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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

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Abstract

The Panel on Food Additives and Flavourings (FAF) provided a scientific opinion re-evaluating the safety of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acids, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f) as food additives. All substances had been previously evaluated by the Scientific Committee for Food (SCF) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Hydrolysis of E472a,b,c,e was demonstrated in various experimental systems, although the available data on absorption, distribution, metabolism, excretion (ADME) were limited. The Panel assumed that E472a-f are extensively hydrolysed in the GI tract and/or (pre-)systemically after absorption into their individual hydrolysis products which are all normal dietary constituents and are metabolised or excreted intact. No adverse effects relevant for humans have been identified from the toxicological database available for E472a-f. The Panel considered that there is no need for a numerical acceptable daily intake (ADI) for E 472a,b,c. The Panel also considered that only L(+)-tartaric acid has to be used in the manufacturing process of E472d,e,f. The Panel established ADIs for E 472d,e,f based on the group ADI of 240 mg/kg body weight (bw) per day, expressed as tartaric acid, for L(+)-tartaric acid-tartrates (E334-337, 354) and considering the total amount of L(+)-tartaric acid in each food additive. Exposure estimates were calculated for all food additives individually, except for E 472e and f, using maximum level, refined exposure and food supplements consumers only scenarios. Considering the exposure estimates, there is no safety concern at their reported uses and use levels. In addition, exposure to tartaric acid released from the use of E 472d,e,f was calculated. The Panel also proposed a number of recommendations.

Keywords: E 472a, E 472b, E 472c, E 472e, E 47f, food additive, ACETEM, LACTEM, CITREM, DATEM, MATEM

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Summary

Following a request from the European Commission, the Panel on Food Additives and Flavourings (FAF) was asked to deliver a scientific opinion on the re-evaluation of acetic acid esters of mono- and diglycerides of fatty acids (E 472a), lactic acid esters of mono- and diglycerides of fatty acids (E 472b), citric acid esters of mono- and diglycerides of fatty acids (E 472c), tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) when used as food additives. Esters of mono and diglycerides of fatty acids (E 472a-f) are all authorised food additives in the European Union (EU) according to Annex II and Annex III of Regulation (EC) No 1333/2008 on food additives and specifications have been defined in the Commission Regulation (EU) No 231/2012.

All the esters of mono- and diglycerides of fatty acids E 472a-f have been evaluated by the Scientific Committee for Food (SCF) (SCF, 1978, 1998b). Only for E 472e an acceptable daily intake (ADI) of 0–50 mg/kg body weight (bw) has been allocated, while for the other food additives, E 472a, b,c,d,f, ADI 'not specified' was established (SCF, 1978).

Commission Regulation 231/2012 does not stipulate which isomer of tartaric acid should be used for the manufacturing process of the food additives E 472d,e,f, and, therefore, currently any isomer of tartaric acid can be used. The Panel considered that only L(+)-tartaric acid should be used in the manufacturing process of E 472d,e,f.

The available studies on the absorption, distribution, metabolism, excretion (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, given the structure of these compounds, the Panel assumes that E 472a,b,c,e,f will be extensively hydrolysed in the gastrointestinal (GI) tract and/or pre-systemically and are unlikely to be present intact systemically. The Panel considered that E 472d would behave similar to E 472e. The hydrolysis products are known to be either readily metabolised or excreted intact. The hydrolysis products are all normal dietary constituents (considering that only L(+)-tartaric acid is used for the manufacturing process of E 472d,e,f) which are metabolised or excreted intact.

The Panel considered that E 472a-f have very low acute oral toxicity and that no relevant adverse effects were noted in a limited number of short-term and subchronic toxicity studies with E 472a,b,c,e.

In vitro genotoxicity studies for E 472e did not show any genotoxic potential. Taking into account the information on structure–activity relationships from in silico evaluation of E472a-f and the observation that fatty acids, glycerol and tartaric acid do not raise concern with respect to genotoxicity, the Panel considered that E 472a-f are not of concern with regard to genotoxicity.

Long-term studies on chronic toxicity and carcinogenicity were available for E 472a and E 472e. There was no evidence of any relevant carcinogenic effects for any of the compounds. There were substance-related gross and histopathological changes observed in studies with E 472a. The Panel, however, considered the study unreliable and the results thus not relevant for risk assessment of acetic acid esters of mono- and diglycerides of fatty acids used as food additive.

E 472e was tested in a dietary two-generation reproductive toxicity in rats and no adverse effects on reproduction were observed. E 472e was also tested in a dietary prenatal developmental toxicity study in rats and no adverse effects were observed either.

The Panel considered that as there is no relevant adverse effects reported for E 472a,b,c and since none of their hydrolysis products raise any safety concerns, presently there is no need for a numerical ADI for E 472a,b,c.

The Panel noted that a group ADI of 240 mg/kg bw per day, expressed as tartaric acid, for L(+)-tartaric acid-tartrates (E334-337, 354) has been established by the EFSA FAF Panel in 2020 and this health-based guidance value should be considered for the risk assessment of food additives E 472d,e,f. Therefore, ADIs for these food additives E 472d,e,f were determined on the basis of the total amount of L(+)-tartaric acid released from the food additives. The Panel thus established an ADI of 480 mg/kg bw per day for E 472d and an ADI of 600 mg/kg bw per day for E 472e,f.

Food consumption data derived from the EFSA Comprehensive European Food Consumption Database was used to estimate the dietary exposure to E 472a-f. Exposure assessment was carried out on infant, toddler, children, adolescents, adults and elderly population groups using two sets of data: the maximum level exposure assessment scenario and the refined exposure assessment scenario. A separate food supplement consumers only scenario was calculated in order to reflect additional exposure from the intake of food supplements. The exposure was estimated for all food additives

individually, except for E 472e and f. Considering the exposure estimates, there is no safety concern at their reported uses and use levels for E472a-f.

Exposure to tartaric acid released from the use of E 472d,e,f was also calculated.

The Panel made a number of recommendations to the European Commission.

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1. Introduction

The present opinion deals with the re-evaluation of acetic acid esters of mono- and diglycerides of fatty acids (E 472a), lactic acid esters of mono- and diglycerides of fatty acids (E 472b), citric acid esters of mono- and diglycerides of fatty acids (E 472c), tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) when used as food additives.

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

1.1.1. Background

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

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

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

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

1.1.2. Terms of Reference

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

1.1.3. Interpretation of Terms of Reference

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) described its risk assessment paradigm in its Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012). This Guidance states, that in carrying out its risk assessments, the Panel sought to define a health-based guidance value e.g. an Acceptable Daily Intake (ADI) (IPCS, 2004) applicable to the general population. However, the ADI as established for the general population does not directly apply to infants below 12 weeks of age (JECFA, 1978; SCF, 1998a). In this context, the re-evaluation of the use of

[1] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008.
[2] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.
[3] COM(2001) 542 final.
[4] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord, 2002, 560.

food additives in food for infants below 12 weeks represents a special case for which specific recommendations were given by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 1972, 1978) and by the SCF (SCF, 1996, 1998a) and EFSA (EFSA Scientific Committee, 2017). The Panel endorsed these recommendations.

In the current EU legislation (Annex II of Regulation (EC) No 1333/2008), use levels of E 472c in food for infants under the age of 12 weeks are included in categories 13.1.1 and 13.1.5.1. The Panel considers that these uses would require a specific risk assessment in line with the recommendations given by JECFA and the SCF and the EFSA Scientific Committee, and endorsed by the ANS Panel in its current Guidance for submission for food additives evaluations (EFSA ANS Panel, 2012). Therefore, a risk assessment as for the general population is not considered applicable for infants under the age of 12 weeks, a risk assessment for the latter will be performed separately.

