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SCIENTIFIC OPINION

Re-evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

Citric acid esters of mono- and diglycerides of fatty acids (E 472c) was re-evaluated in 2020 by the Food Additives and Flavourings Panel (FAF Panel) along with acetic acid, lactic acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a,b,d,e,f). As a follow-up to this assessment, the FAF Panel was requested to assess the safety of citric acid esters of mono- and diglycerides of fatty acids (E 472c) for its use as food additive in food for infants below 16 weeks of age belonging to food categories (FCs) 13.1.1 (Infant formulae as defined by Directive 2006/141/EC) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). In addition, the FAF Panel was requested to address the recommendation of the re-evaluation of E 472c as a food additive to update the EU specifications in Commission Regulation (EU) No 231/2012. For this, a call for data was published to allow interested partied to provide the requested information for a risk assessment. The Panel concluded that the technical data provided by the interested business operators support an amendment of the EU specifications for E 472c. Regarding the safety of the use of E 472c in food for infants below 16 weeks of age, the Panel concluded that there is no safety concern from its use at the reported use levels and at the maximum permitted levels in food for infants below 16 weeks of age (FCs 13.1.1 and 13.1.5.1).

KEYWORDS

citric acid esters of mono- and diglycerides of fatty acids, E 472c, 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 did not cover the use of food additives in food for infants below 12 weeks of age. Additionally, while re-evaluating the safety of food additives referred to above, EFSA identified some concerns, namely (1) Data gaps that have triggered recommendations in the published scientific opinions; and/or; (2) Data gaps that have increased uncertainties linked to the risk assessment and/or which prevented the Panel from concluding on some aspects of it.

On 31 May 2017, EFSA published a guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age, thus enabling EFSA to assess the safety of food additive used in food for infants below this age. The age below 16 weeks was selected in the guidance because infants consume infant formulae and/or breast milk until this age as the only sources of food. Complementary feeding is not supposed to be introduced before.

As follow-up to the above, this Opinion addresses the data gaps previously identified for citric acid esters of mono- and diglycerides of fatty acids (E 472c) during the re-evaluation of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a–f) as food additives and the safety of its use in food for infants below 16 weeks of age.

The process followed involved the publication of a dedicated call for data inviting all interested parties to provide the requested information for completing the assessment and to confirm that E 472c is present in foods belonging to food categories (FCs) 13.1.1 (Infant formulae as defined by Directive 2006/141/EC) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants). The data submitted in response to the call for data comprised technical data, use levels, clinical studies, post-marketing surveillance reports and literature studies.

According to the definition in the Commission Regulation (EU) No 231/2012, citric acid esters of mono- and diglycerides of fatty acids (E 472c) are defined as esters of glycerol with citric acid and fatty acids occurring in food oils and fats. Specifications for citric acid esters of mono- and diglycerides of fatty acids (E 472c) have been defined in Commission Regulation (EU) No 231/2012.

According to Annex II, Part E of Regulation (EC) No 1333/20082, E 472c is permitted in FCs 13.1.1 and 13.1.5.1 at a maximum permitted level (MPL) of 7500 mg/kg as consumed when sold as powder and 9000 mg/kg as consumed when sold as liquid. Based on data submitted by one interested business operator (IBO), E 472c is used in infant formulae for infants below 16 weeks of age at levels up to 1849 mg/L as consumed when sold as powder, and up to 8900 mg/L as consumed when sold as liquid and in special formulae for infants of that age under special medical conditions at levels up to the MPLs. These reported levels are thus in compliance with the MPLs in the EU.

Dietary exposure to E 472c from its use as a food additive in foods for infants below 16 weeks of age was estimated using a mean and high-level consumption value reported at the age of 14 to 27 days of 200 and 260 mL/kg bw per day, respectively. These consumption values were combined with the MPLs according to Annex II and the reported use levels submitted by the IBOs. Different scenarios were used to calculate the exposure. Uncertainties in the exposure assessment were identified and discussed.

Taking into account that brand loyalty is expected, the Panel considered that the mean and high-level exposure scenarios using the maximum use levels reported by the IBOs for infant formulae would be the most relevant scenarios for the safety assessment of E 472c when used in food for infants below 16 weeks of age (FC 13.1.1 and FC 13.1.5.1). The high-level exposure scenario for FC 13.1.1 for infants consuming formula sold as liquid is in the same range as the exposure for FC 13.1.5.1.

In this brand-loyal scenario using the maximum reported use levels for FC 13.1.1, mean exposure was estimated at 370 mg/kg bw per day for formula sold as powder and at 1780 mg/kg bw per day for formula sold as liquid and high-level exposure at 481 and 2314 mg/kg bw per day, respectively.

In response to the EFSA call for data for E 472c for uses as a food additive in foods for all population groups including infants below 16 weeks of age, analytical data on potential impurities and undesirable constituents in commercial samples of E 472c were provided by two IBOs and lowest technologically achievable levels were proposed in some cases. The potential exposure to these impurities/constituents from the use of E 472c was calculated by assuming that they may be present in E 472c to a certain limit value, and then by calculation pro-rata to the mean and high-level exposure estimates of E 472c itself.

Analytical data on levels of four toxic elements (arsenic, lead, cadmium, mercury), free 3-chloro-1,2-propanediol (3-MCPD) and 3-MCPD fatty acids (expressed as 3-MCPD), glycidyl esters (expressed as glycidol) and erucic acid in commercial samples of E 472c were provided by one IBO. The potential exposure to these impurities or constituents from the use of E 472c was compared to the available health-based guidance values (HBGV) and reference points (RP). Taking into account the information provided by the IBO and the calculations performed by the Panel, a series of recommendations for the revisions of the existing EU specifications for E472c laid down in Commission Regulation (EU) No 231/2012 were made.

The Panel noted that a maximum limit of 2 grams of trans-fat per 100 g of fat in food for the final consumer is set by Regulation (EU) No 2019/649 amending Annex III to Regulation (EC) No 1925/2006. Hence, the Panel considered that there is no need for setting a specification limit for the content of trans-fatty acids in the specifications for E 472c.

The Panel also considered that no specification limits for butanetriols, acrolein or oxalates are needed in the EU specifications for E472c, but recommended a modification of the definition indicating that glycerol and citric acid used for the

manufacturing of E 472c should meet the specifications for E 422 (Commission Regulation (EU) No231/2012) and for E 330 (Commission Regulation (EU) No 231/2012), respectively.

According to the call for data, additional toxicological studies to address the safety of the uses in food intended for infants below 16 weeks of age were required only if it cannot be demonstrated that the metabolism of E 472c in infants is comparable to the metabolism in adults. The IBO was of the opinion that the metabolism of E 472c in infants is comparable to the metabolism in adults and that the exposure to fatty acids in infants from breast milk and infant formulae are comparable, therefore, no toxicological studies were provided.

As part of the Panel assessment, consideration was given as to whether the metabolism of E 472c in infants would be similar to the metabolism of the same food additive in adults. In the absence of specific studies on ADME for E 472c in infants below 16 weeks of age, the Panel based its considerations on the information from literature provided by one IBO indicating differences in both fat digestion and absorption between adults and newborns, such as age-dependent enzyme expression, very low levels of pancreatic lipases at birth, higher pH in the upper gastrointestinal tract and lower bile salt levels in infants. In addition, based on in vitro data, the Panel considered that the key lipases expressed in the pancreas, i.e. BSSL and PLRP2, hydrolyse triglycerides synergistically to glycerol and FFA which are then absorbed by the cells and re-esterified to triglycerides. Thus, it can be expected that newborns have the capacity to effectively hydrolyse triglycerides to FFAs, glycerol and citric acid. The Panel considered that these hydrolysis products can be expected to be absorbed and metabolised via the usual pathways, i.e. beta oxidation, gluconeogenesis or the tricarboxylic acid cycle, respectively. Overall, the Panel considered that metabolism of E 472c in infants is similar to the metabolism in adults because the extent of the differences reported are functionally not relevant.

In order to address the safety of the use of E 472c in food for infants below 16 weeks of age, one IBO provided additional information on the clinical studies already available at the time of the 2020 re-evaluation. The Panel re-assessed these studies and considered that they have major methodological flaws. Four new clinical studies were also provided but the Panel noted that none of these studies is appropriate for comparing a formula containing E 472c versus the same formula not containing E 472c. Overall, the Panel considered that the clinical studies do not contribute to the evaluation of the safety of E 472c when used as food additive in food for infants below 16 weeks of age.

The same IBO submitted a document collecting five case studies and a related publication. The Panel considered that these data do not contribute to the evaluation of the safety of E 472c when used as food additive in food for infants below 16 weeks of age due to the methodological flaws and the low number of participating infants. The available post-marketing surveillance reports indicated a low number of symptoms, possibly related to the intake of the formulae covered in the reports, all of which would not raise concern.

In line with the call for data and the proposal from the IBO, the Panel took the approach to compare the content of fatty acids, glycerol and citric acid in the infant formulae /FSMPs containing E 472c with that in breast milk to assess the safety of the use of E 472c in food for infants below 16 weeks of age. According to the comparison performed, the Panel noted that the content of lauric, myristic, palmitic and stearic acid in samples of infant formulae and FSMPs containing E 472c is comparable to their content measured in breast milk. Similarly, the content of total glycerol in infant formulae (3.8 g/L) containing E 472c at the MPL (9 g/L) is in the same range than that in breast milk (estimated content of total glycerol around 4 g/L).

The Panel calculated that the content of total citric acid in infant formulae /FSMPs deriving from the use of E 472c considering the analytical data provided (13%–18% total citric acid in E 472c) and considering the highest MPL would be 1.3–1.7 g/L. The maximum citric acid content in infant formulae containing E 472c (2.2 g/L) at the MPL calculated by the IBO is about 2-fold higher than that in breast milk (1.1 g/L). The Panel considered that the two-fold higher level of citric acid is not of safety concern.

Taking into account the similar content of the hydrolysis products of E 472c (fatty acids, glycerol and citric acid) in the infant formulae/FSMPs containing E 472c and in breast milk, the Panel concluded that there is no safety concern from the uses of E 472c at the reported use levels and at the MPLs in food for infants below 16 weeks of age (FC 13.1.1 and 13.1.5.1).

1 | INTRODUCTION

The present opinion deals with:

- the risk assessment of citric acid esters of mono- and diglycerides of fatty acids (E 472c) to be used in food for infants below 16 weeks of age in food categories 13.1.1 (Infant formulae as defined by Directive 2006/141/EC; reported in this opinion also as infant formulae) and 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants; reported in this opinion also as food for special medical purposes – FSMPs).
- the follow-up on issues on citric acid esters of mono- and diglycerides of fatty acids (E 472c) that were expressed in the recommendations of the Scientific Opinion on the re-evaluation of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f) as a food additive (EFSA FAF Panel, 2020).

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

1.1.1 | Background

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

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

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

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

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

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

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

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

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

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

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

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

[3]See Section 1.1.3.

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

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

1.1.2 | Terms of Reference

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

1.1.3 | Interpretation of Terms of Reference

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

1.2 | Previous evaluations of citric acid esters of mono- and diglycerides of fatty acids (E 472c) as a food additive

All substances of the group of the esters of mono- and diglycerides of fatty acids E 472a-f have been evaluated by the SCF (SCF, 1978, 1998). An ADI 'not specified' was established for all substances except for E 472e (SCF, 1978). The SCF also considered acceptable the use of E 472c in products which contain partially hydrolysed proteins for infants and children in good health (SCF, 1998).

JECFA established an ADI 'not limited' for citric acid esters of mono- and diglycerides of fatty acids (E 472c). Furthermore, in its evaluation on the safety of citric acid esters of mono- and diglycerides of fatty acids in infant formula and formula for special medical purposes intended for infants, JECFA concluded that for these uses there is no toxicological concerns at concentration up to 9 g/L (JECFA, 2014). JECFA introduced a limit of 0.5 mg/kg for lead for use of the additives in infant formula (JECFA, 2016, 2017).

In 2020, the FAF Panel issued a scientific opinion on the re-evaluation of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f) as food additives.

In that opinion the FAF Panel considered that the uses in food for infants under the age of 12 weeks under food categories 13.1.1 and 13.1.5.1 would require a specific risk assessment. Therefore, the performed risk assessment for the general population was not considered applicable for infants under the age of 12 weeks.

The following recommendations relevant for E 472c were reported in that FAF Panel opinion:

- include maximum limits for mercury, arsenic and cadmium, in addition to lead, in EU specifications.
- revise the EU specifications including maximum limits for impurities currently set in the EU specifications for glycerol (E 422) as well as those recommended by the Panel in the re-evaluation of glycerol (E 422) (EFSA ANS Panel, 2017).
- revise the EU specifications including maximum limits for trans-fatty acids because partially hydrogenated fats and/or oils, which may contain significant amounts of trans-fatty acids, can be used as starting materials for E 472c.
- revise the EU specifications including maximum limits for glycidyl esters/glycidol and 3-MCPD esters, because it is likely that residues of those substances occur in the food additive, if they were present in the raw materials used in the manufacturing process of these food additives or formed during the manufacturing process.
- revise the EU specifications including maximum limits for erucic acid since erucic acid can be present among the fatty acids in edible oils, which can be used for manufacturing process of E 472c.
- include maximum limits for oxalates in the EU specifications, since oxalate can be present in the materials that are used in the manufacturing process of this food additive.

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

2 | DATA AND METHODOLOGIES

2.1 | Data

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

- Information submitted by IBOs in response to the EFSA public call for data[6] and subsequent requests for clarifications and/or additional information.
- The recommendations from previous evaluations.
- Information from Mintel's Global New Products Database (GNPD) to identify the use of the food additive citric acid esters of mono- and diglycerides of fatty acids (E 472c) in food products.

2.2 | Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee, 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 citric acid esters of mono- and diglycerides of fatty acids (E 472c) for all population groups and to address the data gaps identified during the re-evaluation in 2020, the FAF Panel assessed the information provided:

- For the risk assessment of E 472c in food for infants below 16 weeks of age in food categories 13.1.1 and 13.1.5.1;
- For the follow-up on issues on E 472c that were expressed in the conclusions and recommendations of the Scientific Opinion on the re-evaluation of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a–f) as food additives (EFSA FAF Panel, 2020).

Dietary exposure to E 472c from its use as a food additive in foods for infants below 16 weeks of age was estimated combining the mean and high-level consumption values for infant formulae reported for the period of 14–27 days of life (which correspond respectively to 200 and 260 mL/kg bw per day; EFSA Scientific Committee, 2017; see Section 3.4), with the maximum levels according to Annex II and reported use levels submitted to EFSA following a call for data. Different scenarios were used to calculate exposure (see Section 3.4). Uncertainties on the exposure assessment were identified and discussed.

3 | ASSESSMENT

3.1 | Identity and specifications

According to the definition in the Commission Regulation (EU) No 231/2012, citric acid esters of mono- and diglycerides of fatty acids (E 472c) are defined as esters of glycerol with citric acid and fatty acids occurring in food oils and fats. They may contain small amounts of free glycerol, free fatty acids, free citric acid and free glycerides. They may be partially or wholly neutralised with sodium, potassium or calcium salts suitable for the purpose and authorised as food additives according to this Regulation. Figure 1 shows a general structural formula for E 472c.

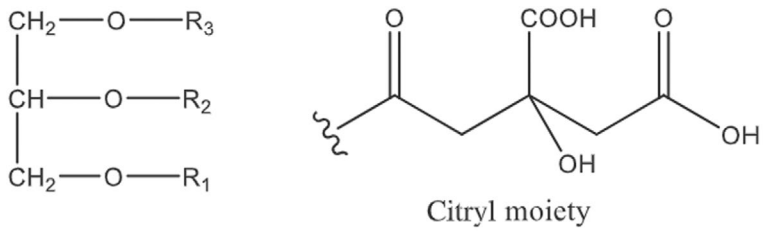

FIGURE 1 General structural formula for E 472c: Where at least one of R1, R2 or R3 represents a citryl moiety, one represents a fatty acyl moiety, and the remaining position has either a citryl moiety or fatty acyl moiety or hydrogen.

[6]Call for technical and toxicological data on of citric acid esters of mono- and diglycerides of fatty acids (E 472c) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 1.12.2021. Available at: https://www.efsa.europa.eu/sites/default/files/2021-11/technical-and-tox-data-citric-acid-esters-mono-and-diglycerides-fatty-acids-e-472-c.pdf.

