3
Meat Snacks	1,117	3	0.3
Liqueur	2,248	6	0.3
Savoury Biscuits/Crackers	4,892	13	0.3
Carbonated Soft Drinks	5,631	14	0.2
Hot Cereals	1,647	4	0.2
Salads	2,887	7	0.2
Processed Cheese	2,119	5	0.2
Potato Snacks	4,744	10	0.2
Gin	1,474	3	0.2
Other Sauces & Seasonings	986	2	0.2
Non-Individually Wrapped Chocolate Pieces	5,832	11	0.2
Individually Wrapped Chocolate Pieces	3,208	6	0.2
Fortified & Other Wines	556	1	0.2
Snack/Cereal/Energy Bars	6,934	12	0.2
Seasonal Chocolate	8,545	14	0.2
Boiled Sweets	690	1	0.1
Coffee	10,432	15	0.1
White Milk	2,109	3	0.1
Eggs & Egg Products	2,160	3	0.1

Mintel subcategory(a)	Total number of products	Products labelled with food additive (E 466)	
		Number	%
Tea	8,666	10	0.1
Savoury Vegetable Pastes/Spreads	2,612	3	0.1
Whisky	2052	2	0.1
Soft Cheese & Semi-Soft Cheese	6,861	6	0.1
Chocolate Spreads	2,348	2	0.1
Potato Products	2,467	2	0.1
Confiture & Fruit Spreads	5,143	4	0.1
Chocolate Tablets	8,140	6	0.1
Stuffing, Polenta & Other Side Dishes	3,196	2	0.1
Seasonings	8,983	5	0.1
Pasta	11,728	6	0.1
RTD (Iced) Tea	1977	1	0.1
Snack Mixes	2000	1	0.1
Pasta Sauces	4,146	2	0.0
Hard Cheese & Semi-Hard Cheese	9,828	2	0.0
Wine	5,473	1	0.0
Pickled Condiments	6,102	1	0.0
Spoonable Yogurt	7,036	1	0.0
Cold Cereals	7,317	1	0.0
Total sample	**390,002**	**4,848**	**1.2**