1.2. Information on existing authorisations and evaluations

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a), lactic acid esters of mono- and diglycerides of fatty acids (E 472b), citric acid esters of mono- and diglycerides of fatty acids (E 472c), tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) authorised food additives in the European Union (EU) according to Annex II and Annex III of Regulation (EC) No 1333/2008 on food additives and specifications have been defined in the Commission Regulation (EU) No 231/2012.[5]

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, 1998b). Only for E 472e, an ADI of 0–50 mg/kg body weight (bw) was allocated, while for the other substances E 472a,b,c,d,f ADI 'not specified' was established (SCF, 1978). However, the SCF concluded in 1997 that *it was prepared to set a temporary ADI of 25 mg/kg bw/day for* mono- and diacetyltartaric acid esters of mono- and diglycerides (E 472e) for general food uses *'but would like to see the full presentation of the recently completed long-term feeding study of laboratory animals'* (SCF, 1998b). Additionally to this, the SCF stated that it would reconsider within 2 years of the publication of the opinion the temporary ADI once the following information would be supplied: an adequate specification with a limitation of tartaric acid up to 20%, submission of the long-term study, studies on reproduction and teratology and a test for chromosomal aberrations in mammalian cells *in vitro*. The Panel noted that the requested combined chronic toxicity and carcinogenicity study (Mitchell, 1999 (Documentation provided to EFSA n. 22)), a bacterial reverse mutation and a chromosomal aberrations assays (Jone 1996; Akhurst, 1996 (Documentation provided to EFSA n. 15 and 1)) were not considered in the SCF evaluation in 1997. The SCF also considered that the use of E 472c was acceptable in products which contain partially hydrolysed proteins for infants and children in good health (SCF, 1998b). For the contrary, the use of E 472e in foods for infants and young children in good health was not accepted (SCF, 1998b).

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a) and lactic acid esters of mono- and diglycerides of fatty acids (E 472b) were evaluated by JECFA in 1973 and ADI 'not limited' was established (JECFA, 1974a,b).

JECFA established an ADI 'not limited' for citric acid esters of mono- and diglycerides of fatty acids (E 472c) and in its latest evaluation on the safety of for citric acid esters of mono- and diglycerides of fatty acids in infant formula and formula for special medical purposes intended for infants, the Committee concluded that there are no toxicological concerns at concentration up to 9 g/L (JECFA, 2014, 2015). JECFA has discussed the levels of lead in citric acid esters of mono- and diglycerides of fatty acids (E 472c) and introduced a limit of 0.5 mg/kg for use in infant formula (JECFA, 2016, 2017).

JECFA established specifications for diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) under the name 'diacetyltartaric and fatty acids esters of glycerol' as the Committee was aware that the two products could not be distinguished analytically and allocated and ADI of 50 mg/kg bw with the provision that the total intake of tartaric acid from food additives should not exceed the ADI for tartaric acid (30 mg/kg bw) (JECFA, 2004).

Regarding tartaric acid esters of mono- and diglycerides (E 472d) and according to JECFA,[6] the ADI of 'not limited' 'was withdrawn at the fifty-seventh meeting (2001) because the specifications for mixed

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

[6] http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=3715

tartaric, acetic and fatty acid esters of glycerol were combined with those of diacetyltartaric and fatty acid esters of glycerol under the latter name at the fifty-first meeting (1998)'. Nevertheless, the title of this notification is 'tartaric, acetic and fatty acid esters of glycerol', while the INS No refers to 472f that relates to another food additive 'mixed tartaric, acetic and fatty acid esters of glycerol (E 472f)' and not to E 472d.

2. Data and methodologies

2.1. Data

The Panel was not provided with a newly submitted dossier. EFSA launched public calls for data[7,8,9,10] to collect relevant information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to January 2020. Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based, however, not always these were available to the Panel.

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

The Mintel's Global New Products Database (GNPD) was used to verify the use of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acids, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f) in food products. The Mintel's GNPD is an online database that contains the compulsory ingredient information present on the label of products.

2.2. Methodologies

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

The ANS Panel assessed the safety of acetic acid esters of mono- and diglycerides of fatty acids (E 472a), lactic acid esters of mono- and diglycerides of fatty acids (E 472b), citric acid esters of mono- and diglycerides of fatty acids (E 472c), tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When in animal studies, the test substance was administered in the feed or in drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake is calculated by the Panel using the relevant default values. In case of rodents, the values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) are applied. In the case of other animal species, the default values by JECFA (2000) are used. In these cases, the dose was expressed as 'equivalent to mg/kg bw per day'.

Dietary exposure to acetic acid esters of mono- and diglycerides of fatty acids (E 472a), lactic acid esters of mono- and diglycerides of fatty acids (E 472b), citric acid esters of mono- and diglycerides of fatty acids (E 472c), tartaric acid esters of mono- and diglycerides of fatty acids (E 472d), mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e), and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) from their use as food additives was estimated by combining the food consumption data available within the EFSA Comprehensive Database with the maximum permitted levels and/or reported use levels submitted to EFSA following a call for data. The exposure was estimated according to different scenarios (see Section 3.4.1). Uncertainties in the exposure assessment were identified and discussed.

[7] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of emulsifiers, stabilisers and gelling agents. Published: 22 November 2009. Available from: http://www.efsa.europa.eu/en/dataclosed/call/ans091123

[8] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption Published 12 October 2015. Available online: http://www.efsa.europa.eu/en/data/call/151012

[9] Call for technical data on salts of fatty acids (E 470a,b) and related food additives authorised in the EU. Published: 19 January 2016. Available online: http://www.efsa.europa.eu/sites/default/files/consultation/160119.pdf

[10] Call for scientific data on L(+)-tartaric acid (E334) and related food additives authorised in the EU. Published: 31 May 2016. Available online: https://www.efsa.europa.eu/sites/default/files/consultation/160531.pdf

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

3. Assessment

3.1. Technical data

3.1.1. Identity of the substance

In general, esters of mono and diglycerides of fatty acids (E 472a-f) are esters of fatty acids occurring in food fats and oils with glycerol with one or two free hydroxyl-groups and/or with some particular acids (acetic, lactic, citric, tartaric and mono- and diacetyltartaric). Based on the definition given in the Commission Regulation (EU) No 231/2012, they are not discrete chemical substances but mixtures. Depending on the complexity of the fatty acid source, the food additives E 472a-f may contain several components. In addition, the number of different positional isomers is high. No Chemical Abstracts Service (CAS) Registration numbers have been assigned to the different food additives. The molecular weight of each food additive E 472a-f depends on the fatty acid sources (EFEMA, 2011 (Documentation provided to EFSA n. 6)).

According to data in literature E 472a-f are insoluble in water at 20°C, soluble in hot ethanol and in propylene glycol (at 50°C). They are dispersible in water (at 50°C and 100°C) and in vegetable oil (at 50°C) and in sucrose solution (at 60°C) (Smith and Hiong-Shum, 2003).

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

According to the definition in the Commission Regulation (EU) No 231/2012, acetic acid esters of mono- and diglycerides of fatty acids (E 472a) are defined as esters of glycerol with acetic acid and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free acetic acid and free glycerides. Figure 1 shows a general structural formula for E472a.