Based on the definition given in the Commission Regulation (EU) No 231/2012, E 472c is not a discrete chemical substance but a mixture. Depending on the complexity of the fatty acid source, the food additives may contain several components. In addition, the number of different positional isomers is high. No Chemical Abstracts Service (CAS) Registration numbers have been assigned and the average molecular weight depends on the fatty acid sources (EFSA FAF Panel, 2020).

Specifications for citric acid esters of mono- and diglycerides of fatty acids (E 472c) have been defined in Commission Regulation (EU) No 231/2012, as described in Table 1.

TABLE 1 Specifications of citric acid esters of mono- and diglycerides of fatty acids (E 472c) according to Commission Regulation (EU) No 231/2012.

Commission regulation (EU) No 231/2012	
Definition	Esters of glycerol with citric acid and fatty acids occurring in food oils and fats. They may contain small amounts of free glycerol, free fatty acids, free citric acid and free glycerides. They may be partially or wholly neutralised with sodium, potassium or calcium salts suitable for the purpose and authorised as food additives according to this Regulation
Description	Yellowish or light brown liquids to waxy solids or semi-solids
Identification	
Test for glycerol	Passes test
Test for fatty acids	Passes test
Test for citric acid	Passes test
Solubility	Insoluble in cold water, dispersible in hot water, soluble in oils and fats, insoluble in cold ethanol
Purity	
Acids other than citric and fatty acids	Less than 1%
Free glycerol	Not more than 2%
Total glycerol	Not less than 8% and not more than 33%
Total citric acid	Not less than 13% and not more than 50%
Sulphated ash	Non-neutralised products: not more than 0.5% (800 ± 25°C). Partially or wholly neutralised products: not more than 10% (800 ± 25°C)
Lead	Not more than 2 mg/kg
Acid value	Not more than 130

3.2 | Technical data submitted

The following was requested in the EFSA call for data[7] (part A of the call for data):

- information on the manufacturing process used for the production of E 472c;
- analytical data on current levels of toxic elements such as arsenic, lead, cadmium and mercury in commercial samples of the food additive E 472c;
- analytical data on current levels of any impurities of toxicological concern identified in the EU specifications for the food additive glycerol (E 422) (e.g. butanetriols, acrolein, chlorinated compounds, 3-monochloropropane-1,2-diol) as well as those mentioned in the call for data for E 422 because glycerol (E 422) can be used in the manufacturing process of E 472c;
- analytical data on the current levels of *trans*-fatty acids in commercial samples of the food additive E 472c;
- analytical data on current levels of glycidyl esters/glycidol and free and bound 3-MCPD in commercial samples of the food additive E 472c;
- analytical data on current levels of erucic acid in commercial samples of the food additive E 472c;
- analytical data on current levels of oxalates in commercial samples of the food additive E 472c;
- the lowest technologically achievable level for any potential impurities mentioned above, including any potential impurities resulting from changes in manufacturing process, in order to adequately define maximum limits in the EU specifications for the food additive E 472c.

Information regarding the follow-up of the conclusions and the recommendations for the citric acid esters of mono- and diglycerides of fatty acids (E 472c) for all uses (Part A in the call) was only provided by one IBO (Documentation provided to EFSA n. 1).

Information regarding Part B of the call for data was provided by another IBO (Documentation provided to EFSA n. 2).

[7] https://www.efsa.europa.eu/en/call/call-technical-and-toxicological-data-citric-acid-esters-mono-and-diglycerides-fatty-acids-e.

3.2.1 | Information on the manufacturing process

The IBO provided a flow chart describing the manufacturing process of 472c, which can be obtained from the reaction of citric acid (E 330) with mono- and diglycerides of fatty acids (E 471), or alternatively, from the reaction of citric acid (E 330), glycerol (E 422) and fatty acids obtained from edible oils and fats (Documentation provided to EFSA n. 1). The IBO expressed that all sodium, potassium or calcium salts used for the neutralisation process are suitable for the purpose and authorised as food additives according to Commission Regulation (EU) No 231/2012 (Documentation provided to EFSA n. 10). According to JECFA (2019), sodium, potassium or calcium salts of weak acids such as acetic, lactic, propionic or carbonic acids are used for the neutralisation.

3.2.2 | Toxic elements

Analytical data on current levels of arsenic, cadmium and mercury in commercial samples of the food additive E 472c (13 samples from four different manufacturers), and lead (19 samples from five different manufacturers) were submitted by one IBO along with information on the methods of analysis and the limits of quantification (LOQs) (Documentation provided to EFSA n. 1 and n.10). Inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectroscopy (ICP-OES) or cold vapour atomic absorption spectroscopy (CV-AAS) according to European Standard (DIN EN) methodologies were used for the analyses. No certificate of analysis was submitted.

As shown in Table 2, from a total of 19 samples, lead was quantified in one sample, as 0.0065 mg/kg (LOQ 0.005 mg/kg). Other analyses, performed by ICP-MS, ICP-MS/MS or ICP-OES, gave values under the LOQs that ranged from 0.005 to 0.6 mg/kg.

TABLE 2 Analytical results for lead in commercial samples of E 472c.

LOQ (mg/kg)	Analytical method	Number of samples	Number of samples < LOQ	Reported values in mg/kg (number of samples)
0.005	ICP-MS (AOAC 999.10)	5	4	0.0065 (1)
0.015	ICP-MS (DIN EN 15763:2010-04)	5	5	–
0.02	ICP-MS (DIN EN 15763:2010-04)	1	1	–
0.02	ICP-MS/MS	1	1	–
0.05	ICP-MS	4	4	–
0.6	ICP-OES	3	3	–

As shown in Table 3, in all 13 analysed samples, mercury was reported below the LOQ (ranging from 0.005 to 0.1 mg/kg) of the methodologies applied, ICP-MS, ICP-MS/MS, ICP-OES or CV-AAS.

TABLE 3 Analytical results for mercury in commercial samples of E 472c.

LOQ (mg/kg)	Analytical method	Number of samples	Number of samples < LOQ	Reported values in mg/kg (number of samples)
0.005	ICP-MS	1	1	–
0.005	CV-AAS	2	2	–
0.010	ICP-MS (DIN EN 15763:2010-04)	6	6	–
0.05	ICP-MS/MS	1	1	–
0.1	ICP-OES	3	3	–

As shown in Table 4, in all 13 analysed samples, cadmium was reported below the LOQ (ranging from 0.005 to 0.2 mg/kg) of the methodologies applied, CV-AAS, ICP-MS, ICP-MS/MS or ICP-OES.

TABLE 4 Analytical results for cadmium in commercial samples of E 472c.

LOQ (mg/kg)	Analytical method	Number of samples	Number of samples < LOQ	Reported values in mg/kg (number of samples)
0.005	ICP-MS/MS	1	1	–
0.010	ICP-MS	1	1	–
0.010	ICP-MS (DIN EN 15763:2010-04)	6	6	–
0.02	ICP-MS	2	2	–
0.2	ICP-OES	3	3	–

As shown in Table 5, in all 13 analysed samples, arsenic was reported below the LOQ (ranging from 0.005 to 0.8 mg/kg) of the methodologies applied, ICP-MS, ICP-MS/MS or ICP-OES.

TABLE 5 Analytical results for arsenic in commercial samples of E 472c.

LOQ (mg/kg)	Analytical method	Number of samples	Number of samples < LOQ	Reported values in mg/kg (number of samples)
0.005	ICP-MS/MS	1	1	–
0.04	ICP-MS (DIN EN 15763:2010–04)	6	6	–
0.1	ICP-MS	3	3	–
0.8	ICP-OES	3	3	–

The IBO proposed lowest technologically achievable levels for each of the four toxic elements (Table 6; Documentation provided to EFSA n. 1 and 10).

TABLE 6 Lowest technologically achievable levels for the toxic elements in commercial E 472c, as proposed by the IBO (Documentation provided to EFSA n. 1 and 10).

Lead	Mercury	Cadmium	Arsenic
0.6 mg/kg	0.6 mg/kg	0.2 mg/kg	0.8 mg/kg

3.2.3 | Carry-over and process impurities

3.2.3.1 | *Butanetriols*

No analytical data on butanetriols were submitted. According to the IBO, the formation of butanetriols is not expected in the esterification reactions in the manufacturing process of E 472c (Documentation provided to EFSA n. 1).

3.2.3.2 | *Acrolein*

The IBO submitted data for the acrolein content in six commercial samples of E 472c from different manufacturers (Documentation provided to EFSA n. 1). No certificate of analysis was submitted. Three commercial samples were analysed by static headspace gas chromatography–mass spectrometry (HS-GC–MS) and acrolein was reported as non-detected (LOD 0.4 mg/kg). In the other three samples, acrolein was analysed by high performance liquid chromatography (HPLC, in-house method) and results reported below the LOQ (ranging from 0.105 to 0.5 mg/kg) (Documentation provided to EFSA n. 1 and 10).

Since acrolein was not found in E 472c under the analytical condition used, the IBO considered that the request for a lowest technologically achievable level for acrolein in E472c is not applicable (Documentation provided to EFSA n. 1 and 10).

3.2.3.3 | *3-MCPD and 3-MCPD fatty acid esters*

The IBO submitted data on the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in 21 commercial samples of E 472c, from five different manufacturers (Documentation provided to EFSA n. 1). No certificate of analysis was submitted. Analyses of 19 commercial samples were performed by GC–MS, based on a modification of AOAC Official Method Cd 29b-13 (Kuhlmann, 2021) and accordingly to ISO 18363-2 (using slow alkaline transesterification) with LOQ values of 0.1 mg/kg. The remaining two samples were analysed by GC–MS/MS with LOQ of 0.05 mg/kg.

In one E 472c sample, 3-MCPD was reported as non-detected, in one sample, it was reported as below the LOQ (0.1 mg/kg), while in three other samples, 3-MPCD was reported at the LOQ value (0.1 mg/kg). The concentrations of the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in the remaining 16 of the 21 samples ranged from 0.1 to 0.8 mg/kg (LOQ = 0.05–0.1 mg/kg).

In order to facilitate the trade of E 472c, the IBO proposed the following lowest technologically achievable levels for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD):

- 2.5 mg/kg for E 472c when it is used in foods consumed by the general population;
- 0.75 mg/kg for E 472c when it is used in foods consumed by infants below 16 weeks of age.

3.2.3.4 | *Glycidyl esters*

The IBO submitted data for glycidyl esters, expressed as glycidol, in 21 commercial samples of E 472c, from six different manufacturers. Thirteen samples were analysed by the modified AOAC Official Method Cd 29b-13 (LOQ = 0.1 mg/kg), six samples using the ISO 18363-2 method (LOQ = 0.1 mg/kg) and two samples were analysed by GC–MS/MS (LOQ = 0.05 mg/kg) (Documentation provided to EFSA n. 1 and 10). No certificate of analysis was submitted.

Glycidyl esters were not detected in three samples (LOQ = 0.1 mg/kg). Two samples had a content of glycidyl esters of 0.07 mg/kg (measured by GC–MS/MS with LOQ 0.05 mg/kg) and 0.7 mg/kg (measured by GC/MS and a LOQ 0.1 mg/kg). The remaining 16 samples were at or below the LOQ (ranging from 0.05 to 0.1 mg/kg).

The IBO proposed 2 mg/kg as the lowest technologically achievable level for glycidyl esters, expressed as glycidol, in E 472c for all uses.

3.2.3.5 | *Oxalates*

At the time of the re-evaluation of E472c (EFSA FAF Panel, 2020), it was noted that EU specifications for the food additive citric acid (E 330) includes a maximum limit for oxalates, while no maximum limit for oxalates was included in EU specifications for E 472c. Therefore, the Panel recommended to include a limit for oxalates in the specifications for E 472c.

The IBO did not provide data on the current levels of oxalates in commercial samples of E 472c. The IBO indicated that there is no method available to measure oxalates in E 472c. Furthermore, the IBO indicated that the content of oxalates in E 472c is only dependent on the content of oxalates in the raw materials, since no oxalates are generated in the production of E 472c and there is a limit of 100 mg/kg for oxalates in the specifications for citric acid (E 330) used in the manufacturing process of E472c (Documentation provided to EFSA n. 1).

3.2.4 | Undesirable fatty acids as constituents of citric acid esters of mono- and diglycerides of fatty acids (E 472c)

3.2.4.1 | *Trans-fatty acids*

The IBO provided analytical data on levels of *trans*-fatty acids in 11 commercial samples of E 472c, from five different manufacturers. Trans-fatty acids were reported as the sum of the individual trans-fatty acids, and results expressed either as w/w in the food additive or as w/w of the total fatty acid content in the product (Table 7) (Documentation provided to EFSA n. 1 and 10).

TABLE 7 Analytical results for *trans*-fatty acids in commercial samples of E 472c.

LOQ (%)	Analytical method	Number of samples	Number of samples < LOQ	Reported values in % w/w of total fatty acid content in the product (number of samples)
0.03	GC (AOCS Ce 1f-96)[a]	3	1	0.12 (1)–0.19 (1)
0.1	GC (ISO 5508)[a]	2	–	0.2 (1)–0.3 (1)
0.1	GC (ISO 15304)[b]	2	2	–
0.05	GC-FID[a]	1	1	–
Not provided	GC-FID (ISO 12966 mod)[b]	3	–	0.02–0.38 (3)

[a]% w/w in food additive.

[b]% w/w of total fatty acids in the product.

The samples were analysed by GC: ISO 5508 (LOQ = 0.1%), ISO 15304 (LOQ = 0.1%) and AOCS Ce 1f-96 methods (LOQ = 0.03%), and by GC-FID: ISO 12966 mod. (no LOQ), GC-FID (LOQ = 0.05%).

In four samples of E 472c, *trans*-fatty acids results were reported below the LOQ (0.03% to 0.1%) and four samples were reported between 0.12% and 0.3% (LOQ 0.03% and 0.1%). In the remaining three samples, results were reported between 0.02% and 0.38% (LOQ not specified) and the IBO indicated that a LOQ can be given for the individual trans-fatty acids but not for the calculated sum (Documentation provided to EFSA n. 1 and 10).

Additionally, four samples of fully hydrogenated oil used for the production of E472c were analysed for the iodine value (ISO 3961) with results up to 1.1%. For E472c manufactured with this kind of fully hydrogenated oil, the IBO reported that, assuming that the manufacturing process does not create a high amount of double bonds, and in a fully hydrogenated oil only small amounts of double bonds remain, the content of *trans*-fatty acids in E 472c cannot exceed the remaining amount of double bonds of the used oil (Documentation provided to EFSA n. 1).

The IBO did not provide the lowest technologically achievable level of *trans*-fatty acids. The IBO stated that the amount of *trans*-fatty acids in E 472c is almost entirely dependent on the *trans*-fatty acid content of the fats, oils or fatty acids used

in the production of E 472c. However, small amounts of *trans*-fatty acids may be formed during the manufacturing process and production control is used to keep this as low as possible (Documentation provided to EFSA n. 1).

The IBO was of the opinion that a lowest technologically achievable level for *trans*-fatty acids in E 472c is not applicable, as consumer safety is already ensured by the existing legal limit of 2 g of *trans*-fat per 100 g fat in foods for the final consumer (Commission Regulation (EU) No 2019/649 amending Annex III to Regulation (EC) No 1925/2006) (Documentation provided to EFSA n. 1).

3.2.4.2 | *Erucic acid*

The IBO submitted information of current levels of erucic acid in 15 commercial samples of E 472c, from six different manufacturers. Values were reported as erucic acid % w/w of total fatty acids or as % w/w of erucic acid in the food additive (Table 8) (Documentation provided to EFSA n. 1 and 10). No certificate of analysis was submitted.

Analyses were performed by GC, according to ISO 12966-2 (LOQ = 1 g/kg), ISO 12966-4 (LOQ = 0.2 g/kg), AOCS surplus Method Ce 1f-96 (LOQ = 1 g/kg), and by GC-FID (LOQ = 0.1 g/kg; LOQ = 0.5 g/kg) and ISO 12966 mod. (LOQ = 0.5 g/kg).

TABLE 8 Analytical results for erucic acids in commercial samples of E 472c.

LOQ (g/kg)	Analytical method	Number of samples	Number of samples < LOQ	Quantified reported values in g/kg) (number of samples)
0.2	GC-FID (ISO 12966-4)[a]	5	4	0.5 (1)
1	GC (ISO 12966-2)[a]	2	2	–
0.3	GC (AOCS Ce 1f-96)[a]	3	3	–
0.1	GC-FID[b]	1	1	–
0.5	GC-FID[a]	1	1	
0.5	GC-FID (ISO 12966-4 mod.)[a]	3	3	–

[a]% w/w of total fatty acids.

[b]% w/w in food additive.