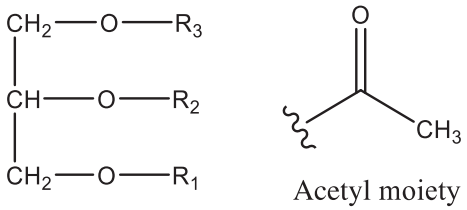

Figure 1: General structural formula for E 472a: where at least one of R_1, R_2 or R_3 represents an acetyl moiety and a fatty acyl moiety and the remaining position has either an acetyl moiety or fatty acyl moiety or hydrogen

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a) are described as clear, oily liquids to waxy solids from white to pale yellow colour. The physical state of E 472a at ambient temperatures is strongly influenced by the fatty acid profile, and degree of acetylation (EFEMA, 2010a (Documentation provided to EFSA n. 4)).

Known synonyms for E 472a are acetic acid esters of mono- and diglycerides; acetoglycerides; acetylated mono- and diglycerides; acetic and fatty acid esters of glycerol (Regulation (EU) 231/2012), ACETEM (Gaupp and Adams, 2015).

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

According to the definition in the Commission Regulation (EU) No 231/2012, lactic acid esters of mono- and diglycerides of fatty acids (E 472b) are defined as esters of glycerol with lactic acid and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free lactic acid and free glycerides.

The Panel noted that the specifications in Regulation 231/2012 for the food additives E 472b do not stipulate which isomer of lactic acid should be used for their production; therefore, currently any stereoisomer can be used. Figure 2 shows a general structural formula for E472b.

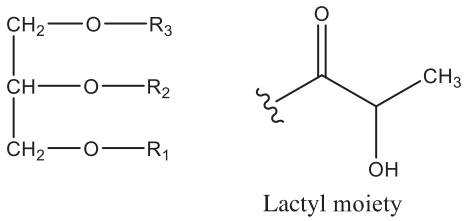

Figure 2: General structural formula for E 472b: where at least one of R_1, R_2 or R_3 represents a lactyl moiety and a fatty acyl moiety and the remainder position has either a lactyl moiety or fatty acyl moiety or hydrogen

According to the Commission Regulation (EU) No 231/2012, lactic acid esters of mono- and diglycerides of fatty acids (E 472b) are described as clear, mobile liquids to waxy solids of variable consistency, from white to pale yellow in colour. Lactic acid esters of mono- and diglycerides of fatty acids (E 472b) are insoluble in cold water but dispersible in hot water. According to Gaupp and Adams (2015), it is not soluble in hot water and 1,2-propylenglycol, but soluble in some hot alcohols i.e. ethanol, iso-propanol and xylol.

Known synonyms for E 472b are lactoglycerides, lactic acid esters of mono- and diglycerides; mono- and diglycerides of fatty acids esterified with lactic acid (Regulation (EU) 231/2012), LACTEM, lactylated mono- and diglycerides (Gaupp and Adams, 2015).

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

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 fats and oils. 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. Figure 3 shows a general structural formula for E472c.

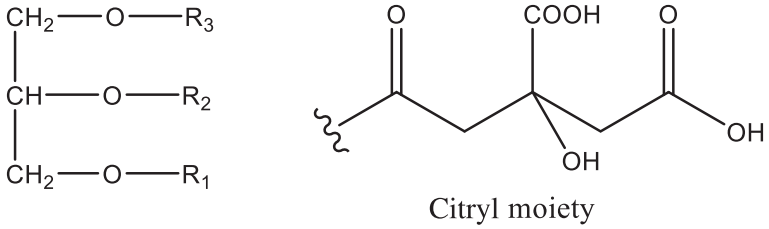

Figure 3: General structural formula for E 472c: where at least one of R_1, R_2 or R_3 represents a citryl moiety and a fatty acyl moiety and the remaining position has either a citryl moiety or fatty acyl moiety or hydrogen

According to the Commission Regulation (EU) No 231/2012, citric acid esters of mono- and diglycerides of fatty acids (E 471c) are described as yellowish or light brown liquids to waxy solids or semi-solids.

The physical form of the esters at room temperature is dependent on the fatty acid profile of the E 472c (Documentation provided to EFSA n. 23). E 472c is an anionic molecule due to its free acid groups and will show normally two pK-points (Palsgaard, 2010 (Documentation provided to EFSA n. 23)). They are able to bind traces of metals as citric acid complexes (Gaupp and Adams, 2015).

Known synonyms for E 472c mono- and diglycerides of fatty acids esterified with citric acid CITREM, citroglycerides, citric acid esters of mono- and diglycerides (Commission Regulation (EU) 231/2012), monoglyceride citrate (Gaupp and Adams, 2015).

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

According to the definition in the Commission Regulation (EU) No 231/2012, tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) are defined as esters of glycerol with tartaric acid and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric acid and free glycerides. Figure 4 shows a general structural formula for E472d.

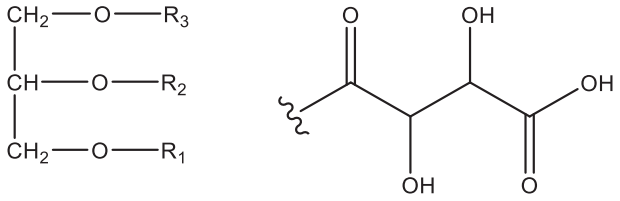

Figure 4: General structural formula for E 472d: where at least one of R_1, R_2 or R_3 represents a tartaryl moiety and a fatty acyl moiety and the remaining position has either a tartaryl moiety or fatty acyl moiety or hydrogen

According to the Commission Regulation (EU) No 231/2012, tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) are described as sticky vicious yellowish liquids to hard yellow waxes.

Synonyms for E 472d are tartaric acid esters of mono- and diglycerides; mono- and diglycerides of fatty acids esterified with tartaric acid (Commission Regulation (EU) No 231/2012; TATEM (Gaupp and Adams, 2015).

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

According to the definition in the Commission Regulation (EU) No 231/2012, mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) are defined as mixed esters of glycerol with mono- and diacetyltartaric acids (obtained from tartaric acid) and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric and acetic acids and their combinations, and free glycerides. They may contain also tartaric and acetic esters of fatty acids.

According to the literature, they contain also acetic and tartaric acid esters of monoglycerides, where, as free glycerides, di- and triglycerides can occur (Sudraud et al., 1981).

As an example, the general structural formula of diacetyltartaric acid esters of mono glycerides only of fatty acids is shown in Figure 5. Other generic forms of chemical substances could be monoacetyltartaric acid esters of monoglycerides of fatty acids, diacetyltartaric acid esters of diglycerides of fatty acids and monoacetyltartaric acid esters of diglycerides of fatty acids.