Erucic acid was reported in one sample at the level of 0.5 g/kg and below the LOQ value of each analytical method (ranging from 0.3 to 1 g/kg) in the remaining 14 samples.

The IBO did not propose lowest technologically achievable levels for erucic acid in E 472c.

3.2.5 | Information on particular specifications requirements for the additive E 472c for use in infant formulae

The following was requested in the EFSA call for data:

- proposals for particular EU specification requirements for identity and purity of citric acid esters of mono- and diglycerides of fatty acids (E 472c) when used in these food categories.

An IBO proposed to align E 472c specifications intended for use in food and FSMP for infants below 16 weeks with the JECFA specifications (JECFA, 2019) (Documentation provided to EFSA n. 2). For foods, infant formula and formula for special medical purposes intended for infants, JECFA specifications for E 472c indicate a limit of 0.5 mg/kg for lead.

According to information presented in Section 3.2.2–3.2.4, another IBO proposed a lowest technologically achievable level of 0.75 mg/kg for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) for E 472c when used in foods for infants below 16 weeks (i.e. lower than the limit of 2.5 mg/kg proposed for food consumed by the general population), while for the others impurities/ undesirable constituents no differentiation was made.

3.2.6 | Fate and reaction products of E 472c when used for infants below 16 weeks

The following was requested in the EFSA call for data:

- information on the fate and the reaction products of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in these foods.

An IBO stated that E472c is stable in dry and cool conditions but that changes are observed at elevated temperatures and humidity. For example, during storage at 66°C for 15 days, some hydrolysis and a consequent increase in acid value and free glycerol is observed. The IBO further stated that the additive is stable and able to withstand harsh processing conditions such as spray drying and ultra-heat treatment (both processes lasting for seconds only) (Documentation provided to EFSA n. 2).

Although no data were provided to support these statements, the Panel found them to be reasonable. The Panel also noted that any partial hydrolysis would form the same products as are formed in vivo during metabolism. The Panel therefore considered that the additive is sufficiently stable and did not request further information.

3.3 | Authorised uses and use levels for citric acid esters of mono- and diglycerides of fatty acids (E 472c)

Maximum levels of E 472c in foods for infants below 16 weeks of age are defined in Regulation (EC) No 1333/2008 on food additives, as amended. In this opinion, these levels are termed Maximum Permitted Levels (MPLs).

According to Regulation (EC) No 1333/2008, Annex II, Part E, E 472c is authorised in foods for infants and young children in food category (FC) 13.1.1 (Infant formulae as defined by Directive 2006/141/EC) and FC 13.1.5.1 (Dietary foods for infants for special medical purposes and special formulae for infants), see Table 9.

TABLE 9 Maximum permitted levels (MPLs) of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in foods for infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008.

Food category number	Food category name	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)[a]
13.1.1	Infant formulae as defined by Directive 2006/141/EC	E 472c	Only when sold as powder	7500[b]
13.1.1	Infant formulae as defined by Directive 2006/141/EC	E 472c	Only when sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids	9000[b]
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 472c	Only when sold as powder; From birth onwards	7500
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 472c	Only when sold as liquid; From birth onwards	9000

[a]The maximum permitted levels of use refer to foods ready for consumption prepared following manufacturers' instructions.

[b]If more than one of the substances E 322, E 471, E 472c and E 473 are added to a foodstuff, the maximum level established for that foodstuff for each of those substances is lowered with that relative part as is present of the other substances together in that foodstuff (Regulation (EC) No 1333/2008).

According to Regulation No1333/2008, the MPLs refer to foods that are prepared for consumption following manufacturers' instructions. Therefore, infant formulae sold as powder should be mixed with water before feeding whereas foods sold as liquid are ready for consumption.

According to Annex III, Part 5, Section B to Regulation N°1333/2008, E 472c is authorised to be used in nutrient preparations in infant formulae and follow-up formulae for infants and young children in good health, 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 | Exposure assessment

3.4.1 | Exposure data

E 472c is authorised in the EU in infant formulae as defined by Commission Delegated Regulation (EU) 2016/127/EC (FC 13.1.1) and in dietary foods for infants for special medical purposes and special formulae for infants (FC 13.1.5.1) at a specific MPL (see Table 9). However, E 472c may be used at a lower level than the MPL. Therefore, actual use levels are required for performing a realistic exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a public call[8] for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) as food additive for uses in foods for all population groups including infants below 16 weeks of age. In response to this public call, information on actual use levels of E 472c in foods was made available to EFSA by one IBO (Documentation provided to EFSA n. 2 and 6). No analytical data on the concentration of E 472c in foods were made available by the Member States.

[8]Call for technical and toxicological data on of citric acid esters of mono- and diglycerides of fatty acids (E 472c) as a food additive for uses in foods for all population groups including infants below 16 weeks of age. Published: 01.12.2021. Available from: https://www.efsa.europa.eu/sites/default/files/2021-11/technical-and-tox-data-citric-acid-esters-mono-and-diglycerides-fatty-acids-e-472-c.pdf.

3.4.1.1 | *Reported use levels as food additive*

One IBO provided EFSA with 28 use levels of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in FC 13.1.1 (infant formula) and 23 use levels in FC 13.1.5.1 (foods for infants for special medical purposes and special formulae (FSMPs)) (Documentation provided to EFSA n. 2, 6). Some of the use levels provided were indicated as used in combination with other additives (e.g. lecithins (E 322), mono- and diglycerides of fatty acids (E 471)). According to the IBO, the mean reported typical use levels of E 472c as consumed was 1300 mg/kg and the highest reported maximum use level was 1849 mg/kg for foods under FC 13.1.1 that are sold in powder form. For foods under FC 13.1.1 that are sold in liquid form, the levels as consumed were 6611 and 8901 mg/kg, respectively. For foods under FC 13.1.5.1 that are sold in powder form, the mean reported typical use level as consumed was 1123 mg/kg, with a highest reported maximum use level of 7500 mg/kg and for those sold in liquid form 5276 and 9000 mg/kg, respectively.

The Panel observed differences in the MPLs specified in Regulation (EC) No 1333/2008 and the use levels reported by the IBO, depending on whether infant foods were sold in powder or liquid form. As a result, the Panel decided to conduct separate exposure assessments for each form. More detailed information on the use levels reported by the IBO are shown in Annex A, table A1.

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

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 4.5 million food and beverage products of which more than 1,400,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 24 out of its 27 member countries, and Norway is also presented in the Mintel GNPD.[9]

For the purpose of this Scientific Opinion, Mintel's GNPD[10] was used for checking the labelling of infants and young children food and beverage products for E 472c within the EU's food market as the database contains the compulsory ingredient information on the label.

According to Mintel's GNPD, E 472c was labelled on 31 products of 'Baby formula (0–6 months)' which is within the 'baby food' category, between January 2019 and December 2024, which represent 8% of the total number of food products belonging to this subcategory present in Mintel GNPD. In the category 'baby food' (including fruit products, desserts and yoghurts, 'growing up milk 1–4 years',[11] biscuits and rusks, cereals, formulae, …), 25 products other than 'Baby formula (0–6 months)' were found to be labelled with citric acid esters of mono- and diglycerides of fatty acids (E 472c). The average percentage of baby food and beverage products labelled to contain E 472c was 5.3%.

Annex A, Table A2 lists the percentage of the food and beverage products labelled with E 472c out of the total number of food and beverage products per food subcategory according to Mintel's GNPD food classification.

3.4.2 | Dietary exposure estimates

Dietary exposure estimates for infants below 16 weeks of age

Exposure to E 472c from its use as a food additive in formulae (FC 13.1.1) and FSMP formulae (FC 13.1.5.1) for infants below 16 weeks of age was estimated based on the recommended consumption levels from the SC Guidance (EFSA Scientific Committee, 2017). This guidance 'recommends values of 200 and 260 mL formula[12]/kg bw per day as conservative mean and high-level consumption values to be used for performing the risk assessments of substances which do not accumulate in the body present in food intended for infants below 16 weeks of age'. These recommended consumption levels correspond to consumption values for infants aged 14–27 days. For the regulatory maximum level exposure assessment scenario, the MPLs for infant formulae (FC 13.1.1) and infant FSMP (FC 13.1.5.1) in the food as consumed when sold in powder (7500 mg/kg) or in liquid form (9000 mg/kg) were used. The mean reported typical and the highest reported maximum use levels provided by one IBO were used for the refined scenario.

3.4.2.1 | *Dietary exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c) for infants below 16 weeks of age*

Table 10 summarises the estimated exposure to E 472c from its use as a food additive in FC 13.1.1 for infants below 16 weeks of age based on MPLs and reported use levels.

[9]Missing Cyprus, Luxembourg and Malta.
[10]https://www.gnpd.com/sinatra/home/.
[11]Sub category from Mintel GNPD 'growing up milk 1–4 years' should correspond to young children from Regulation 2013/609.
[12]Editorial.

TABLE 10 Dietary exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c) considering the consumption of infant formulae (FC 13.1.1) by infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008 (in mg/kg bw per day).

	Infants (< 16 weeks of age) consuming formula sold as powder[a]	Infants (< 16 weeks of age) consuming formula sold as liquid where the product contains partially hydrolysed proteins, peptides or amino acids
Regulatory maximum level exposure assessment scenario		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	1500 1950	1800 2340
Refined estimated exposure assessment scenario		
Scenario using maximum use level reported by the IBO		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	370 481	1780 2314
Scenario using mean of typical use levels reported by the IBO		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	260 338	1322 1719

Abbreviations: bw, body weight; IBO, interested business operator.

[a]The concentration data used (MPLs and use levels) refer to the levels of the additive in the food as consumed.

Table 11 summarises the estimated exposure to E 472c from its use as a food additive in FC 13.1.5.1 for infants below 16 weeks of age.

TABLE 11 Dietary exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c) considering the consumption of FSMPs (FC 13.1.5.1) by infants below 16 weeks of age according to Annex II to Regulation (EC) No 1333/2008 (in mg/kg bw per day).

	Infants (< 16 weeks of age) consuming FSMP formula sold as powder	Infants (< 16 weeks of age) consuming FSMP formula sold as liquid where the product contains partially hydrolysed proteins, peptides or amino acids
Regulatory maximum level exposure assessment scenario[a]		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	1500 1950	1800 2340
Refined estimated exposure assessment scenario		
Scenario using maximum use level reported by the IBO[a]		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	1500 1950	1800 2340
Scenario using mean of typical use levels reported by the IBO[a]		
• Mean consumption (200 mL/kg bw per day) • High-level consumption (95th percentile, 260 mL/kg bw per day)	225 292	1055 1372

Abbreviations: bw, body weight; IBO, interested business operator.

[a]The concentration data used (MPLs and use levels) refer to the levels of the additive in the food as consumed.

Taking into account that brand loyalty is expected, the Panel considered that the mean and high-level estimates based on the maximum use levels reported by one IBO for FC 13.1.1 would be the most representative estimates for the safety assessment of E 472c when used in food for infants below 16 weeks of age. In addition, the Panel noted that the high-level exposure estimate for FC 13.1.1 in infants consuming formula sold as liquid (2314 mg/kg bw per day) is in the same range as the exposure for FC 13.1.5.1 (2340 mg/kg bw per day).

3.4.3 | 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 12.

TABLE 12 Qualitative evaluation of influence of uncertainties on the dietary exposure estimate.

Sources of uncertainties	Direction[a]
Infants < 16 weeks of age	
Consumption data: one reference point only to estimate exposure during the period of up to 16 weeks of age	+/–
Regulatory maximum level exposure assessment scenario: – exposure calculations based on the maximum permitted levels (MPLs) according to Annex II to Regulation (EC) No 1333/2008	+
Refined exposure assessment scenarios: – exposure calculations based on the maximum use level reported by IBO – exposure calculations based on the mean typical level reported by IBO	+ +/– +/–

[a]+, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause under-estimation of exposure; +/–: uncertainty with potential to cause either an over- or under-estimation of the exposure.

E 472c is authorised in foods for infants (FCs 13.1.1 Infant formulae as defined by Directive 2006/141/EC and 13.1.5.1 Dietary foods for infants for special medical purposes and special formulae for infants) according to Annex II to Regulation (EC) No 1333/2008.

The regulatory maximum level exposure assessment scenario may overestimate the exposure in some cases. However, based on the assumption that carers of children are brand-loyal to an infant formula (FC 13.1.1) or an infant formula for special medical purposes (FC 13.1.5.1), this brand-loyal exposure assessment scenario will provide a reliable estimation of exposure for infants below 16 weeks of age (Table 10) consuming infant formula that contains E 472c at the maximum reported use level.

3.5 | Proposed revision to existing EU specifications for citric acid esters of mono- and diglycerides of fatty acids (E 472c)

In this opinion, also the recommendations of the re-evaluation of E 472c as a food additive regarding an update the EU specifications in Commission Regulation (EU) No 231/2012 are addressed (see Section 1.1.2). To address this, the potential exposure to impurities and undesirable constituents from the use of E 472c was calculated by assuming that they are 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.

For this, the exposure estimates of E 472c for the general population as reported in the re-evaluation of E 472c were used (EFSA FAF Panel, 2020). In the re-evaluation, the Panel considered the exposure calculations of E 472c as presented in the re-evaluation (EFSA FAF Panel, 2020). The FAF Panel considered the non-brand-loyal scenario covering the general population as the most appropriate and realistic scenario for the risk assessment for this food additive. For the current assessment of E 472c, the highest rounded exposure levels for the mean and 95th percentile among the different population groups were considered: 66 and 135 mg/kg bw per day, respectively, for toddlers (Table 13).

TABLE 13 Summary of dietary exposure to E 472c from its use as a food additive in the non-brand-loyal refined exposure scenario, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day) as estimated in the 2020 re-evaluation (EFSA FAF Panel, 2020).

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Mean	24.0	44.8	18.0	**65.9**	22.4	61.6	10.7	30.5	3.2	18.8	3.3	20.4
95th percentile	61.8	102.9	56.9	**134.9**	53.1	133.4	26.7	66.9	11.6	46.6	12.9	54.0

The exposure to the impurities and undesirable constituents was also calculated using the dietary exposure estimates of E 472c for infants below 16 weeks of age. As argued in Section 3.4.2, the Panel considered the mean and high-level estimates of exposure based on the maximum use levels for FC 13.1.1 as most relevant for this evaluation.

The potential level of impurities and undesirable constituents in the food additive combined with the estimated exposure levels of E 472c (Tables 10 and 13), results in exposure estimates that can be compared with the reference points (RP) or health-based guidance values (HBGV) for the undesirable impurities and constituents potentially present in E 472c (Table 14). It is considered that any mercury or arsenic in E 472c corresponds to the element in the inorganic form rather than organic form. Consequently, the HBGV for inorganic mercury and the RP for inorganic arsenic were used for comparison (Table 14).

TABLE 14 Reference points/health-based guidance values for impurities and undesirable constituents potentially present in E 472c.