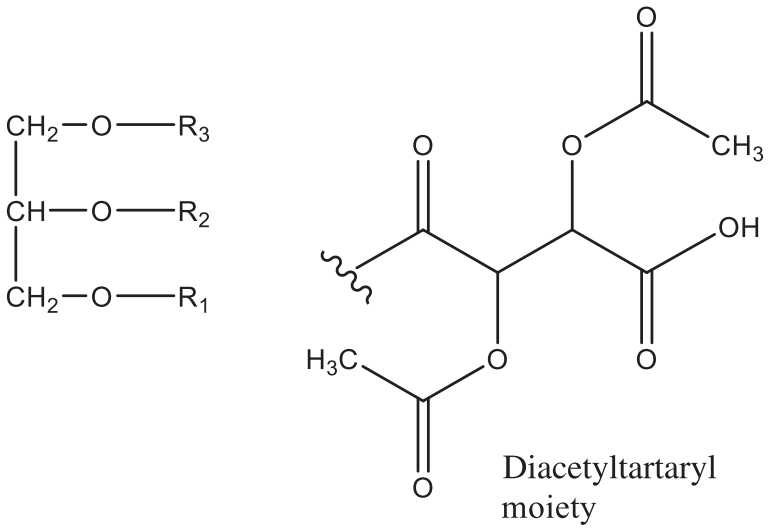

Figure 5: General structural formula for E 472e: where at least one of R_1, R_2 or R_3 represents a monoacetyltartaryl moiety or diacetyltartaryl moiety and a fatty acyl moiety and the remaining position has either a monoacetyltartaryl moiety or diacetyltartaryl moiety or fatty acyl moiety or hydrogen but also acetyl moiety or tartaryl moiety

According to the description in the Commission Regulation (EU) No 231/2012, mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) are sticky viscous liquids through a fat-like consistency to yellow waxes, which hydrolyse, in moist air to liberate acetic acid. They are dispersible in cold and hot water, soluble in methanol and ethanol (JECFA, 2009).

Known synonyms of E 472e are diacetyltartaric acid esters of mono- and diglycerides; mono-and diglycerides of fatty acids esterified with mono- and diacetyltartaric acid; diacetyltartaric and fatty acid esters of glycerol (Regulation (EU) 231/2012); DATEM (Gaupp and Adams, 2015).

According to information from industry (EFEMA, 2010b (Documentation provided to EFSA n. 5)), E 472e can be a liquid or a solid. Liquid E 472e are typically clear viscous liquids and may be obtained by using mono- and diglycerides based on unsaturated fatty acids, sourced for example from sunflower, rapeseed or palm oils. The viscosity of liquid E 472e may be modified by carefully controlling the degree of esterification to produce products with low polarity. Solid E 472e are slightly sticky solids at ambient temperatures and are manufactured using mono- and diglycerides based on hydrogenated or fully saturated fatty acids. The functionality of E 472e may be controlled by varying the total tartaric acid content. Solid E 472e with a high degree of esterification (high tartaric acid content, high saponification value) tend to be softer and lower melting. To reduce the stickiness and tendency to form lumps, the composition of solid E 472e is carefully controlled with respect to di- and triglyceride.

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

According to the definition in the Commission Regulation (EU) No 231/2012, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) are defined as esters of glycerol with acetic and tartaric acids and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric and acetic acids, and free glycerides. They may contain mono- and diacetyltartaric esters of mono- and diglycerides of fatty acids.

According to the Commission Regulation (EU) No 231/2012, E 472f appears from sticky liquids to solids and from white to pale yellow in colour. The food additive is dispersible in water and soluble in methanol, ethanol and acetone (Gaupp and Adams, 2015).

Known synonyms of E 472f are mono- and diglycerides of fatty acids esterified with acetic acid and tartaric acid (Regulation (EU) 231/2012); MATEM, diacetylated tartaric-, acetic- and fatty acid esters of glycerol (Gaupp and Adams, 2015).

The Panel noted that the food additive mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) is not markedly different from the food additive mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e), when considering the description of their manufacturing processes and their compositions.

The Panel noted that the specifications in Commission Regulation 231/2012 for the food additives E 472d,e,f do not stipulate which isomer of tartaric acid should be used for their production; therefore, currently any isomer of tartaric acid can be used.

3.1.2. Specifications

Specifications for E 472a-f have been defined in Commission Regulation (EU) No 231/2012 and for some of them also by JECFA. Their specifications are listed in Tables 1–6.

The Panel noted that the same following footnote is indicated in the EU specifications for E 472a-f: 'Purity criteria apply to the additive free of sodium, potassium and calcium salts of fatty acids; however these substances may be present up to a maximum level of 6% (expressed as sodium oleate)'.

Table 1: Specifications for acetic acid esters of mono- and diglycerides of fatty acids (E 472a) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation (EU) No 231/2012	(JECFA, 2006a)
Definition	Esters of glycerol with acetic and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free acetic acid and free glycerides	Mixed glycerol esters of acetic acid and fatty acids of food fats. Contains mono- and diesters of fatty acids with glycerol, which is itself partially acetylated; may also contain free glycerol and free fatty acids

	Commission Regulation (EU) No 231/2012	(JECFA, 2006a)
Description	Clear, mobile liquids to solids, from white to pale yellow in colour	From liquid to solid in consistency; white to pale yellow, may have the odour of acetic acid The article of commerce may be further specified as the saponification value, acid value, free fatty acid content, solidification point of the free fatty acids, Reichert-Meissl value, iodine value and free glycerol content
Identification		
Test for glycerol	Passes test	Passes test
Test for fatty acids	Passes test	Passes test
Test for acetic acid	Passes test	Passes test
Solubility	Insoluble in water. Soluble in ethanol	Insoluble in water; soluble in ethanol
Purity		
Acids other than acetic and fatty acids	Less than 1%	Acids other than acetic and fatty acids shall not be detectable
Free glycerol	Not more than 2%	Not more than 7%
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total acetic acid	Not less than 9% and not more than 32%	–
Free fatty acids (and acetic acid)	Not more than 3% estimated as oleic acid	–
Total glycerol	Not less than 14% and not more than 31%	–
Sulfated ash	Not more than 0.5% determined at 800 ± 25°C	–

Table 2: Specifications for lactic acid esters of mono- and diglycerides of fatty acids (E 472b) according to Commission Regulation (EU) No 231/2012 and JECFA (2006b)

	Commission Regulation (EU) No 231/2012	(JECFA, 2006b)
Definition	Esters of glycerol with lactic acid and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free lactic acid and free glycerides	Mixed glycerol esters of lactic acid and fatty acids of food fats. The article of commerce may be further specified as to monoglyceride content, total lactic acid, acid value, saponification value, free fatty acid content, solidification point of the free fatty acids, iodine value, free glycerol content and water content
Description	Clear, mobile liquids to waxy solids of variable consistency, from white to pale yellow in colour	Waxy solids of variable consistency and conforms to the following specifications
Identification		
Test for glycerol	Passes test	Passes test
Test for fatty acids	Passes test	Passes test
Test for lactic acid	Passes test	Passes test
Solubility	Insoluble in cold water but dispersible in hot water	Insoluble in cold water but dispersible in hot water
Purity		
Acids other than lactic and fatty acids	Less than 1%	Acids other than lactic and fatty acids shall not be detectable

	Commission Regulation (EU) No 231/2012	(JECFA, 2006b)
Free glycerol	Not more than 2%	–
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–
Total lactic acid	Not less than 13% and not more than 45%	–
Free fatty acids (and lactic acid)	Not more than 3% estimated as oleic acid	–
Total glycerol	Not less than 13% and not more than 30%	–
Sulfated ash	Not more than 0.5% determined at 800 ± 25°C	–

Table 3: Specifications of citric acid esters of mono- and diglycerides of fatty acids (E 472c) according to Commission Regulation (EU) No 231/2012 and JECFA (2020)