Impurity/constituent/HBGV/RP	Basis/Reference
Lead (Pb)/0.5 μg/kg bw per day ($BMDL_{01}$)	The reference point is based on a study demonstrating perturbation of intellectual development in children with the critical response size of 1 point reduction in IQ. The EFSA CONTAM Panel mentioned that a 1 point reduction in IQ is related to a 4.5% increase in the risk of failure to graduate from high school and that a 1 point reduction in IQ in children can be associated with a decrease of later productivity of about 2%. A risk cannot be excluded if the exposure exceeds the $BMDL_{01}$ (MOE lower than 1) EFSA CONTAM Panel (2010)
Inorganic mercury (iHg)/4 μg/kg bw per week (TWI)	The HBGV was set using kidney weight changes in male rats as the pivotal effect. Based on the $BMDL_{10}$ of 0.06 mg/kg bw per day, expressed as mercury, and an uncertainty factor of 100 to account for inter and intra species differences, with conversion to a weekly basis and rounding to one significant figure, a TWI for inorganic mercury of 4 μg/kg bw per week, expressed as mercury was established. EFSA CONTAM Panel (2012)
Cadmium (Cd)/2.5 μg/kg bw per week (TWI)	The derivation of the reference point is based on a meta-analysis to evaluate the dose–response relationship between selected urinary cadmium and urinary beta-2-microglobulin as the biomarker of tubular damage recognised as the most useful biomarker in relation to tubular effects. A group-based $BMDL_5$ of 4 μg Cd/g creatinine for humans was derived. A chemical specific adjustment factor of 3.9 was applied to account for human variability in urinary cadmium within each dose-subgroup in the analysis resulting in a reference point of 1.0 μg Cd per g creatinine. In order to remain below 1 μg Cd/g creatinine in urine in 95% of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 μg Cd/kg bw, corresponding to a weekly dietary intake of 2.5 μg Cd/kg bw. EFSA CONTAM Panel (2009)
Inorganic arsenic (iAs)/0.06 μg/kg bw per day ($BMDL_{05}$)	The reference point is based on a benchmark dose lower confidence limit ($BMDL_{05}$) of 0.06 μg/kg bw per day identified for skin cancer. The reference point is considered to cover lung cancer, bladder cancer, skin lesions, ischemic heart disease, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects. A MOE of 1 would correspond to the exposure level that is associated with a 5% increase relative to the background incidence for skin cancer, based on the available data. A MOE of 1 raises a health concern. Because there are no precedents in EFSA for identification of a MOE of low concern when using a BMDL derived from human cancer data, the CONTAM Panel decided not to determine a value for a MOE of low concern. EFSA CONTAM Panel (2024)
3-MCPD and 3-MCPD fatty acid esters/2 μg/kg bw per day (TDI)	The HBGV is based on increased incidence of kidney tubular hyperplasia. BMD analysis using model averaging resulted in a $BMDL_{10}$ of 0.20 mg/kg bw per day in male rats, which was selected as the reference point for renal effects. This reference point was considered to derive a group TDI of 2 μg/kg bw per day for 3-MCPD and 3-MCPD fatty acid esters and was considered protective also for effects on male fertility. EFSA CONTAM Panel (2018)
Glycidyl esters (GEs)/10,200 μg/kg bw per day (T25)	Based on the EFSA Guidance on substances that are genotoxic and carcinogenic, T25 values were calculated for the incidence of tumours observed in rats and mice following long-term exposure to glycidol. A T25 of 10.2 mg/kg bw per day for peritoneal mesothelioma in male rats was used as the reference point. An MOE of 25,000 or higher is considered of low health concern. EFSA CONTAM Panel (2016a)
Erucic acid/7000 μg /kg bw per day (TDI)	The heart is the principal target organ for toxic effects after exposure to erucic acid. Myocardial lipidosis was identified by EFSA as the critical effect for chronic exposure to erucic acid. This effect is reversible and transient during prolonged exposure. A tolerable daily intake (TDI) of 7000 μg/kg bw per day for erucic acid was established, based on a no observed adverse effect level of 0.7 g/kg bw per day for lipidosis in young rats and newborn piglets. EFSA CONTAM Panel (2016b)
Acrolein/7.5 μg/kg bw per day (provisional TC)	A provisional tolerable concentration (TC) was developed on the basis of the NOEL for non-neoplastic lesions in the gastrointestinal tract of rats. WHO (2002)

Abbreviations: 3-MCPD, 3-monochloropropanediol; BMDL, lower confidence limit of the benchmark dose; HBGV, health-based guidance value; MOE, margin of exposure; NOEL, no observed effect level; PDE, permitted daily exposure.; RP, Reference point; T25, the chronic dose rate, which will give 25% of the animals with tumours at a specific tissue site, after specific correction for the spontaneous incidence within the standard life time of that species; TC, tolerable concentration; TDI, tolerable daily intake; TWI, tolerable weekly intake.

The risk assessment of the impurities and undesirable constituents helps to determine whether there could be a possible health concern if these impurities and undesirable constituents would be present at a certain level in the food additive. The assessment is performed by calculating the margin of exposure (MOE) by dividing the reference point (e.g. BMDL (Table 14)) by the exposure estimate (Tables 10 and 13), or by estimating the contribution of the use of E 472c to the HBGV (expressed as percentage of the HBGV).

3.5.1 | Toxic elements

The results of the analyses for arsenic, cadmium, lead and mercury in samples of E 472c are reported in Section 1.2.1.2. The Panel noted that the occurrence data on lead submitted by the IBO are substantially lower than the current limit in the EU specifications. Currently, no limits for arsenic, cadmium and mercury are included in the EU specifications for E 472c. As

indicated in Table 6, the IBO proposed lowest technologically achievable levels for lead (0.6 mg/kg), mercury (0.6 mg/kg), cadmium (0.2 mg/kg) and arsenic (0.8 mg/kg) (Documentation provided to EFSA n. 1 and 10).

The Panel assessed the risk that would result if these toxic elements were present in the food additive E 472c:

(i) at the current maximum limit in the EU specifications;
(ii) at the lowest technologically achievable levels proposed by one IBO, which are coincident with the highest LOQ; and
(iii) at levels based on lowest reported LOQ and applying a factor of 10 to allow flexibility with respect to representativeness and homogeneity (Table 15).

TABLE 15 Toxic elements concentrations (mg/kg) in E 472c used for the calculation of their potential exposure from the use of E 472c.

Toxic elements concentrations in E 472c	Pb	Hg	Cd	As
(i) Current limits in the EU specifications for E 472c	2	–	–	–
(ii) Lowest technologically achievable levels proposed by the IBO	0.6	0.6	0.2	0.8
(iii) Lowest reported LOQ and applying a factor of 10	0.05	0.05	0.05	0.05

Abbreviations: IBO, interested business operator; LOQ, limit of quantification.

The outcome of the risk assessment of the Panel is presented in Table 16.

TABLE 16 Risk assessment for toxic elements from the use of E 472c.

(i) Considering the presence of toxic elements at the current limits of the EU specifications for E 472c (Commission Regulation (EU) No 231/2012)				
Exposure to E 472c (mg/kg bw/day)	**MOE for Pb at 2 mg/kg**			
66[a]	3.8	–	–	–
135[b]	1.8	–	–	–
370[c]	0.7	–	–	–
481[d]	0.5	–	–	–
1780[e]	0.1	–	–	–
2314[f]	0.1	–	–	–
(ii) Considering the lowest technologically achievable levels proposed by the IBO for toxic elements				
Exposure to E 472c (mg/kg bw/day)	**MOE for Pb at 0.6 mg/kg**	**% of the TWI for Hg at 0.1 mg/kg**	**% of the TWI for Cd at 0.2 mg/kg**	**MOE for As at 0.8 mg/kg**
66[a]	13	7	4	1.1
135[b]	6	14	8	0.6
370[c]	2.2	38	21	0.2
481[d]	1.7	50	27	0.2
1780[e]	0.5	187	97	< 0.1
2314[f]	0.4	243	130	< 0.1
(iii) Considering the presence of toxic elements at the lowest reported LOQ and applying a factor of 10				
Exposure to E 472c (mg/kg bw/day)	**MOE for Pb at 0.05 mg/kg**	**% of the TWI for Hg at 0.05 mg/kg**	**% of the TWI for Cd at 0.05 mg/kg**	**MOE for As at 0.05 mg/kg**
66[a]	152	0.6	0.9	18
135[b]	74	1	1.9	9
370[c]	26	3	5	3
481[d]	20	4	7	2
1780[e]	5	16	26	< 0.1
2314[f]	4	22	35	< 0.1

Abbreviations: bw, body weight; MOE, margin of exposure; TWI, tolerable weekly intake.

[a]Mean exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – mean (Table 13).

[b]Highest exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – 95th percentile (Table 13).

[c]Mean consumption scenario for infants consuming formula sold as powder and considering the maximum use levels reported by the IBO (Table 10).

[d]High-level consumption scenario for infants consuming formula sold as powder and considering the maximum use level reported by the IBO (Table 10).

[e]Mean consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use levels reported by the IBO (Table 10).

[f]High-level consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use level reported by the IBO (Table 10).

Regarding the general population, the values in Table 16 show that the presence of lead, mercury and cadmium in E 472c would not give rise to concern at any of the concentrations considered. For arsenic, the calculated MOE values would give rise to concern at the proposed lowest technologically achievable level.

In the case that E 472c is used in solid formula for infants below 16 weeks of age, the values in Table 16 for arsenic even at the lowest LOQ and applying a factor of 10 would still indicate a concern. In the case that E472c is used in liquid formula, the presence of all four toxic elements at the proposed lowest technologically achievable level would give rise to a concern.

The Panel noted that maximum levels for lead, cadmium and arsenic in infant formula are set by Commission Regulation (EU) 2023/915[2] and therefore the Panel calculated the impact of the level of these toxic elements in the food additive on the final product (infant formulae) and compared that with the legal limits for these elements in the final formula (see Appendix A).

The Panel recommended to lower the EU specification limit for lead and include limits for arsenic, mercury and cadmium, taking into account (i) the results of the calculations performed by the Panel (Table 16 and Appendix A), (ii) the fact that the food additive is not the only potential dietary source of toxic elements and that (iii) the maximum limits should be established based on actual levels in the commercial food additive. If the European Commission decides to revise the current limits in the EU specifications, the values in Table 16 and Appendix A could be considered.

3.5.2 | Carry-over and process impurities

3.5.2.1 | *Butanetriols*

No analytical data on butanetriols were submitted and the IBO indicated that it is not expected to be produced during the manufacturing process of E 472c.

Considering that glycerol used for the manufacturing of E 472c meets the EU specifications for glycerol (E 422), the Panel agreed that no specification limit for butanetriols is needed in the EU specifications for E472c as laid down in Commission Regulation (EU) No 231/2012.

Therefore, the Panel recommended a modification of the definition of E 472c indicating that glycerol used for the manufacturing of E 472c should meet the specifications for E 422 (Commission Regulation (EU) No 231/2012).

3.5.2.2 | *Acrolein*

Acrolein was analysed in samples of E 472c and reported as below LOQ or LOD (Section 3.2.3.2). Acrolein is not expected to be formed during the manufacturing process of E 472c.

Considering that glycerol used for the manufacturing of E 472c meets the EU specifications for glycerol (E 422), the Panel agreed that no specification limit for acrolein is needed in the EU specifications for E 472c laid down in Commission Regulation (EU) No 231/2012.

Therefore, the Panel recommended a modification of the definition of E 472c indicating that glycerol used for the manufacturing of E 472c should meet the specifications for E 422 (Commission Regulation (EU) No 231/2012).

3.5.2.3 | *3-MCPD and 3-MCPD fatty acid esters*

The results of analyses for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in samples of E 472c are reported in section 3.2.3.3), indicating the presence of these impurities up to 0.8 mg/kg in the analysed samples. The IBO proposed a lowest technologically achievable level for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) of 2.5 mg/kg in E 472c when used in foods consumed by the general population and of 0.75 mg/kg when E 472c is used in foods consumed by infants below 16 weeks of age.

The Panel assessed the risk that would result if 3-MCPD and 3-MCPD fatty acid esters are present in E 472c at:

(i) the lowest technologically achievable level proposed by the IBO for E 472c when used in foods consumed by the general population (2.5 mg/kg)
(ii) the lowest technologically achievable level proposed by the IBO for E 472c when used in foods consumed by infants below 16 weeks of age (0.75 mg/kg)

The outcome of the risk assessment is presented in Table 17.

TABLE 17 Risk assessment for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) from the use of E 472c.

Exposure to E 472c (mg/kg bw/day)	% of the TDI for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) at 2.5 mg/kg in E 472c	% of the TDI for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) at 0.75 mg/kg in E 472c
66[a]	8	–
135[b]	17	–
370[c]	–	14
481[d]	–	18
1780[e]	–	67
2314[f]	–	87

Abbreviations: bw, body weight; IBO, interested business operator; TDI, tolerable daily intake.

[a]Mean exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – mean) (Table 13).

[b]Highest exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – 95th percentile) (Table 13).

[c]Mean consumption scenario for infants consuming formula sold as powder and considering the maximum use levels reported by the IBO (Table 10).

[d]High-level consumption scenario for infants consuming formula sold as powder and considering the maximum use level reported by the IBO (Table 10).

[e]Mean consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use levels reported by the IBO (Table 10).

[f]High-level consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use level reported by the IBO (Table 10).

The Panel noted that maximum levels for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in infant formulae are set in Commission Regulation (EU) 2023/915 and therefore the Panel calculated the impact of the levels of the impurities in the food additive on the final product and compared those with the legal limits for these impurities in the final formulae (see Appendix A).

The Panel recommended including a specification limit, taking into account the proposal from the IBO, for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in the EU specifications for E472c as laid down in Commission Regulation (EU) No 231/2012, considering the occurrence of 3-MCPD and/or 3-MCPD fatty acid esters in E 472c and the results of the calculations performed by the Panel (Table 17 and Appendix A).

3.5.2.4 | *Glycidyl esters*

The results of the analyses of glycidyl esters in samples of E 472c are reported in Section 3.2.3.4. The highest reported level was 0.7 mg/kg. The IBO proposed a lowest technologically achievable level for glycidyl esters of 2.0 mg/kg. The Panel assessed the risk that would result if glycidyl esters were present in E 472c at the lowest technologically achievable level indicated by the IBO.

The outcome of the risk assessment is presented in Table 18.

TABLE 18 Risk assessment for glycidyl esters (expressed as glycidol) from the use of E 472c.

Exposure to E 472c (mg/kg bw per day)	MOE for glycidyl esters at 2 mg/kg in E 472c
66[a]	77,390
135[b]	37,806
370[c]	19,615
481[d]	15,089
1780[e]	3858
2314[f]	2967

Abbreviations: bw, body weight; MOE, margin of exposure.

[a]Mean exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – mean) (Table 13).

[b]Highest exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – 95th percentile) (Table 13).

[c]Mean consumption scenario for infants consuming formula sold as powder and considering the maximum use levels reported by the IBO (Table 10).

[d]High-level consumption scenario for infants consuming formula sold as powder and considering the maximum use level reported by the IBO (Table 10).

[e]Mean consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use levels reported by the IBO (Table 10).

[f]High-level consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use level reported by the IBO (Table 10).

The Panel noted that maximum levels for glycidyl esters in infant formulae are set in Commission Regulation (EU) 2023/915 and therefore the Panel calculated the impact of the level of this impurity in the food additive on the final product and compared that with the legal limits for glycidyl esters in the final formula (see Appendix A).

The Panel recommended including a specification limit for glycidyl esters (expressed as glycidol) in the EU specifications for E472c as laid down in Commission Regulation (EU) No 231/2012, considering their occurrence in E 472c and the results of the calculations performed by the Panel (Table 18 and Appendix A).

3.5.2.5 | *Oxalates*

The IBO did not report analytical data on oxalic acid content in E 472c. The IBO referred to the limit of 100 mg/kg for oxalates (expressed as oxalic acid) in the specifications for citric acid (E 330) and stated that oxalates are not formed during the production process of E 472c.

The Panel considered that a modification of the definition of E 472c indicating that it should be produced from citric acid meeting the specifications for E 330 (Commission Regulation (EU) No 231/2012), and, therefore, a specification limit for oxalates would not be needed for E472c.

3.5.3 | Undesirable fatty acids as constituents of citric acid esters of mono- and diglycerides of fatty acids (E 472c)

3.5.3.1 | *Trans-fatty acids*

The results of the analyses of trans-fatty acids in commercial samples of E 472c are reported in Section 3.2.4.1. The highest value reported was 0.38% w/w of total fatty acids in the product.

The IBO stated that the concentration of *trans*-fatty acids in E 472c is almost entirely dependent on the *trans*-fatty acid content of the fats, oils or fatty acids used in the production of E 472c. However, small amounts of *trans*-fatty acids may be formed during the production process and production control is used to keep this as low as possible.

The content of *trans*-fat is regulated by the existing legal limit of 2 g of *trans*-fat per 100 g fat in food for final consumer (Regulation (EU) No 2019/649 amending Annex III to Regulation (EC) No 1925/2006). Hence, the Panel considered that there is no need for setting a specification limit in Commission Regulation (EU) No 231/2012 for the content of *trans*-fatty acids in E 472c.

3.5.3.2 | *Erucic acid*

The results of analyses for erucic acid in samples of E 472c are reported in Section 3.2.4.2. In only one of the analysed samples erucic acid was reported at a level of 0.5 g/kg. The IBO did not propose a lowest technologically achievable level for erucic acid in E 472c.

The Panel noted that there is a limit of 20 g/kg for erucic acid in vegetable oils and fats (Commission Regulation (EU) No 2023/915). Therefore, the Panel assessed the risk that would result if erucic acid was present in E 472c at this limit.

The outcome of the risk assessment for erucic acid is presented in Table 19.

TABLE 19 Risk assessment for erucic acid from the use of E 472c.

Exposure to E 472c (mg/kg bw/day)	% of the TDI for erucic acid, at an illustrative limit of 20 g/kg
66[a]	19
135[b]	38
370[c]	106
481[d]	137
1780[e]	508
2314[f]	661

Abbreviations: bw, body weight; TDI, tolerable daily intake.