	Commission Regulation (EU) No 231/2012	(JECFA, 2020)
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	Consists of mixed esters of citric acid and edible fatty acids with glycerol. It is obtained by esterification of glycerol with citric acid and edible fatty acids, or by reaction of a mixture of mono- and diglycerides of edible fatty acids with citric acid. It may contain minor amounts of free fatty acids, free glycerol, free citric acid and mono- and diglycerides. The mono- and diglycerides may include either one or two edible fatty acids from C12:0 to C18:0, mainly palmitic (C16:0) and stearic (C18:0) acids. It may also contain minor amounts of other fatty acids such as myristic (C14:0), oleic (C18:1), linoleic (C18:2) and arachidic acid (C20:4). It may be partially or wholly neutralised with sodium hydroxide or potassium hydroxide or by using sodium, potassium or calcium salts of weak acids such as acetic, lactic, propionic or carbonic acids
Description	Yellowish or light brown liquids to waxy solids or semi-solids	White to ivory coloured, oily to waxy material
Identification		
Test for glycerol	Passes test	Passes test
Test for fatty acids	Passes test	Passes test
Test for citric acid	Passes test	Passes test
Solubility	Insoluble in cold water, dispersible in hot water, soluble in oils and fats, insoluble in cold ethanol	Insoluble in water; soluble in oils and fats; insoluble in ethanol
Purity		
Acids other than citric and fatty acids	Less than 1%	–
Free glycerol	Not more than 2%	Not more than 4%
Total glycerol	Not less than 8% and not more than 33%	8–33%
Total citric acid	Not less than 13% and not more than 50%	13–50%
Total fatty acid	–	37–81%

	Commission Regulation (EU) No 231/2012	(JECFA, 2020)
Sulfated ash	Non-neutralised products: not more than 0.5% (800 ± 25°C) Partially or wholly neutralised products: not more than 10% (800 ± 25°C)	Not neutralised products: not more than 0.5% Partially neutralised products: not more than 3% Wholly neutralised products: not more than 10%
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg (Not more than 0.5 mg/kg for use in infant formula and formula for special medical purposes intended for infants)
Acid value	Not more than 130	–

Table 4: Specifications of tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) according to Commission Regulation (EU) No 231/2012. No JECFA specifications are available

	Commission Regulation (EU) No 231/2012
Definition	Esters of glycerol with tartaric acid and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric acid and free glycerides
Description	Sticky viscous yellowish liquids to hard yellow waxes
Identification	
Test for glycerol	Passes test
Test for fatty acids	Passes test
Test for citric acid	Passes test
Purity	
Acids other than tartaric and fatty acids	Less than 1.0%
Free glycerol	Not more than 2%
Total glycerol	Not less than 12% and not more than 29%
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total tartaric acid	Not less than 15% and not more than 50%
Free fatty acids	Not more than 3% estimated as oleic acid
Sulfated ash	Not more than 0.5% (800 ± 25°C)

Table 5: Specifications for E 472e and E 472f according to Commission Regulation (EU) No 231/2012 and for 'diacetyltartaric and fatty acid esters of glycerol' (JECFA, 2009)

	Commission Regulation (EU) No 231/2012		**(JECFA, 2009)**
	E 472e	**E 472f**	**Diacetyltartaric and fatty acid esters of glycerol**
Definition	Mixed esters of glycerol with mono- and diacetyltartaric acids (obtained from tartaric acid) and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric and acetic acids and their combinations, and free glycerides. Contains also tartaric and acetic esters of fatty acids	Esters of glycerol with acetic and tartaric acids and fatty acids occurring in food fats and oils. They may contain small amounts of free glycerol, free fatty acids, free tartaric and acetic acids, and free glycerides. May contain mono- and diacetyltartaric esters of mono- and diglycerides of fatty acids	The product consists of mixed glycerol esters of mono- and diacetyltartaric acid and fatty acids from edible fats and oils. It is made by the interaction of diacetyltartaric anhydride and mono- and diglycerides of fatty acids in the presence of acetic acid, or by interaction of acetic anhydride and mono- and diglycerides of fatty acids in the presence of tartaric acid. Because of inter- and intramolecular acyl-group exchange, both methods of production lead to the same essential components, the distribution of which depends on the relative proportions of the basic raw materials, on temperature, and on reaction time. The product may contain small amounts of free glycerol, free fatty acids and free tartaric and acetic acids
Description	Sticky viscous liquids through a fat-like consistency to yellow waxes which hydrolyse in moist air to liberate acetic acid	Sticky liquids to solids, from white to pale-yellow in colour	Liquid, paste, or wax-like solid
Identification			
Test for glycerol	Passes test	Passes test	Passes test
Test for fatty acids	Passes test	Passes test	Passes test
Test for tartaric acid	Passes test	Passes test	Passes test
Test for acetic acid	Passes test	Passes test	Passes test
Solubility	–		Dispersible in cold and hot water; soluble in methanol, ethanol, acetone, and ethyl acetate
1,2-diols	–		To a solution of 500 mg in 10 ml methanol, add dropwise, lead acetate TS. A white, flocculent, insoluble precipitate is formed
Purity			
Acids other than acetic, tartaric and fatty acids	Less than 1%	Less than 1%	Acids other than acetic, tartaric and fatty acids, shall not be detectable
Free glycerol	Not more than 2%	Not more than 2%	Not more than 2.0%

	Commission Regulation (EU) No 231/2012		(JECFA, 2009)
	E 472e	**E 472f**	**Diacetyltartaric and fatty acid esters of glycerol**
Total glycerol	Not less than 11% and not more than 28%	Not less than 12% and not more than 27%	Not less than 11% and not more than 28% after saponification
Sulfated ash	Not more than 0.5% determined at 800 ± 25°C	Not more than 0.5% determined at 800 ± 25°C	Not more than 0.5% determined at 800 ± 25°C
Arsenic	Not more than 3 mg/kg	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	Not more than 1 mg/kg	–
Total tartaric acid	Not less than 10% and not more than 40%	Not less than 20% and not more than 40%	Not less than 10% and not more than 40% after saponification
Total acetic acid	Not less than 8% and not more than 32%	Not less than 10% and not more than 20%	Not less than 8% and not more than 32% after hydrolysis
Acid value	Not less than 40 and not more than 130		Not less than 40 and not more than 130
Free fatty acids		Not more than 3% estimated as oleic acid	

The Panel noted that the specifications for E 472e and E 472f are nearly identical apart from small differences in the ranges of certain parameters.

According to EFEMA (2010b (Documentation provided to EFSA n. 5)), only L(+)-tartaric acid is used as starting material of E 472e. The Panel noted that only L(+)-tartaric acid is authorised for the food additive E334. Given the adverse effects reported for DL-tartaric acid (EFSA FAF Panel, 2020), only L(+)-tartaric acid should be used for the manufacturing process of food additives containing tartaric acid (e.g. E 472d, E 472e, E 472f).

The Panel noted that, according to the EU specifications for E 472a, E 472b, E 472d, E 472e and E 472f impurities of the toxic elements – arsenic, cadmium, lead and mercury – are accepted up concentrations of 3, 1, 2 and 1 mg/kg, respectively. For E 472c, only a maximum limit of 2 mg/kg for lead is set. Contamination at those levels could have a significant impact on the exposure to these metals, for which the intake is already close to the health-based values or benchmark doses (lower confidence limits) established by EFSA (EFSA CONTAM Panel, 2009a,b, 2010, 2012a,b,c, 2014).

According to the available information on the manufacturing process (Section 3.1.3), E 472a-f can be manufactured by using glycerol as starting material. Therefore, the Panel considered the need to include maximum limits for impurities currently included in the EU specifications for the food additive glycerol (E 422) or recommended by the Panel in its re-evaluation (EFSA ANS Panel, 2017a) in the EU specifications for the esters of mono- and diglycerides of fatty acids (E 472a-f).