[a]Mean exposure level among the different population groups (refined non-brand-loyal scenario – toddlers – mean (Table 13).

[b]Highest exposure level among the different population groups (refined non-brand-loyal scenario—toddlers—95th percentile (Table 13).

[c]Mean consumption scenario for infants consuming formula sold as powder and considering the maximum use levels reported by the IBO (Table 10).

[d]High-level consumption scenario for infants consuming formula sold as powder and considering the maximum use level reported by the IBO (Table 10).

[e]Mean consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use levels reported by the IBO (Table 10).

[f]High-level consumption scenario for infants consuming formula sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids and considering the maximum use level reported by the IBO (Table 10).

The Panel noted that if erucic acid would be present in E472c at the limit of 20 g/kg, it could lead to an exceedance of its TDI (Table 19). However, the data submitted for E 472c show that erucic acid is well below that limit.

The Panel noted that according to the IBO, oils and fats used in the manufacturing of E472c are from edible oils and fats. However, according to the current definition of this food additive in the EU specifications, the fats and oils that can be used for the production of this food additive are not specified. he Panel recommended including a specification limit for erucic acid in the EU specifications for E 472c as laid down in Commission Regulation (EU) No 231/2012, considering its potential occurrence in E 472c and the results of the calculations performed by the Panel (Table 19).

3.5.4 | Summary of the proposed revisions to the EU specifications

Overall, based on the information provided by the IBO in response to the call for data (Documentation provided to EFSA n. 1, 2 and 10) and on the above considerations, the Panel proposed revisions of the existing EU specifications for citric acid esters of mono- and diglycerides of fatty acids (E 472c) as listed in Table 20. The Panel noted that the choice of maximum limits for impurities and undesirable constituents in the EU specifications is in the remit of risk management.

TABLE 20 Proposal for a revised version of the existing EU Specifications for E 472c.

	Commission Regulation (EU) No 231/2012	Comment/justification for revision
Definition	See Table 1	The Panel recommended a modification of the definition indicating that glycerol used for the manufacturing of E 472c should meet the specifications for E 422 (Commission Regulation (EU) No231/2012) and citric acid meets the specifications for E 330 (Commission Regulation (EU) No 231/2012) and, therefore, specification limits for butanetriols, acrolein and oxalates would not be needed for E 472c.
Assay	See Table 1–4	Unchanged
Description	See Table 1	Unchanged
Identification	See Table 1	Unchanged
Infrared absorption spectrum Tests for glycerol and polyglycerols	See Tables 1–4	Unchanged
Tests for fatty acids	See Table 1	Unchanged
Solubility	See Table 1	Unchanged
Purity	See Tables 1–4	Unchanged
Sulphated ash	See Table 1	Unchanged
Acids other than fatty acids	See Table 1	Unchanged
Free fatty acids	See Tables 1–4	Unchanged
Total glycerol	See Table 1	Unchanged
Free glycerol	See Table 1	Unchanged
Arsenic	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel
Lead	Not more than 2 mg/kg	Lowering the limit on the basis of the information provided and the considerations of the Panel
Mercury	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel.
Cadmium	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel.
Sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD)	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel
Glycidyl esters (expressed as glycidol)	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel
Erucic acid	Not presently specified	Maximum limit to be included on the basis of the information provided and the considerations of the Panel.

3.6 | Biological and toxicological data

3.6.1 | Data submitted

The following information relevant for the risk assessment of E 472c for uses as a food additive in foods for infants below 16 weeks of age was requested in the EFSA call for data:

- Information to demonstrate that the metabolism of E 472c in infants below 16 weeks of age is comparable to the metabolism in adults i.e. it can be expected that E 472c is extensively hydrolysed in the infants' gastrointestinal tract and/or (pre)systemically after absorption into its individual hydrolysis products which are all normal dietary constituents and are metabolised or excreted intact, see also EFSA FAF Panel (2020)
- Comparative data to demonstrate that the exposure of infants to fatty acids through infant formulae containing E 472c is comparable to the exposure to fatty acids through breast milk.
- Any available clinical data to assess the safety of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in the relevant age group.
- Post-marketing surveillance reports on undesired and adverse 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, associated with the oral administration of citric acid esters of mono- and diglycerides of fatty acids (E 472c) to infants and young children.
- Literature searches relevant for the safety evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c) when used in foods for infants below 16 weeks of age, should be conducted as described in the Guidance for submission for food additive evaluations (Section 5.3)

Data to address the above requests were provided by two IBOs and are summarised in the following sections (Documentation provided to EFSA n.1, 2, 3, 4, 5, 7, 8, 9). The IBOs performed a literature search[13] and did not find any new publications relevant for the safety evaluation of E 472c as food additive (Documentation provided to EFSA n.1 and 2).

3.6.1.1 | *ADME*

ADME of citric acid esters of mono- and diglycerides of fatty acids (E 472c) was already evaluated by the Panel in its re-evaluation of E 472a-f. The Panel concluded that '*the available studies on the ADME of the esters of mono- and diglycerides of fatty acids have not been performed according to current standards. Hydrolysis of E 472a,b,c,e was demonstrated in various experimental systems, although the available data on ADME were limited. However, the Panel presumed that E 472a,b,c,e,f will be extensively hydrolysed in the GI tract and/or pre-systemically and are unlikely to be present intact systemically' (*EFSA FAF Panel, 2020*).*

This assumption was based on the following data as described in EFSA FAF Panel (2020):

In groups of 10 male and 10 female Sprague–Dawley rats fed a caloric-restricted basal diet for 10 days the digestibility of E 472c was compared with a mixture of its constituents and with lard. The dietary levels for E 472c were 23.1 or 37.5% (ca. *1500 or 3000 mg/rat per day) and 16.7% or 33.3% for lard* (ca. *1000 or 2000 mg/rat per day). Faecal fat estimation and body fatty acid distribution showed that the ester was completely digestible, although the absorption of the ester or its component mixture was about 50% (Huntingdon Research Centre, 1966 (Documentation provided to EFSA n. 12)). Groups of five male and five female weanling rats (not further specified) were fed diets supplemented with 0% or 20% E 472c for 7 days. The food intake and body weight maintenance were the same in both groups, and the digestibility of the ester was calculated to be 99% (Rosner, 1959; as referred to by JECFA, 1967). The* in vitro *hydrolysis by pancreatic lipase and liver esterase produced nearly the same yield of citric acid in a 2-hour period as spontaneous hydrolysis at pH 7.5–8.5 (Lang, 1964, as referred to by JECFA, 1967).*

In another study, the test material used was E 472c, which contained 36% of citric acid esters of mono- and diglycerides of fatty acids (Amara et al., 2014). A two-step in vitro *digestion model mimicking lipolysis in the stomach and upper small intestine of term and preterm infants was then used to evaluate the digestibility of E 472c alone, E 472c containing infant formula and fat emulsions, and the isolated citric acid ester of mono- and diglycerides fraction. The analysis of the individual constituents of the food additive (E 472c) was carried out by using TLC for quantification assisted by ^{1}H- and ^{13}C-NMR (for identification) and by liquid chromatography–mass spectrometry (LC–MS) analysis. Overall, it was shown that fat digestion is not significantly changed by the presence of E 472c, and only one-fourth of the fatty acids contained in the citric acid esters of mono- and diglycerides were released. Nevertheless, undigestible water-soluble compounds containing glycerol and citric acid units were identified, indicating that the ester bond between citric acid and glycerol is not hydrolysed throughout the proposed digestion as initially expected and citric acid esters of glycerol are the end product of the hydrolysis. The authors state that the degree of hydrolysis of the citric acid esters of glycerol during human digestion remains as a topic to be studied. The Panel noted that citric acid esters of glycerol resist full hydrolysis in this* in vitro *model of the upper small intestine. According to the authors, the two-step digestion model is suitable for simulating lipid digestion in the upper part of the GI tract (stomach and duodenum). It is not well adapted, however,*

[13]Timeframe: from January 2020 to October 2022 (Documentation provided to EFSA n. 2) and from 1 January 2020 to 1 December 2022 (Documentation provided to EFSA n. 1).

for reproducing the entire digestion process and the completion of lipolysis that occurs further down in the small intestine. The Panel agreed with this conclusion'.

In response to the EFSA call for data, one IBO provided additional information to substantiate the safety of E 472c for its uses as food additive in food for infants below 16 weeks of age (Documentation provided to EFSA n. 2, 3). The provided information was expected to address the following main issues: (i) the metabolism in infants compared to that in adults and (ii) the comparison of the exposure to hydrolysis products of E 472c in infants from breast milk and from infant formulae containing E 472c (see Section 3.6.1.6).

Based on a large body of information from the literature which included also studies already assessed during the re-evaluation (Documentation provided to EFSA n. 2, 3), one IBO concluded that E 472c will be rapidly and extensively hydrolysed via lipolytic enzymes to free fatty acids (FFAs; mainly palmitic and stearic acid), glycerol and citric acid. The hydrolysis of E 472c was studied by Amara et al. (2014) using an in vitro digestion model mimicking the stomach and upper small intestine environments, and was already evaluated by the Panel (EFSA FAF Panel, 2020) with the conclusion that citric acid esters of glycerol resist full hydrolysis in this in vitro model of the upper small intestine. This is probably due to the fact that the two-step digestion model is not well adapted for reproducing the entire digestion process and the completion of lipolysis that occurs further down in the small intestine.

The IBO further noted that newborn infants exhibit hydrolysing enzymes (lingual, gastric, and pancreatic lipases and pancreatic lipase-related protein 2 (PLRP2), and lipase enzymatic activity). Differences of both fat digestion and absorption between newborn infants and adults, such as age-dependent enzyme expression, higher pH in the upper gastrointestinal tract and lower bile salt levels in infants have to be considered (Andersson et al., 2011). The activity of preduodenal/gastric lipase increases from 18 weeks of gestation until the first few months of age while pancreatic lipase is secreted from 30 weeks of gestation onwards but is very low at birth. Breast milk lipase/bile salt stimulated lipase (BSSL) is found in term and preterm milk—with the highest levels in colostrum (Manson & Weaver, 1997).

The Panel noted that the secretion of pancreatic lipase and bile salts is immature in the first months of life and that the predominant lipases involved in fat digestion in the newborn are preduodenal/gastric lipase in the stomach as well as PLRP2 and BSSL in the small intestine (He et al., 2020). Key lipases expressed in the pancreas of newborns, i.e. BSSL and PLRP2 were studied in Caco-2 cells grown on a Transwell membrane (Andersson et al., 2011). In this in vitro model using conditions resembling the small intestinal milieu of the newborn infants (i.e. 4 mM bile salt), both enzymes synergistically hydrolyse triglyceride (triolein) to glycerol and (free) oleic acid which were then efficiently absorbed by the cells and re-esterified to triglycerides: The cellular uptake of lipids increased approximately four-fold when PRLP2 and BSSL were added simultaneously, compared with when each lipase was added alone at the same concentration.

The IBO provided further evidence from literature data showing that newborn infants have the endogenous capacity to absorb and metabolise fatty acids (such as palmitic and stearic acid), glycerol and citric acid. The absorption of fatty acids in infants is not only dependent upon chain length and degree of unsaturation but is also dependent on the position of their esterification at the triglyceride. Palmitic acid in breast milk is primarily present at the *stereospecific numbering* (*sn)* -2 position (equal to position R-2, see Figure 1) and absorbed as monoacylglyceride (Tomarelli et al., 1968). Conversely, palmitic acid in vegetable oils is predominately bound in the *sn*-1 and *sn*-3 position (equal to position R-1 and R-3, see Figure 1) and hydrolysed by the pancreatic lipase-colipase system to free palmitic acid which in the presence of high calcium levels can precipitate leading to a reduced absorption (Innis, 2011). The Panel noted that a reduced absorption of palmitic acid would only be relevant in case E 472c is manufactured from vegetable oils with citric acid and has no toxicological consequences.

In a randomised study performed in infants aged 5 weeks receiving from birth a formula with palmitic acid at different amount and structural position, Carnielli et al. (1996) observed that fat absorption was highest (97.6 ± 0.9%) in infants fed the 'high'formula (24% palmitic acid, 66% at the sn-2 position), intermediate absorption (93.0 ± 1.8%) in those fed with the 'intermediate'formula (24% palmitic acid, 39% at the *sn*-2 position) and lowest absorption (90.4 ± 4.6%) in those fed the 'regular'formula (20% palmitic acid; 13% at the *sn*-2 position). The Panel noted that these differences were statistically significant ($p < 0.001$), however, small and not clinically relevant.

Sadava et al. (1987) studied the activities of three key enzymes of glycerol metabolism, i.e. glycerol kinase, cytoplasmic and mitochondrial glycerol-3-phosphate dehydrogenase measured in human foetal and infant livers from autopsies. The specific activity of the cytoplasmic enzyme increased from day 1–3 ($n = 3$) until day 129–765 ($n = 2$) of age while the other two enzyme activities remained at similar levels indicating that glycerol can be metabolised in human neonatal and infant liver.

Overall, the Panel considered that the metabolites resulting from the hydrolysis of E 472c, e.g. fatty acids, glycerol and citric acid, can be expected to be absorbed and metabolised by infants below 16 weeks of age via the usual pathways, i.e. beta oxidation, gluconeogenesis, tricarboxylic acid cycle, respectively.

3.6.1.2 | *Toxicological data*

It is noted that according to the call for data, additional studies were required only if it cannot be demonstrated that the metabolism of E 472c in infants is comparable to the metabolism in adults. The IBO was of the opinion that the metabolism of E 472c in infants is comparable to the metabolism in adults and that the exposure of infants to hydrolysis product of E 472c from breast milk and infant formulae are comparable, therefore, no toxicological studies were provided. The Panel took the approach to compare the content of fatty acids, glycerol and citric acid in the infant formulae/FSMPs containing E 472c with the respective content in breast milk and considered that new toxicological data are not needed in case the levels were comparable.

3.6.1.3 | *Clinical studies*

Previously assessed studies

In the opinion on the re-evaluation of E 472c (EFSA FAF Panel, 2020), reference is made to several clinical trials where E 472c (reported also as CITREM) has been investigated in children in several studies. In the following paragraph the assessment of these studies by the EFSA FAF Panel (2020) is reported:

In the JECFA monograph (2015), it is reported that CITREM (synonym of E 472c) has been investigated in children (Clarke et al., 2007; De Boissieu & Dupont, 2000, 2002; Evans et al., 2006; Giampietro et al., 2001; Harvey et al., 2014; Isolauri et al., 1995; Mabin et al., 1995; Niggemann et al., 2001; Vandenplas et al., 1993; Verwimp et al., 1995). Details on the recording of side effects (e.g. spontaneous reporting of the caregivers; questionnaire filled by nurses) are not given in the JECFA monograph. When evaluating the studies mentioned in JECFA (2015), it turned out that it could not be verified that formulae containing E 472c were used in the studies of De Boissieu and Dupont (2000), Clarke et al. (2007), Evans et al. (2006) and Mabin et al. (1995). In the remaining studies (Giampietro et al., 2001; Harvey et al., 2014; Isolauri et al., 1995; Niggemann et al., 2001; Vandenplas et al., 1993; Verwimp et al., 1995), E 472c could be identified as an ingredient of some formulae tested based on information on the label of these products reported in Mintel's Database and Open Food Facts. The Panel noted that the studies reported in JECFA (2015) were not intended to test the tolerability of E 472c but the tolerability of the formulae in atopic dermatitis and urticaria due to cow milk allergy in children of different age. The number of children included varies between 45 and 555 and their age between newborn and 3 years. The study duration was from 1 week up to 6 months. The endpoints tested were mainly related to the outcome concerning cow milk allergy. In some studies, the development was followed (weight, height, head circumference). In all studies, the tolerability was described. The results were given in terms of a general sentence stating that the development showed no noticeable deviation compared with the normal population or the control group. There were no reports with the exception of one study (Harvey et al., 2014) on the number of cases which dropped out or were lost to follow-up. The Panel noted that the content of E 472c was not given in the papers which were published between 1993 and 2012. Details of the studies are presented in Appendix S. In J ECFA (2015), it is also reported that 'The Committee was also provided with a summary of five case reports on infants given a liquid, peptide-based formula containing a high concentration of E 472c (8.56 g/L) (Nutricia, 2014)'. The Panel noted that these case reports were not made available to EFSA. JECFA concluded that 'there are no toxicological concerns about the use of E 472c in infant formula and formula for special medical purposes at concentrations up to 9 g/L'. The Panel noted that, according to use levels submitted to EFSA, E 472c is used at a level of 0.665 g/kg or g/L in FC 13.1.1, which indicates a current use level much lower than the ones reported in the studies of the JECFA (2015) monograph (0.95 to 1.62 g/L and 8.56 g/L). Studies, mostly in infants diagnosed with cow milk's protein allergy have been reported, in which the tolerability and side effects of citric acid esters of mono- and diglycerides (E 472c) have been investigated. No effect was reported on the incidence of cow milk allergy, the primary endpoint investigated, nor on developmental growth. The Panel noted that the information from these studies is hampered by the fact that the content of the food additive E 472c in the tested formulae is unknown.