Esters of 3-monochloropropane-1,2-diol (3-MCPD) were found at the highest levels in palm oil/fat (EFSA CONTAM Panel, 2016a), which can be used as a raw material for E 472a-f. It has been confirmed that the toxicity of 3-MCPD fatty acid esters should be considered equivalent (on a molar basis) to that of the parent compound (3-MCPD) (EFSA CONTAM Panel, 2016a, 2018). The Panel noted that there is no limit for 3-MCPD/3-MCPD esters in the specifications for E 472a-f. The Panel considered that the possible presence of 3-MCPD esters in those food additives would need further assessment, as their presence could raise a safety concern.

According to EU specifications, E 472a-f can be manufactured by using food oils and fats. Beside natural oils and fats, also hydrogenated fats and or oils can be used for manufacturing process (EFEMA, 2016 (Documentation provided to EFSA n. 7)). According to EFSA (EFSA NDA Panel, 2004), industrial hydrogenation (used to produce semi-solid and solid fats that can be used for the production of foods such as margarines, shortenings and biscuits) and deodorisation (a necessary step in refining) of unsaturated vegetable oils high in polyunsaturated fatty acids is one of the three main pathways for the formation of trans fatty acids in food. According to EFSA (EFSA NDA Panel, 2010), higher intakes of trans fatty acids have consistently been found to be associated with an increased risk of coronary heart disease and it was recommended that trans fatty acids intake should be as low as possible within the context of a nutritionally adequate diet. The Panel noted that there is no limit for *trans*-fatty acids in the specifications for E 472a-f.

According to EFSA Panel on Contaminants (CONTAM), refined vegetable oil, which can be used for manufacturing of E 472a-f (EFEMA, 2016 (Documentation provided to EFSA n. 7)), is the only identified source of glycidyl esters of fatty acids (EFSA CONTAM Panel, 2016a). Glycidyl esters of fatty acids are hydrolysed in the GI tract to produce free glycidol, which is recognised as probably carcinogenic to humans 2A (IARC, 2000) and as a carcinogenic and genotoxic compound by the EFSA CONTAM Panel (2016a). The Panel noted that there is no limit for glycidyl esters in the specifications for E 472a-f. The Panel considered that the possible presence of glycidol in E 472a-f would need further assessment as their presence could raise a safety concern.

Rapeseed oil, which contains erucic acid, can be used for the manufacturing of E 472a-f. According to the industry, only rapeseed oil low in erucic acid is used for the manufacturing process (EFEMA, 2016 (Documentation provided to EFSA n. 7)). Nevertheless, it cannot be excluded that high erucic acid rapeseed oil can be used. Maximum permitted levels for erucic acid have been established in EU according to Commission Regulation (EU) No 696/2014[12] in edible oils and fats as well as in food containing fats and oils. A tolerable daily intake (TDI) of 7 mg/kg bw per day for erucic acid has been established by the EFSA CONTAM Panel based on a no observed adverse effect levels (NOAEL) of 700 mg/kg bw per day for myocardial lipidosis observed in a 7-day feeding study in young (5–7 weeks) rats and in a 2-week feeding study in new-born piglets (EFSA CONTAM Panel, 2016b). The Panel noted that there are no limits for erucic acid in the current EU specifications for E 472a-f.

[12] Commission Regulation (EU) No 694/2014 of 24 June 2014 amending Regulation (EC) No 1881/2006 as regards maximum levels of erucic acid in vegetable oils and fats and foods containing vegetable oils and fats. OJ L 184, 25.6.2014, p 1-2.

In addition, EU specifications for the food additive L(+)-tartaric acid (E 334) and citric acid (E 330) include a maximum limit for oxalates. No maximum limit for oxalates has been included in EU specifications for the citric acid esters, tartaric acid esters and mono- and diacetyltartaric acid esters and mono- and diglycerides of fatty acids (E 472c-f). The Panel considered that a limit for oxalates should be included in the specifications for E 472c,d,e,f.

3.1.3. Manufacturing process

Following a public call for data, EFSA received information about the manufacturing process used for E 472a, E 472c and E 472e.

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a) are commercially manufactured using the following processes: (1) trans-esterification of triglycerides with triacetin; (2) trans-esterification of triglycerides with glycerol and triacetin; (3) reaction of mono- and diglycerides of edible fatty acids with acetic acid anhydride (EFEMA, 2010a (Documentation provided to EFSA n. 4)). The trans-esterification of triglycerides with triacetin (process 1) will result in a number of different triple esterified glycerol species, esterified either with fatty acids or acetic acid. The reaction of mono- and diglycerides with acetic acid anhydride (process 3) will result in a mixture of reaction products with varying number of free hydroxyl groups. It is noted that a small amount of non-esterified mono- and diglycerides will always be present (Gaupp and Adams, 2015). Surplus unreacted starting materials (e.g. triacetin, acetic anhydride, acetic acid) are removed by distillation (EFEMA, 2010a (Documentation provided to EFSA n. 4)).

According to information from industry (EFEMA, 2010a (Documentation provided to EFSA n. 4)), the application for which E 472a is intended will determine the degree of acetylation. This can be achieved by varying the fatty acid profile of the fat or monoglyceride, and the quantity of acetic anhydride or triacetin used.

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b) are manufactured either by esterification of glycerol with lactic acid and edible fatty acids, or by lactylation of a mixture of mono- and diglycerides of edible fatty acids. The by-products will be glycerol, free lactic acid, polymerised lactic acid, esters and free fatty acids (Gaupp and Adams, 2015).

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

Citric acid esters of mono- and diglycerides of fatty acids (E 472c) are manufactured by the esterification of glycerol with citric acid and edible fatty acids, or by the reaction of a mixture of mono- and diglycerides of edible fatty acids with citric acid, at reaction temperatures in the range of 125–155°C. The esterified product may be partially or totally neutralised (Gaupp and Adams, 2015; Palsgaard, 2010 (Documentation provided to EFSA n. 23)).

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

No manufacturing method for this food additive was found in the literature. Moreover, no additional information on the manufacturing process has been made available via the EFSA public call.

According to Gaupp and Adams (2015), 'there are no manufacturers for these substances, nor any individual applications which will specifically need such types of emulsifiers'.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e) may be manufactured by the esterification of mono- and diglycerides with tartaric and acetic acid in the presence of acetic anhydride, or by the reaction of diacetyl tartaric anhydride with mono- and diglycerides in the presence of acetic acid (EFEMA, 2010b (Documentation provided to EFSA n. 5)). The latter method is mostly used and breaks down into two distinct steps. First, tartaric acid reacts with acetic anhydride using an acidic catalyst in order to form diacetyltartaric anhydride and acetic acid. Second, mono- and diglycerides react with diacetyltartaric anhydride optionally in acetic acid and with an alkali catalyst. At the end of the process, residual acetic acid is removed by distillation under reduced pressure. According to information provided by industry, the additive may be mixed with

mono-, di- or triglycerides, either to control crystallisation or to provide specific functionalities to the mixture before use (EFEMA, 2010b (Documentation provided to EFSA n. 5)).

According to EFEMA (2010b (Documentation provided to EFSA n. 5)), only L(+)-tartaric acid is used as starting material.

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) are obtained either by reaction of mono- and diglycerides of fatty acids with tartaric acid anhydride in the presence of acetic acid, or by esterification of mono- and diglycerides with tartaric acid and acetic acid in the presence of acetic acid anhydride (Gaupp and Adams, 2004).

Information on the fatty acids composition of the raw materials used for the manufactured of E 472a,e as provided by industry (EFEMA, 2016 (Documentation provided to EFSA n. 7)) is presented in the EFSA opinion on the re-evaluation of polyglycerol esters of fatty acids (E 475) (EFSA ANS Panel, 2017b)

3.1.4. Methods of analysis in food

Liquid chromatography in combination with atmospheric-pressure chemical ionisation mass spectrometry (LC–APCI-MS) is proposed for the qualitative evaluation of E 472(a-f) in complex food matrices. The validation of the method was performed on spiked minicake samples reaching limits of detection and limits of quantification ranging from 0.3–4.0 mg/kg and 0.9–12 mg/kg, respectively, depending on the additive. The method was then successfully applied to commercial additives containing mixtures of emulsifiers (especially E 472b and e), as well as to a few food products, such as margarines and minicakes (Suman et al., 2009).

Thin-layer chromatography (TLC) has been used for the detection of the non-fatty acid constituents of the emulsifiers, i.e. lactic, citric, tartaric and acetyl tartaric acids in a dairy cream. The emulsifiers have been separated, then hydrolysed and analysed (Gernert, 1968). In another publication, E 472a and E 472e have been extracted from a baking powder and detected via TLC (Regula, 1975). According to Inoue et al. (1981), E 472e has been extracted from dairy and non-dairy coffee cream powders via ethyl acetate. After saponification, the liberated tartaric acid has been derivatised and quantified via gas chromatography–flame ionisation detector (GC/FID). Wirsta and Corbel (1994) report a qualitative method for E 472e and f comprising extraction of the emulsifiers from flour with ethyl acetate, hydrolysis with potassium hydroxide and precipitation of the fatty acids with hydrochloric acid prior to the separation by ion pair chromatography.

The Panel considered that application of LC-APCI-MS has the potential to identify and quantify the intact food additives E 472a-f.

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

The food additives E 472a-f are esters of glycerol and hence show reactions of rearrangement, inter- and intramolecular migration of acylic-groups and certain sensitivity towards hydrolysis (Gaupp and Adams, 2015). If unsaturated fatty acids are available, the food additive is susceptible for autoxidation (Moonen and Bas, 2004).

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a) are known to be oxidative stable if saturated fat has been used for their manufacture (Baur, 1954). Alfin-Slater et al. (1958) report that shortenings and liquid base stocks for shortening, both containing acetic acid esters of mono- and diglycerides of fatty acids, did not exhibit any evidence of acetic acid odour or flavour on being stored at 38°C for 1 month. Feuge et al. (1953) conclude that acetic acid esters of mono- and diglycerides of fatty acids are temperature stable as most hydrogenated vegetable oils. If E 472a is in contact with water at 40°C, hydrolysis will occur more rapidly compared to the corresponding fat (Feuge et al., 1953). However, the thermostability of pure E 472a depends on the degree of acetylation, especially in the range between 60°C and 80°C for a 50% acetylated monoglyceride. The more acetylated species present in the system, the higher its acid value will be, where the less acetylated ones may lead to a decrease of 1–monoglyceride content at high temperatures, due to a migration via hydrolysis of acylic groups (Gaupp and Adams, 2015). In general, E 472a show a low sensitivity towards hydrolysis (Gaupp and Adams, 2015).

If heated (above 90°C), the acetic acid esters of fatty acids may dissociate and show migration of acylic groups (Gaupp and Adams, 2015). The degree of this migration depends on the time and intensity of the thermal stress and on the degree of acetylation of monoglyceride with acetic acid.

Hydrolysis with alkaline solutions will result in the alkaline salts of the fatty acids, acetic acid and glycerol and the hydrolysis with acidic solutions will result in their free forms. The latter is also the outcome of an enzymatic hydrolysis, which can be fast. Non-catalysed hydrolysis depends on time and temperature and is rather slow (Gaupp and Adams, 2015).

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b) are quite stable at ambient temperatures for a period of about 10 days. Under thermal stress, E 472b may show migration of acylic groups. The amount of this migration depends on the time and intensity of the thermal stress. E 472b are very sensitive towards any hydrolytic reaction (Gaupp and Adams, 2015). According to Gaupp and Adams (2015), the non-catalysed hydrolysis of E 472b depends on temperature and time, and is rather slow. However, they are hydrolysed similar to triglycerides, using acids, alkaline solutions and lipolytic enzymes. Hydrolysis of E 472b with acids will result in free fatty acids, lactic acid and glycerol; and hydrolysis with alkaline solutions will result in the alkaline salts of the fatty acids and the lactic acid, as well as glycerol. The enzymatic hydrolysis will result in free fatty acids, lactic acid and glycerol. All these hydrolytic reactions are rapid and complete when the concentration of enzymes, acids and alkaline solutions is sufficient.

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

According to information from industry (Palsgaard, 2010 (Documentation provided to EFSA n. 23)), citric acid esters of mono- and diglycerides of fatty acids (E 472c) may be unstable at elevated temperature and humid conditions, and humidity will allow slow saponification. However, a 25% solution of E 472c in palm oil kept at 66°C for 15 days was reported to be stable.

Due to the presence of free carboxylic- and hydroxyl groups, esterification may result depending on the time and intensity of the thermal exposure (Gaupp and Adams, 2015). At elevated temperatures, a drastic colouration will occur due to decomposition of citric acid and the formation of polymeric substances. This will also occur during cooking of food. Irrespective of whether neutralised or not, E 472c shows a certain sensitivity towards hydrolysis. E 472c may be cleaved using acids, alkaline solutions or lipolytic enzymes, in the same way as triglycerides. Hydrolysis with acids will result in free fatty acids, citric acid and glycerol; and hydrolysis with alkaline solutions will release their alkaline salts with fatty acids or citric acid, and free glycerol. The result of the enzymatic hydrolysis will be free fatty acids, citric acid and glycerol. The non-catalysed hydrolysis depends on temperature and time, and runs remarkably slower. They show a high sensitivity towards hydrolysis in humid matrices and at low pH.

Citric acid esters of monodiglycerides also act as a sequestrant, binding traces of heavy metals (Gaupp and Adams, 2015; Palsgaard, 2010 (Documentation provided to EFSA n. 23)).

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

According to Gaupp and Adams (2015), the free carboxyl- and hydroxyl groups may be esterified. Heating E 472e for a maximum period of 7 h up to 180°C may result in further esterification. During storage, there is always a slight hydrolysis in moist air (liberating acetic acid) even at lower temperatures. Hydrolysis with alkaline solutions will result in the alkaline salts of the fatty acids, tartaric acid, acetic acid and glycerol and the hydrolysis with acidic solutions will result in their free forms. Enzymatic hydrolysis will result in diacetylated tartaric acid and then mono-acetylated and mono- and diglycerides of fatty acids. They are hydrolysed further into glycerol and fatty acids. Non-catalysed hydrolysis depends on time and temperature and is rather slow.

According to EFEMA (2016 (Documentation provided to EFSA n. 7)), tartaric acid is stable in E 472e regarding possible racemisation during normal conditions of storage, and is thermostable during standard conditions of food processing (i.e. backed wares). Racemisation of L(+)-tartaric acid occurs only in strongly alkaline medium, which is not representative for its use as a food additive. The Panel noted that this information was not substantiated by experimental data.

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

JECFA reported that E 472f is spontaneously hydrolysed in an aqueous medium into free tartaric acid and glycerol esters of acetic and fatty acids (Kieckebusch et al., 1967, as referred to by JECFA, 2001).