In the EFSA FAF Panel opinion on E 472a,b,c,d,e,f from 2020, it was stated that the information from these studies was hampered by the fact that the concentration of the food additive E 472c in the tested formulae was unknown. In answer to the EFSA call for data on E 472c, one IBO submitted additional information related to these clinical studies (Documentation provided to EFSA n.2). Namely, the IBO provided a table with the concentration of E 472c in g/L for 10 studies (De Boissieu & Dupont, 2000; De Boissieu & Dupont, 2002; Evans et al., 2006; Giampietro et al., 2001; Harvey et al., 2014; Isolauri et al., 1995; Mabin et al., 1995; Niggemann et al., 2001; Vandenplas et al., 1993; Verwimp et al., 1995). However, the source of this additional information, which was not contained in the original publications, was not indicated by the IBO. The concentration of E 472c was said to be 0.95 g/L (Giampietro et al., 2001; Mabin et al., 1995; Vandenplas et al., 1993; Verwimp et al., 1995), 1.26–1.36 g/L (Isolauri et al., 1995), 1.26–1.38 g/L (De Boissieu & Dupont, 2000; De Boissieu & Dupont, 2002; Niggemann et al., 2001), 1.36 g/L (Harvey et al., 2014) and 1.62 g/L (Evans et al., 2006).

The Panel re-assessed these studies and considered that these studies have major methodological flaws: control group fed a formula with a different composition (besides the content of E 472c in the test formula) than the test formula (Isolauri et al., 1995; Niggemann et al., 2001; Vandenplas et al., 1993 and Verwimp et al., 1995); non-blinded open studies (Giampietro et al., 2001; Mabin et al., 1995); duration of the study which lasted only for 1 week (Giampietro et al., 2001) or 2 weeks (Evans et al., 2006); studies performed without a control group (de Boissieu and Dupont, 2000 and 2002) or with an inappropriate control group (Evans et al., 2006; Harvey et al., 2014).

The Panel considered that, even when the additional information on exposure is taken into account, these studies do not provide sufficient information on E 472c to confirm the safe use of this food additive in food for infants below 16 weeks of age due to major methodological flaws.

New studies submitted in the EFSA call for data

Following the EFSA call for data an IBO provided four studies which were not submitted at the time of the re-evaluation of E 472c (Documentation provided to EFSA n. 2). The Panel noted that all these studies were not planned to assess the safety of E 472c as food additive in food for infants below 16 weeks of age.

The study of **Burks et al. (2015)** was a prospective, randomised, double-blind controlled study, in full-term infants with diagnosed cow's milk allergy (average age at inclusion: 4.5 ± 2.4 months). The study compared an amino acid-based formula (AAF) (control group; $n = 56$) with the same AAF containing synbiotics (test group; $n = 54$) and lasted for 16 weeks.

According to the information provided by the IBO, which is not contained in the publication (Documentation provided to EFSA n. 2), both AAFs contained E 472c in a concentration of 1.005% in the finished product. The primary endpoint was growth (weight, length and head circumference). Secondary endpoints included allergic symptoms and stool characteristics. With respect to the assessment of the safety of E 472c, because the study is comparing two formulae both containing E 472c in the same concentration, the Panel considered that the study cannot be considered as a controlled study and should rather be regarded as an uncontrolled prospective observational study which may provide information on tolerability. In infants (total $n = 110$), 81 adverse events (AEs) occurred from which 33 were scored as moderate and 6 as severe (the Panel noted a discrepancy in the reporting of the severe AE; according to the Table 2 in the publication the number of severe AEs was 10). The study investigators considered the severe AEs as being unrelated to the study formulae. Because no description has been provided for the moderate and the severe AEs, the Panel is unable to assess the cases and to comment on the tolerability of E 472c in this study not including a study group without E 472c which could serve as control group.

The study of **Picaud et al. (2020)** was a multi-country, multicenter, randomised, double blind, controlled clinical trial, in which the test formulae, i.e. a partially hydrolyzed protein formula (PHF) ($n = 134$) or intact cow's milk protein formula (IPF) ($n = 134$) were compared. According to information not contained in the publication, but provided by the IBO, the PHF contained E 472c (0.512%). The population included was healthy term infants, with a postnatal age ≤ 14 days and a birth weight between the 10th and 90th percentile. The study duration was up to 17 weeks of age and the primary endpoint of the study was daily weight gain. The study was planned as an equivalence study with a pre-defined equivalence margin of ±3 g/day. Adverse effects, including gastrointestinal events were recorded. With respect to the assessment of the safety of E 472c, the Panel is of the opinion that this study cannot be considered as a controlled study because the study compared two formulae with different compositions, one of which contained E472c. For the safety parameters, no remarkable differences were noted except for a higher percentage of watery stools in the PHF group containing E 472c versus the IPF group at 17 weeks of age (12.7% vs. 8.4%; $p = 0.022$). The clinical relevance of this finding is questionable. In addition, the finding that, in the PHF containing E 472c, a statistically significant higher percentage of watery stools were observed in week 17 cannot be clearly attributed to the E 472c contained in this formula as other constituents of the PHF were not identical with the constituents of the IPF. Hence, the Panel considered that the study does not provide sufficient information to confirm the safe-use of E 472c when used as food additive in food for infants below 16 weeks of age.

The study of **Wang et al. (2021)** was performed in a Chinese population of infants less than 45 days of age. The study was a randomised, double-blind, controlled, multicenter trial aimed at comparing a partially hydrolyzed protein formula (PHF) with a synbiotic mixture (test formula; $n = 112$) with an intact protein infant formula (IPF) with a different synbiotic mixture (control formula; $n = 112$). The study period was until 17 weeks of age. According to information, not contained in the publication, but provided by the IBO, both the formulae contained E 472c (0.512%). With respect to the assessment of the safety of E 472c, because the study compared two formulae with different composition, both containing E 472c in the same concentration, the Panel considered that the study cannot be considered as a controlled study. Concerning the tolerability and side effects, the occurrence of at least one AE was reported for 52.9% of the infants fed with PHF and 43.0% of the infants fed the IPF. The most common AEs were infections and infestations in 36 (20.5%), skin and subcutaneous tissue disorders with eczema in 35 (19.5%) and GI disorders in 29 (14.9%) of the 175 infants remaining in the study. The occurrence of at least one serious AE was reported for 8 infants (5.3%). According to the authors, none of the AEs reported as serious was related to the study product. Because no description has been provided for the severe AEs, the Panel was unable to assess the cases and to comment on the tolerability of E 472c in this study not including a study group without E 472c exposure.

Abrahamse-Berkeveld et al. (2016) performed a double-blind, placebo-controlled, randomised prospective intervention study in 228 infants younger than 35 days. The study compared an extensively hydrolysed protein formula with the same formula containing synbiotics. According to the IBO, both the formulae contained E 472c, the control formula contained 0.0025% E 472c in the finished formula and the test formula contained 0.204%. This information is not reported in the publication. The formulae were given for a period of 13 weeks. The primary endpoint of the study was weight gain, and the study was planned as an equivalence study. Tolerance and stool characteristics were registered on a daily basis using a Likert scale. The study compared two formulae with different compositions. With respect to the assessment of the safety of E 472c, even if one of the formulae contained E 472c in a concentration of 0.0025% and the other in a concentration of 0.204%, the study cannot be considered as a controlled study. It is remarkable that from 123 infants included, for 12 the requested information on tolerability was not provided and that further 54 infants were excluded which is an attrition rate of 54%. Because of this high attrition rate (Genaidy et al., 2007), the Panel considered that this study cannot be used as a source of information on the tolerability of E 472c in food for infants below 16 weeks of age.

The Panel noted that none of the provided studies was appropriate for comparing a formula containing E 472c versus the same formula not containing E 472c. These studies were not planned to assess the tolerability of E 472c itself but the tolerability of formulae with other components or degree of hydrolisation, testing mainly for growth and allergy.

3.6.1.4 | *Other studies*

Upon EFSA request, one IBO submitted case studies evaluating the gastrointestinal tolerance, compliance and intake, and palatability of a ready-to-use liquid FSMP formula (FC 13.1.5.1) (Documentation provided to EFSA n. 4). According to the provided data the ready-to-use liquid FSMP *'is a nutritionally complete 1 kcal/mL peptide-based and feed for infants (from birth up to 18 months or < 9 kg in body weight), based on short chain peptides and MCT (medium chain triglycerides) for the dietary management of disease related malnutrition in infants with malabsorption and/or maldigestion and is suitable as a sole source of*

nutrition' and is also fibre-free. The document reports on gastrointestinal tolerance, compliance and intake, anthropometry and palatability of this formula in five infants with severe medical conditions and malnutrition followed in three different hospitals (aged 2, 5, 6, 8 and 11 months). These infants received the formula for a duration of 2 weeks ($n = 1$) or 4 weeks ($n = 4$). They were fed orally (n = 1), via nasogastric/nasojejunal tube ($n = 2$) or via jejunostomy (n = 2). No information on the content of E 472c in the formula was found. However, in the cover letter accompanying this document, the IBO stated that the referred product in the five case studies corresponds to a formula in production during year 2011 with the E 472c content being 8970 mg/L.

Given the small number of case studies ($n = 5$) of which only one was on an infant aged less than 16 weeks, and the observational design, i.e. without control group, the Panel considered that these case studies do not contribute to the evaluation of the safety of E 472c when used as food additive in food for infants below 16 weeks of age.

The IBO also provided a publication from 2018 reporting on a study aimed at investigating gastrointestinal tolerance, nutritional intake and compliance, anthropometry and growth in 18 infants (mean age 6.11 +/− 4.69 (SD) months; range: 2–14 months) during 4 weeks of enteral nutritional support with a ready-to-use liquid FSMP (Smith et al., 2018). The IBO stated that the five abovementioned case studies (Documentation provided to EFSA n. 4) are included in this publication. Considering the observational design (i.e. without control group) of this unblinded, prospective, multicentre study, the Panel considered that this study does not contribute to the evaluation of the safety of E 472c when used in food for infants below 16 weeks of age.

3.6.1.5 | *Post-marketing surveillance data*

One IBO sent post-marketing surveillance reports on two different products named product A and B. (Documentation provided by EFSA n.1 and 4). Product A – food for special medical purposes for infants and young children (Food Category 13.1.5.1 and 13.1.5.2) was used for around 82,000,000 patient-treatment days between January 2020 and December 2022. In this time period, 20 cases of vomiting/nausea, 16 cases of allergic reactions, 14 cases of diarrhoea and fewer than 10 cases of either stomach ache, bloating/distension, constipation or illness were reported. Product B – food for special medical purposes for infants and young children (Food Category 13.1.5.1 and 13.1.5.2) was used for around 97,000,000 patient-treatment days between 2016 and 2022. Sixty-three cases of unspecific nutritional disorders (e.g. diarrhoea, vomiting, obstipation etc.) were reported and four allergic reactions. The Panel considered that the data indicate a low number of reported symptoms possibly related to the intake of products A and B; all of which would not raise concern.

3.6.1.6 | *Comparison between content of E 472c hydrolysis products in human milk and infant formulae and FSMPs*

One IBO stated that the different hydrolysis products of E 472c (i.e. palmitic and stearic acid, citric acid and glycerol) are present both in breast milk and in infant formula. In agreement with the EFSA call for data, the IBO provided data, including published studies, on the content of fatty acids, glycerol and citric acid in breast milk and infant formulae (only FC 13.1.1; Documentation provided to EFSA n. 2). Upon request, the submitted information was further clarified and complemented by the IBO (i) by expressing the content of fatty acids, glycerol and citric acid as g/L (ii) by including information on the content of lauric and myristic acid in breast milk and IF, and (iii) by providing any additional information available on the content of palmitic acid, stearic acid, myristic acid and lauric acid in FSMPs (FC 13.1.5.1; Documentation provided to EFSA n.4, 5, 7).

The Panel retrieved several additional papers with respect to those already provided by the IBO and identified a systematic review and meta-analysis on the composition of human milk (Arthur et al., 1989; Holt, 1993; Jozwik et al., 2013; Kent et al., 1992; Peaker & Linzell, 1975; Zhang et al., 2022).

Upon request, another IBO (a manufacturer of E 472c) provided data for free-, bound- and total levels of glycerol, palmitic acid, stearic acid, lauric acid, myristic acid and citric acid in batches/samples of E 472c (Documentation provided to EFSA n. 8 and 9). According to this information, the free-, bound- and total content of glycerol, palmitic acid, stearic acid, lauric acid, myristic acid and citric acid in E 472c depends on the composition of the vegetable oils used to manufacture the batches (i.e. sunflower oil or palm oil).

Table 21 shows the mean and maximum content of fatty acids, citric acid and glycerol in breast milk compared with the content in samples of infant formulae and FSMPs containing E 472c (ranges). According to the IBO total and free levels of citric acid and glycerol in infant formulae /FSMP are not determined routinely by analysis by the dossier submitters (manufacturers of the final products). Information on the content of these substances in samples of infant formulae and FSMPs containing E 472c were, therefore, not provided.

The Panel noted that the IBO also provided the following information captured in Table 21:

- 'Typical concentration in infant formulae', i.e. commonly reported values for palmitic acid, stearic acid, glycerol and citric acid found in the literature on IFs found on the market in different geographies, without accounting for potential additives usage such as E 472c.
- 'Theoretical sum combining the typical concentrations in infant formulae plus E 472c at levels of 9000 mg/L (MPL)' for palmitic acid, stearic acid, glycerol and citric acid. Explanation from the IBO: infant formulae are purposefully formulated by the dossier submitters so that the lipid content remains within the regulatory limit of 6 g/100 kcal. At the highest quantity of E 472c (9000 mg/L) in infant formulae, a total lipid content of 4.2 g/100 kcal is calculated, taking into consideration

contribution from E 472c and other fatty acids. This is assuming an infant consumes the 95th percentile of infant formula consumption (260 mL/kg bw/day) and a calorie conversion factor of 67 kcal/100 mL.

- Literature data on the level of myristic acid and lauric acid in infant formulae.

TABLE 21 Content of fatty acids, citric acid and glycerol in breast milk, infant formulae-IF (FC 13.1.1) and FSMPs (13.1.5.1), Documentation provided to EFSA n. 2, 4, 5, 7).

	Breast milk		Formula (IF/FSMPs)				
	(Range of) mean content in breast milk (g/L)	Maximum content in breast milk (g/L)	Content in IF (g/L) reported by the IBO as 'typical'[a]	Content in IF (g/L) coming from the use of E 472c at the MPL (9 g /L)	Total content in IF containing E 472c at the MPL (g/L)[b]	Content in samples of IF (13.1.1) containing E 472c	Content in samples of FSMPs (13.1.5.1) containing E 472c
Lauric acid (C12:0)	0.8–3.8[c]		0.7–10[h]	Not provided	Not provided	0.04–3.9	0.03–5.0
Myristic acid (C14:0)	1.0–4.1[c]		0.4–2.2[h]	Not provided	Not provided	0.07–1.7	0.1–2.5
Palmitic acid (C16:0)	7.4–9.4[c] ***7.7***	***11.2***	6.0–6.4[i]	5.1	11.1–11.5	1.7–6.7	2.7–6.1
Stearic acid (C18:0)	1.3–3.0[c] ***2.3***	***3.8***	0.9–1.5[g]	3.6	4.5–5.1	0.8–2.5	0.9–4.2
Citric acid	0.3–1.1[d] ***0.5–0.6***	***1.1***	0.3–1.0[j]	>1.2[k]	>1.5–2.2	Not available	Not available
Glycerol	0.05–0.1 (free)[e]	***0.18 (free) 4***[f] ***(total)***	1.1–1.7[g]	2.1	3.2–3.8	Not available	Not available

Notes: Values in ***bold and italic*** correspond to data from papers retrieved by the Panel from Zhang et al., 2022; Kent et al., 1992, Peaker et al. 1975; Holt, 1993; Arthur, 1989; Jozwik et al., 2013.

Abbreviations: FSMPs, food for special medical purposes; IBO, interested business operator; IF, infant formulae.

[a]The 'typical concentration in IF' reported by the IBO as commonly reported values for fatty acids (i.e. palmitic acid and stearic acid), glycerol and citric acid found in the literature on typical IFs found on the market in different geographies, without accounting for potential additives usage such as E 472c.

[b]Theoretical sum combining the typical concentrations in IF plus E 472c at levels of 9000 mg/L (MPL). Explanation from the IBO: IF are purposefully formulated by the dossier submitters so that the lipid content remains within the regulatory limit of 6 g/100 kcal. At the highest quantity of E 472c (9000 mg/L) in IF, a total lipid content of 4.2 g/100 kcal is calculated, taking into consideration contribution from E 472c and other fatty acids. This is assuming an infant consumes the 95th percentile of infant formula consumption (260 mL/kg bw per day) and a calorie conversion factor of 67 kcal/100 mL.

[c]From Lepage and Roy (1984), Shehadeh et al. (2006) and Nguyen et al. (2021). The IBO also provided two publications from Szabó et al. (2010) and Ramiro-Cortijo et al. (2020). The figures reported in these papers when converted to g/L are in agreement with the concentration ranges from Lepage and Roy (1984), Shehadeh et al. (2006) and Nguyen et al. (2021).

[d]From the literature (Hoppe et al., 1998; Poulsen et al., 2022).

[e]From the literature (Cavalli et al., 2006).

[f]The fat content of human milk during the first 16 weeks after birth is up to ca. 35 g/L (Gidrewicz & Fenton, 2014). Most of the fat in breast milk is triacylglycerols (98%). Based on the molecular weights of glycerol and the triacylglycerols in human milk, approximately one-ninth of the mass of the milk fat is glycerol. Therefore, a fat content of 35 g/L corresponds to a total content of glycerol (i.e. after full hydrolysis) of ca. 4 g/L.

[g]Reported by the IBO as 'sponsor estimation'.

[h]Data from the literature (Mendonça et al. 2017a; Cheong et al., 2018) as reported by the IBO (Documentation provided to EFSA n. 5); the data in the paper reported as % of total fatty acids.

[i]From the literature (Bongers et al., 2007; Schmelzle et al. 2003).

[j]From the literature (Hoppe et al. 1998).

[k]Calculated by the IBO *'contribution of bound citric acid from CITREM can be determined based on the theoretical % contribution of citric acid in CITREM (13%–25%) as reported by the Food and Agriculture Organization (FAO) of the United Nations Technical Assessment on CITREM. Therefore, contribution of bound citric acid in IF from CITREM only at 9 g/L (highest use level) would be between 1.17% and 2.25% (a value of > 1.2 g/L was used in the calculations provided)'*. The Panel noted that the total citric acid in E 472c according to JECFA (2019) and the EU specification ranges from 13% to 50%. Therefore, contribution of bound citric acid in IF from CITREM only at 9 g/L (highest use level) would be between 1.17% and 4.5%.

According to the available data, the content of lauric, myristic, palmitic and stearic acid in samples of infant formulae and FSMPs containing E 472c is comparable to their content measured in breast milk.

The Panel calculated that the content of total citric acid in infant formulae/FSMPs deriving from the use of E 472c, i.e. considering the analytical data provided (15%–19% total citric acid in E 472c; Documentation provided to EFSA n. 8, 9) and considering the highest MPL, would be 1.3 to 1.7 g/L. This is in line with the calculations provided by the IBO (> 1.2 g/L; see Table 21).

The total content of citric acid in infant formulae containing E 472c (2.2 g/L) at the MPL (9 g/L), calculated by the IBO (2.2 g/L), is about two-fold higher than that in breast milk (1.1 g/L). It is noted that data from the literature provided a content range for citric acid in infant formulae of 0.6–0.68 g/L (Hoppe et al. 2008; Documentation provided to EFSA n. 4 and 7), however, from the publication it is not clear whether the tested formula contained E 472c. The Panel noted that a multicenter, randomised, double-blind clinical trial performed in 675 children aged 1 to 24 months with acute diarrhoea showed the safety of an oral rehydration solution (ORS) with a citrate concentration of 10 mmol/L (1.9 g/L) (Choice Study

Group, Pediatrics, 2001). This concentration in ORS is recommended by WHO since 2006 (WHO, 2006). However, since acute diarrhoea is a self-limited disorder, ORSs are only used in infants for a few days in order to prevent/treat dehydration. Overall, the Panel considered that the two-fold higher content of citric acid in infant formulae/FSMPs containing E 472c with respect to breast milk is not of concern.

The IBO estimated that total glycerol coming from typical infant formulae ingredients would be 1.1–1.7 g/L and total glycerol coming from the use of E 472c at the highest MPL (9 g/L) would be 2.1 g/L. Combining these two sources would give a total glycerol content of 3.2–3.8 g/L in the formula feed and this is in the same range as that in breast milk (estimated content of total glycerol around 4 g/L, see Table 21).

3.7 | Discussion

The current assessment addresses the recommendations indicated during the re-evaluation of citric acid esters of mono- and diglycerides of fatty acids E 472c as a food additive (EFSA ANS Panel, 2020) to update the EU specifications in Commission Regulation (EU) No 231/2012. In addition, the safety of the use of E 472c in food for infants below 16 weeks of age (FC 13.1.1 and 13.15.1) is addressed.

According to Annex II, Part E of Regulation (EC) No 1333/20082, E 472c is permitted in food categories (FCs) 13.1.1 'infant formulae' and 13.1.5.1 'dietary foods for infants for special medical purposes and special formulae' (FSMP) for infants at a maximum permitted level (MPL) of 7500 mg/kg as consumed when sold as powder and 9000 mg/kg as consumed when sold as liquid. Based on data submitted by one IBO, E 472c is used in infant formulae for infants below 16 weeks of age at a level up to 1849 mg/L as consumed when sold as powder, and up to 8900 mg/L as consumed when sold as liquid. The levels in special formulae for infants of that age under special medical conditions are up to the MPL. All levels are thus in compliance with the MPLs in the EU.

For infants below 16 weeks of age consuming infant formulae (FC 13.1.1) or infant food for special medical purposes (FSMP) (FC 13.1.5.1), mean exposure to E 472c was estimated to be respectively 1500 and 1800 mg/kg bw per day for formula sold in powder and in liquid form in the *regulatory maximum level exposure assessment scenario* (based on MPLs). The high-level exposure (95th percentile) was respectively 1950 and 2340 mg/kg bw per day.

Taking into account that brand loyalty is expected, the Panel considered that the mean and high-level scenarios using the maximum use levels reported by the IBO for FC 13.1.1 would be the most representative estimates for the safety assessment of E 472c when used in food for infants below 16 weeks of age (FC 13.1.1 and FC 13.1.5.1). The high-level exposure to E 472c for infants consuming formula sold as liquid was in the same range as the exposure for infant FSMP.

In this refined scenario using the maximum reported use levels for FC 13.1.1, mean exposure was estimated at 370 mg/kg bw per day for infant formula sold as powder and at 1780 mg/kg bw per day for formula sold as liquid. The high-level exposure was estimated at 481 and at 2314 mg/kg bw per day, respectively.

In response to the 2021 EFSA call for data for E 472c for use as a food additive in foods for all population groups including infants below 16 weeks of age, analytical data on potential impurities and undesirable constituents in commercial samples of E 472c were provided by an IBO and lowest technologically achievable levels were proposed in some cases. The potential exposure to these impurities and undesirable constituents from the use of the food additive E 472c was calculated by assuming that they may be present in the food additive at a certain limit value and then by calculation pro-rata to the estimates of exposure to the food additive itself.

Analytical data on levels of four toxic elements (arsenic, lead, cadmium, mercury) in commercial samples of E 472c were provided by an IBO. The Panel noted that the occurrence data on lead submitted by the IBO are substantially lower than the current limit in the EU specifications. Currently, no limits for arsenic, cadmium and mercury are defined in the specifications for E 472c. The IBO proposed lowest technologically achievable levels for the four toxic elements at the highest reported LOQ values. The Panel performed a risk assessment considering: (i) the current limit for lead in the EU specifications (Commission Regulation (EU) No 231/2012); (ii) the lowest technologically achievable levels proposed by the IBO; and (iii) the lowest reported LOQ and applying a factor of 10. The potential exposure to the toxic elements from the use of E 472c was compared to the available health-based guidance values (HBGV) and reference points (RP) (Table 14). The Panel recommended lowering the specification limit for lead and including limits for arsenic, mercury and cadmium, taking into account (i) the results of the calculations performed by the Panel (Table 16 and Appendix A), (ii) the fact that the food additive is not the only potential dietary source of toxic elements and that (iii) the maximum limits should be established based on actual levels in the commercial food additive.

Analytical data on the levels of butanetriols were requested in line with the recommendations from the re-evaluation (EFSA ANS Panel, 2020), but no data were submitted. Considering that glycerol used for the manufacturing of E 472c meets the EU specifications for glycerol (E 422) and butanetriols are not expected to be formed during the manufacturing process, the Panel considered that no specification limit for butanetriols is needed in the EU specifications for E472c laid down in Commission Regulation (EU) No 231/2012.

Similarly, considering that glycerol used for the manufacturing of E472c meets the EU specifications for glycerol (E 422) and acrolein is not expected to be formed during the manufacturing process of E 472c, the Panel considered that no specification limit for acrolein is needed in the EU specifications for E472c laid down in Commission Regulation (EU) No 231/2012.

Analytical data on levels of free 3-MCPD and 3-MCPD fatty acids (expressed as 3-MCPD) in commercial samples of E 472c were submitted (section 3.2.3.3). Based on these data, the IBO proposed the following lowest technologically achievable

levels for the sum of 3-MCPD and 3-MCPD fatty acids (expressed as 3-MCPD): 2.5 mg/kg for E 472c when used in foods consumed by the general population and 0.75 mg/kg for E 472c when used in foods for infants below 16 weeks of age. The Panel recommended including a specification limit for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in the EU specifications for E472c laid down in Commission Regulation (EU) No 231/2012, considering their occurrence in E 472c and the calculations performed by the Panel (Table 17 and Appendix A).

Analytical data on levels of glycidyl esters (expressed as glycidol) in commercial samples of E 472c were submitted (Section 3.2.3.4). The Panel assessed the risk that would results if glycidyl esters were present in E 472c at the lowest technologically achievable level proposed by the IBO of 2 mg/kg. The Panel recommended including a specification limit for glycidyl esters (expressed as glycidol) in the EU specifications for E 472c as laid down in Commission Regulation (EU) No 231/2012, considering their potential occurrence in E 472c and the calculations performed by the Panel (Table 18 and Appendix A).

No analytical data on the content of oxalates in commercial samples of E 472c were provided and no lowest technologically achievable level was proposed. Considering that citric acid used for the manufacturing of E 472c meets the EU specifications for citric acid E 330 and oxalates are not expected to be formed during the manufacturing process of E 472c, the Panel considered that no specification limit for oxalic acid/oxalates is needed in the EU specifications for E 472c as laid down in Commission Regulation (EU) No 231/2012.

Analytical data on the content of *trans*-fatty acids in commercial samples of E 472c were provided by the IBO. The Panel noted that a maximum limit of 2 grams of *trans*-fat per 100 g fat in food for the final consumer is set by Regulation (EU) No 2019/649 amending Annex III to Regulation (EC) No 1925/2006. Hence, the Panel considered that there is no need for setting a specification limit for the content of *trans*-fatty acids in the specifications for E 472c.

Analytical data on the content of erucic acid in commercial samples of E 472c were provided by the IBO. The IBO did not propose a lowest technologically achievable level for erucic acid in E 472c. The Panel assessed the risk that would result if erucic acid was present in E 472c at the limit of 20 g/kg in vegetable oils and fats (Commission Regulation (EU) No 2023/915). The Panel noted that according to the current definitions of E 472c in the EU specifications, the oils and fats that can be used for their manufacturing processes are not specified. The Panel recommended including a specification limit for erucic acid in the EU specifications for E 472c laid down in Commission Regulation (EU) No 231/2012, considering its potential occurrence in E 472c and the calculations performed by the Panel (Table 19).

Overall, the Panel considered it feasible to amend the EU specifications based on the information submitted in response to the call for data and supports an amendment of the specifications for (E 472c) as laid down in Commission Regulation (EU) No 231/2012, and as presented by the recommendations made in Table 20.

According to the call for data additional toxicological studies to address the safety of the uses in food intended for infants below 16 weeks of age were required only if it cannot be demonstrated that the metabolism of E 472c in infants is comparable to the metabolism in adults. The IBO was of the opinion that the metabolism of E 472c in infants is comparable to the metabolism in adults and that the exposure to fatty acids in infants from breast milk and infant formulae are comparable, therefore, no toxicological studies were provided.

As part of the Panel assessment, consideration was given as to whether the metabolism of E 472c in infants would be similar to the metabolism of the same food additive in adults. In the absence of specific studies on ADME for E 472c in infants below 16 weeks of age, the Panel based its considerations on the information from literature provided by one IBO indicating differences in both fat digestion and absorption between adults and newborns, such as age-dependent enzyme expression, very low levels of pancreatic lipases at birth, higher pH in the upper gastrointestinal tract and lower bile salt levels in infants. In addition, based on in vitro data the Panel considered that the key lipases expressed in the pancreas, i.e. BSSL and PLRP2 hydrolyse triglycerides synergistically to glycerol and FFA which are then absorbed by the cells and re-esterified to triglycerides. Thus, it can be expected that newborns have the capacity to effectively hydrolyse triglycerides to FFAs, glycerol and citric acid. The Panel considered that these hydrolysis products can be expected to be absorbed and metabolised via the usual pathways, i.e. beta oxidation, gluconeogenesis or the tricarboxylic acid cycle, respectively.

Overall, the Panel considered that metabolism of E 472c in infants is similar to the metabolism in adults because the extent of the differences mentioned in Section 3.6.1.1 ADME are functionally not relevant.

In order to address the safety of the use of E 472c in food for infants below 16 weeks of age, one IBO provided additional information on the clinical studies already available at the time of the 2020 re-evaluation. The Panel re-assessed these studies and considered that they have major methodological flaws. Four new clinical studies were also provided but the Panel noted that none of these studies is appropriate for comparing a formula containing E 472c vs. the same formula not containing E 472c. Overall, the Panel considered that the clinical studies do not contribute to the evaluation of the safety of E 472c when used as food additive in food for infants below 16 weeks of age.

The same IBO submitted case studies from an evaluation of the gastrointestinal tolerance, compliance and intake, and palatability of a ready-to-use formula' and a related publication from 2018. The Panel considered that these data do not contribute to the evaluation of the safety of E 472c when used as food additive in food for infants below 16 weeks of age due to the methodological flaws and the low number of participating infants.

The available post-marketing surveillance reports indicated a low number of symptoms possibly related to the intake of the formulae covered in the reports all of which would not raise concern.

In line with the call for data and the proposal from the IBO, the Panel took the approach to compare the content of fatty acids, glycerol and citric acid in the infant formulae /FSMPs containing E 472c with that in breast milk to assess the safety of the use of E 472c in food for infants below 16 weeks of age. According to the comparison performed, the Panel noted that

the content of lauric, myristic, palmitic and stearic acid in samples of infant formulae and FSMPs containing E 472c is comparable to their content measured in breast milk. Similarly, the content of total glycerol in infant formulae (3.8 g/L) containing E 472c at the MPL (9 g/L) is in the same range than that in breast milk (estimated content of total glycerol around 4 g/L).

The Panel calculated that the content of total citric acid in infant formulae /FSMPs deriving from the use of E 472c considering the analytical data provided (13–18% total citric acid in E 472c) and considering the highest MPL would be 1.3 to 1.7 g/L. The maximum citric acid content in infant formulae containing E 472c (2.2 g/L) at the MPL calculated by the IBO is about 2-fold higher than that in breast milk (1.1 g/L). The Panel considered that the two-fold higher level of citric acid is not of safety concern.

4 | CONCLUSIONS

As a follow-up of the re-evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c), the Panel concluded that the technical data provided by the IBOs support an amendment of the specifications for citric acid esters of mono- and diglycerides of fatty acids (E 472c) laid down in Commission Regulation (EU) No 231/2012, as presented by the recommendations made in Table 20.

Regarding the safety of E 472c in food for infants below 16 weeks of age, the Panel considered that metabolism of E 472c in infants is similar to the metabolism in adults. Taking into account the similar content of the hydrolysis products of E 472c (fatty acids, glycerol and citric acid) in the infant formulae/FSMPs containing E 472c and in breast milk, the Panel concluded that there is no safety concern from the uses of E 472c at the reported use levels and at the MPLs in food for infants below 16 weeks of age (FC 13.1.1 and 13.1.5.1).

5 | DOCUMENTATION AS PROVIDED TO EFSA

1. European Food Emulsifiers Manufacturers Association, 2023. Submission of data in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 29 June 2023.
2. Specialised Nutrition Europe, 2023. Submission of data in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 30 June 2023.
3. Specialised Nutrition Europe, 2023. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 27 July 2023.
4. Specialised Nutrition Europe, 2023. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 13 October 2023.
5. Specialised Nutrition Europe, 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 19 January 2024. https://dms.efsa.europa.eu/otcs/cs.exe/app/nodes/30280680
6. Specialised Nutrition Europe, 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 12 April 2024.
7. Specialised Nutrition Europe, 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 31 May 2024.
8. European Food Emulsifiers Manufacturers Association (EFEMA), 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 7 March 2024.
9. European Food Emulsifiers Manufacturers Association (EFEMA), 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 29 April 2024.
10. European Food Emulsifiers Manufacturers Association (EFEMA), 2024. Response to a clarification request on the data submitted in response to the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. Submitted on 31 July 2024.

ABBREVIATIONS

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
ANS Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
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
FSMPs	food for special medical purposes
IBO	interested business operator
ICP-MS	inductively coupled plasma-mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectroscopy
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
MPL	maximum permitted levels
OECD	Organisation for Economic Co-operation and Development
SC	Scientific Committee of EFSA
SCF	Scientific Committee on Food
TWI	tolerable weekly intake
WG	Working Group

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COMPETING INTEREST

In line with EFSA's policy on declarations of interest, the Panel member Patricia Morales did not participate in the adoption of this scientific output since she was involved in the development of the same opinion under the Framework Partnership Agreement (GP/EFSA/FIP/2022/01)

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Estimation of the fraction of the levels of toxic elements and other impurities in E 472c with respect to the regulatory maximum levels in the final food product (infant formulae) for which E 472c is used

The Panel noted that maximum levels for lead, arsenic, cadmium and other impurities present in E472c are established in infant formulae (Regulation (EC) No 2023/915). Therefore, the Panel calculated the impact of the level of these impurities in the food additive on infant formulae as placed on the market and compared that with the legal limits for these impurities in the final formula for the infants below 16 weeks of age.

A.1. | Toxic Elements

The Panel estimated the fraction (%) of the levels of the toxic elements (lead, cadmium and arsenic) from the use of E 472c with respect to the regulatory maximum levels in the final product (infant formulae) as sold as laid down in Regulation (EC) No 2023/915 considering:

- The current specification limit for lead of 2 mg/kg for E 472c according to Regulation (EU) No 231/2012.
- The lowest technologically achievable levels for lead, cadmium and arsenic, as proposed by one IBO, of 0.6, 0.2 and 0.8 mg/kg, respectively, (Documentation provided to EFSA n. 1).
- The lowest reported LOQ and modulated by the Panel applying a factor of 10
- The MPLs of E472c in infant formulae (FC 13.1.1) and infant FSMP (FC 13.1.5.1) when sold in powder (7500 mg/kg) or in liquid form (9000 mg/kg)
- The range of permitted levels for lead and arsenic (0.01 mg/kg (liquid form) – 0.02 mg/kg (powder form)), and cadmium (0.005 mg/kg (liquid form) – 0.02 mg/kg (powder form)) in infant formulae as laid down in Regulation (EC) No 2023/915.

The results of the calculations can be found in Tables A.1 and A.2 for lead, Tables A.3 and A.4 for cadmium and Tables A.5 and A.6 for arsenic.

TABLE A.1 Estimation of the fraction of the levels of lead (Pb) in E 472c with respect to the regulatory maximum levels in the final product (liquid formulae for infants below 16 weeks of age).

Specification for toxic element status	Pb in E472c (mg/kg)	Use level of E472c in final product (mg kg)	Concentration of Pb in final product (mg/kg)	Level of Pb in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of Pb from use of E472c on Pb level permitted in final product
Current EU specifications	2.0	9000	0.0180	0.010	180%
Proposed by the IBO (Section 3.5.1)	0.6	9000	0.0054	0.010	54%
Modulated by the Panel (Section 3.5.1)	0.05	9000	0.0005	0.010	4.5%

TABLE A.2 Estimation of the fraction of the levels of lead in E 472c with respect to the regulatory maximum levels in the final product (powder formulae for infants below 16 weeks of age).

Specification for toxic element status	Pb in E472c (mg/kg)	Use level of E472c in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of Pb in final product (mg/kg)	Level of Pb in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of Pb from use of E472c on Pb level permitted in final product
Current EU specifications	2.0	7500	60,000	0.120	0.020	600%
Proposed by the IBO (Section 3.5.1)	0.6	7500	60,000	0.036	0.020	180%
Modulated by the Panel (Section 3.5.1)	0.05	7500	60,000	0.003	0.020	15%

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

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, 2018, available online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

TABLE A.3 Estimation of the fraction of the levels of cadmium (Cd) in E 472c in the final product (liquid formulae for infants below 16 weeks of age).

Specification for toxic element status	Cd in E472c (mg/kg)	Use level of E472c in final product (mg kg)	Concentration of Cd in final product (mg/kg)	Level of Cd in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of Cd from use of E472c on Cd level permitted in final product
Proposed by the IBO (Section 3.5.1)	0.2	9000	0.002	0.005	36%
Modulated by the Panel (Section 3.5.1)	0.05	9000	0.0005	0.005	9%

TABLE A.4 Estimation of the fraction of the levels of cadmium (Cd) in E 472c in the final product (powder formulae for infants below 16 weeks of age).

Specification for toxic element status	Cd in E472c (mg/kg)	Use level of E472c in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of Cd in final product (mg/kg)	Level of Cd in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of Cd from use of E472c on Cd level permitted in final product
Proposed by the IBO (Section 3.5.1)	0.2	7500	60,000	0.012	0.020	60%
Modulated by the Panel (Section 3.5.1)	0.05	7500	60,000	0.003	0.020	15%

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

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, 2018, available online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

TABLE A.5 Estimation of the fraction of the levels of arsenic (As) in E 472c in the final product (liquid formulae for infants below 16 weeks of age).

Specification for toxic element status	As in E472c (mg/kg)	Use level of E472c in final product (mg kg)	Concentration of As in final product (mg/kg)	Level of As in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of As from use of E472c on As level permitted in final product
Proposed by the IBO (Section 3.5.1)	0.8	9000	0.0072	0.010	72%
Modulated by the Panel (Section 3.5.1)	0.05	9000	0.0005	0.010	4.5%

TABLE A.6 Estimation of the fraction of the levels of arsenic (As) in E 472c in the final product (powder formulae for infants below 16 weeks of age).

Specification for toxic element status	As in E472c (mg/kg)	Use level of E472c in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of As in final product (mg/kg)	Level of As in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of As from use of E472c on As level permitted in final product
Proposed by the IBO (Section 3.5.1)	0.8	7500	60,000	0.0480	0.020	240%
Modulated by the Panel (Section 3.5.1)	0.05	7500	60,000	0.003	0.020	15%

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

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, 2018, available online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the results of the above calculations and the fact that the food additive is not the only potential source of toxic elements, the Panel emphasises the need to lower the specification limit value for lead, as well as to set limit values for cadmium and arsenic in Regulation (EU) No 231/2012.

A.2. | Other impurities

The Panel estimated the fraction (%) of the levels of the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) and glycidyl esters in E 472c with respect to the regulatory maximum levels in the final product (infant formulae) as sold as laid down in Regulation (EC) No 2023/915 considering:

- The limit proposed for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) of 0.75 mg/kg and the proposed lowest technologically achievable level for glycidyl esters of 2 mg/kg, respectively (Documentation provided to EFSA n. 3).
- The MPLs of E472c in infant formulae (FC 13.1.1) and infant FSMP (FC 13.1.5.1) when sold in powder (7500 mg/kg) or in liquid form (9000 mg/kg)
- The range of maximum levels (ML) for the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) (0.015 mg/kg (liquid form) – 0.125 mg/kg (powder form)) and for glycidyl esters (0.006 mg/kg (liquid form) – 0.050 mg/kg (powder form)) in formulae for infants as laid down in Regulation (EC) No 2023/915.

The results of the calculations can be found in Tables A.7 and A.8 for the sum of 3-MCPD and 3-MCPD fatty acid esters and Tables A.9 and A.10 for glycidyl esters.

TABLE A.7 Estimation of the fraction of the level of the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD) in E 472c in the final product (liquid formulae for infants below 16 weeks of age).

Specification for 3MCPD* status	3MCPD in E472c (mg/kg)	Use level of E472c in final product (mg kg)	Concentration of 3MCPD in final product (mg/kg)	Level 3MCPD in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of 3MCPD from use of E472c on level permitted in final product
Limit proposed by IBO	0.75	9000	0.0068	0.015	45%

TABLE A.8 Estimation of the fraction of the levels of the sum of 3-MCPD and 3-MCPD fatty acid esters (expressed as 3-MCPD)in E 472c in the final product (powder formulae for infants below 16 weeks of age).

Specification for MCPD* status	3MCPD in E472c (mg/kg additive)	Use level of E472c in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of 3MCPD in final product (mg/kg)	Level 3MCPD in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of 3MCPD from use of E472c on level permitted in final product
Limit proposed by IBO	0.75	7500	60,000	0.045	0.125	36%

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

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, 2018, available online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

TABLE A.9 Estimation of the fraction of the levels of glycidyl esters (GEs) (expressed as glycidol) in E 472c with respect to the regulatory maximum levels in the final product (liquid formulae for infants below 16 weeks of age).

Specification for GE status	GEs in E472c (mg/kg additive)	Use level of E472c in final product (mg kg)	Concentration of GEs in final product (mg/kg)	Level GEs in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of GEs from use of E472c on level permitted in final product
Proposed by the IBO (Section 3.5.2.4)	2.0	9000	0.018	0.006	300%

Abbreviation: GEs, Glycidyl esters.

TABLE A.10 Estimation of the fraction of the levels of glycidyl esters (GEs) (expressed as glycidol) in E 472c with respect to the regulatory maximum levels in the final product (powder formulae for infants below 16 weeks of age).

Specification for GE status	GEs in E472c (mg/kg additive)	Use level of E472c in final product (mg/kg) as reconstituted[a]	Use level considering the dilution[b]	Concentration of GEs in final product (mg/kg)	Level GEs in infant formulae (Reg. 2023/915) (mg/kg)	Fraction of GEs from use of E472c on level permitted in final product
Proposed by the IBO (Section 3.5.2.4)	2.0	7500	60,000	0.12	0.05	240%

Abbreviation: GEs, Glycidyl esters.

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

[b]Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure, EFSA, 2018, available online: https://zenodo.org/record/1256085#.X89vU9hKiUk.

Considering the results of the above calculations and the fact that the food additive is not the only potential source of 3-MCPD and glycidyl esters, the Panel emphasises the need to set limit values for these impurities in the EU specifications for E 472c laid down in Commission Regulation (EU) No 231/2012.

APPENDIX B

Data requested in the call for technical and toxicological data on citric acid esters of mono- and diglycerides of fatty acids (E 472c) 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 for the food additive citric acid esters of mono- and diglycerides of fatty acids (E 472c) for all uses			
1. Technical data	• Information on the manufacturing process(es) used for the production of E 472c. The list of potential impurities outlined below is based on the information provided for the re-evaluation of E 472a-f as food additives. In case changes have been implemented in the manufacturing process(es) for E 472c in comparison to that information, then other impurities may arise. Depending on the information provided on the manufacturing process(es) used, analytical data on any other additional impurities of toxicological concern should be provided too. • Analytical data on current levels of toxic elements such as arsenic, lead, cadmium and mercury in commercial samples of the food additive E 472c. • Analytical data on current levels of any impurities of toxicological concern identified in the EU specifications for the food additive glycerol (E 422) (e.g. butanetriols, acrolein, chlorinated compounds, 3-monochloropropane-1,2-diol) as well as those mentioned in the call for data for E 422 because glycerol (E 422) can be used in the manufacturing process of E 472c. • Analytical data on the current levels of trans-fatty acids in commercial samples of the food additive E 472c. • Analytical data on current levels of glycidyl esters/glycidol and free and bound 3-MCPD in commercial samples of the food additive E 472c. • Analytical data on current levels of erucic acid in commercial samples of the food additive E 472c. • Analytical data on current levels of oxalates in commercial samples of the food additive E 472c. • The lowest technologically achievable level for any potential impurities mentioned above, including any potential impurities resulting from changes in manufacturing process(es), in order to adequately define maximum limits in the EU specifications for the food additive E 472c. The analyses should be performed on at least five independently produced batches of the food additive (as recommended in the Guidance for submission for food additive evaluations), with appropriate analytical methods applying state of the art techniques. The results of the analysis should be supported by certificates of analysis. In addition, information on the representativeness of the tested batches should be provided. Specific information on the methods of analysis used should be provided. This includes, but is not limited to, e.g. the principle of the method, the scope of the method (i.e. the range of sample types that the method is used for), the concentration units used to express the analytical result(s), validation of the method (in particular limit of detection (LOD) and quantitation (LOQ)).	Provided	Assessed
2. Toxicological data	Available toxicological information should be provided to support the risk characterisation at the lowest technologically achievable level of any impurities of toxicological concern.	Not provided	No further follow-up needed, see Sections 3.5, 3.7 and 4
3. Literature searches	Literature searches, from 1/1/2020 up to the date of the data submission, should be conducted relevant for the safety evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c) for all uses in foods for all population groups, as described in the Guidance for submission for food additive evaluations (Section 5.3 [of the same Guidance])	Provided	Assessed

[14]Available from: https://www.efsa.europa.eu/en/call/call-technical-and-toxicological-data-citric-acid-esters-mono-and-diglycerides-fatty-acids-e.

Kind of data	Data requested in the call for data	Responses from interested business operators	Comment
B. Information required for the risk assessment of citric acid esters of mono- and diglycerides of fatty acids (E 472c) for uses as food additive in foods for infants below 16 weeks of age			
1. Technical data	For the uses of citric acid esters of mono- and diglycerides of fatty acids (E 472c), in foods for infants below 16 weeks (food categories 13.1.1 and 13.1.5.1) EFSA seeks: • Information on the levels of citric acid esters of mono- and diglycerides of fatty acids (E 472c) alone or in combination with the food additives E 322, E 471 and E 473. In the case of use in combination, the name and levels of the food additive(s) used together with E 472c should be provided. • Information on the fate and the reaction products of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in these foods. • Proposals for particular EU specification requirements for identity and purity of citric acid esters of mono- and diglycerides of fatty acids (E 472c) when used in these food categories.	Provided	Assessed.
2. Toxicological data	Within the frame of the EFSA Guidance of the Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age the following information on the toxicological properties of citric acid esters of mono- and diglycerides of fatty acids (E 472c) and its adverse effects relevant for its use in food categories for infants below 16 weeks of age (13.1.1 and 13.1.5.1.) is required: • Information to demonstrate that the metabolism of E 472c in infants below 16 weeks of age is comparable to the metabolism in adult i.e. it can be expected that E 472c is extensively hydrolysed in the infants' gastrointestinal tract and/or (pre)systemically after absorption into its individual hydrolysis products which are all normal dietary constituents and are metabolised or excreted intact, see also EFSA FAF Panel (2020). • Comparative data to demonstrate that the exposure in infants to fatty acids through infant formulae containing E 472c is comparable to the exposure to fatty acids through breast milk. If it cannot be demonstrated that the metabolism of E 472c in infants is comparable to the metabolism in adults and that the exposure to fatty acids in infants from breast milk and infant formulae are comparable, additional toxicological data should be provided i.e. a repeated dose study with direct oral administration of E 472c to neonatal animals. The study shall be performed in piglets unless justification for the relevance of a study in another species is given. Additionally, the following information is required: • Any available clinical data to assess the safety of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in the relevant age group. • Post-marketing surveillance reports on undesired and adverse 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, associated with the oral administration of citric acid esters of mono- and diglycerides of fatty acids (E 472c) to infants and young children.	Provided	Assessed
3. Literature searches	Literature searches relevant for the safety evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c) when used in foods for infants below 16 weeks of age, should be conducted as described in the Guidance for submission for food additive evaluations (Section 5.3 [of the same Guidance])	Provided	Assessed

ANNEXES

Annex A can be found in the online version of this output ('Supporting information' section).

Annex A – Exposure data and estimates