3.2. Authorised uses and use levels

Maximum levels of esters of mono- and diglycerides of fatty acids (E 472a-f) have been defined in Annex II to Regulation (EC) No 1333/2008 on food additives, as amended. In this opinion, these levels are named maximum permitted levels (MPLs).

The esters of mono- and diglycerides of fatty acids (E 472a-f) are included in the Group I of food additives authorised at *quantum satis* (QS).

Table 6 lists the food categories that are permitted to contain esters of mono- and diglycerides of fatty acids (E 472a-f) and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008. In the majority of food categories, E 472a-f are authorised at QS, except for six food categories related to foods for infants/babies and young children (Table 6).

Table 6: MPLs of E 472a-f in foods according to Annex II to Regulation (EC) No 1333/2008

Food Category number	Food categories	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
1.3	Unflavoured fermented milk products, heat-treated after fermentation	Group I		*Quantum satis*
1.4	Flavoured fermented milk products including heat-treated products	Group I		*Quantum satis*
1.6.3	Other creams	Group I		*Quantum satis*
1.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	*Quantum satis*
1.7.5	Processed cheese	Group I		*Quantum satis*
1.7.6	Cheese products (excluding products falling in category 16)	Group I		*Quantum satis*
1.8	Dairy analogues, including beverage whiteners	Group I		*Quantum satis*
2.1	Fats and oils essentially free from water (excluding anhydrous milk fat)	E 472c	Only for cooking and/or frying purposes or for the preparation of gravy, except virgin oils and olive oils	*Quantum satis*
2.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		*Quantum satis*
2.3	Vegetable oil pan spray	Group I		*Quantum satis*
3	Edible ices	Group I		*Quantum satis*
4.2.1	Dried fruit and vegetables	Group I		*Quantum satis*
4.2.2	Fruit and vegetables in vinegar, oil or brine	Group I		*Quantum satis*
4.2.4.1	Fruit and vegetable preparations excluding compote	Group I		*Quantum satis*
4.2.5.4	Nut butters and nut spreads	Group I		*Quantum satis*
4.2.6	Processed potato products	Group I		*Quantum satis*
5.1	Cocoa and Chocolate products as covered by Directive 2000/36/ECe	Group I	Only energy-reduced or with no added sugar	*Quantum satis*
		E 472c		*Quantum satis*
5.2	Other confectionery including breath freshening microsweets	Group I		*Quantum satis*
5.3	Chewing gum	Group I		*Quantum satis*
5.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		*Quantum satis*

Food Category number	Food categories	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
6.2.2	Starches	Group I		*Quantum satis*
6.3	Breakfast cereals	Group I		*Quantum satis*
6.4.2	Dry pasta	Group I	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	*Quantum satis*
6.4.4	Potato gnocchi	Group I	Except fresh refrigerated potato gnocchi	*Quantum satis*
6.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		*Quantum satis*
6.5	Noodles	Group I		*Quantum satis*
6.6	Batters	Group I		*Quantum satis*
6.7	Pre-cooked or processed cereals	Group I		*Quantum satis*
		E 472a	Only quick-cook rice	*Quantum satis*
7.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	*Quantum satis*
7.1.1	Bread prepared solely with the following ingredients: wheat flour, water, yeast or leaven, salt	E 472a, E 472d, E 472e, E 472f		*Quantum satis*
7.2	Fine bakery wares	Group I		*Quantum satis*
8.3.1	Non-heat-treated meat products	Group I		*Quantum satis*
8.3.2	Heat-treated meat products	Group I	Except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*	*Quantum satis*
8.3.3	Casings and coatings and decorations for meat	Group I		*Quantum satis*
9.2	Processed fish and fishery products including molluscs and crustaceans	Group I		*Quantum satis*
9.3	Fish roe	Group I	Only processed fish roe	*Quantum satis*
10.2	Processed eggs and egg products	Group I		*Quantum satis*
11.2	Other sugars and syrups	Group I		*Quantum satis*
12.1.2	Salt substitutes	Group I		*Quantum satis*
12.2.2	Seasonings and condiments	Group I		*Quantum satis*
12.3	Vinegars and diluted acetic acid (diluted with water to 4–30% by volume)	Group I		*Quantum satis*
12.4	Mustard	Group I		*Quantum satis*
12.5	Soups and broths	Group I		*Quantum satis*
12.6	Sauces	Group I		*Quantum satis*
12.7	Salads and savoury-based sandwich spreads	Group I		*Quantum satis*
12.8	Yeast and yeast products	Group I		*Quantum satis*
12.9	Protein products, excluding products covered in category 1.8	Group I		*Quantum satis*

Food Category number	Food categories	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
13.1.1[(a)]	Infant formulae as defined by Directive 2006/141/EC	E 472c	Only when sold as powder	*7,500*
			Only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids	*9,000*
13.1.2[(a)]	Follow-on formulae as defined by Directive 2006/141/EC	E 472c	Only when sold as powder	*7,500*
			Only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids	*9,000*
13.1.3[(b)]	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	E 472a, E 472b, E 472c	Only biscuits and rusks, cereal-based foods, baby foods	*5,000*
13.1.4[(a)]	Other foods for young children	E 472c	Only when sold as powder	*7,500*
			Only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids	*9,000*
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	*7,500*
			Only when sold as liquid; From birth onwards	*9,000*
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 472c	Only when sold as powder; From birth onwards	*7,500*
			Only when sold as liquid; From birth onwards	*9,000*
		E 472a, E 472b[(c)]	Only biscuits and rusks, cereal-based foods, baby foods	*5,000*
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		*Quantum satis*
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	Group I		*Quantum satis*
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	*Quantum satis*
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	*Quantum satis*
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	*Quantum satis*
14.1.4	Flavoured drinks	Group I		*Quantum satis*

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

MPL: maximum permitted level.
(a): 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.
(b): E 471, E 472a, E 472b and E 472c are authorised individually or in combination.
(c): Additives from FCs 13.1.2 and 13.1.3 are applicable.

Authorisations of esters of mono- and diglycerides of fatty acids (E 472a-f) according to Annex III, of Regulation (EC) No 1333/2008 are presented in Table 7.

Table 7: Authorisations of esters of glycerides of fatty acids (E 472a-f) according to Annex III, of Regulation (EC) No 1333/2008

Annex III, of Regulation (EC) No 1333/2008	Esters of mono- and diglycerides of fatty acids					
	E 472a	E 472b	E 472c	E 472d	E 472e	E 472f
Part 1: QS as carriers in colours and fat-soluble antioxidants	x		x		x	
Part 2: QS in all food additive preparations having a function other than as a carrier	x	x	x	x	x	x
Part 3: QS in all food enzyme preparations (can also be used as carriers)	x	x	x	x	x	x
Part 3: QS in all food flavouring preparations	x	x	x	x	x	x

Annex III, of Regulation (EC) No 1333/2008	Esters of mono- and diglycerides of fatty acids					
	E 472a	E 472b	E 472c	E 472d	E 472e	E 472f
Part 5 Section A: QS in all nutrient preparations except from the ones intended to be used in FC 13.1 (can also be used as carriers)	x	x	x	x	x	x
Part 5 Section B: in all nutrient preparations used in food categories 13.1.1 and 13.1.2 of Part E of Annex II under the condition that the maximum level in foods mentioned therein is not exceeded			x			

3.3. Exposure data

3.3.1. Reported use levels of esters of mono- and diglycerides of fatty acids (E 472a-f)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives, which are authorised at QS in all, or part of the authorised food categories.

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 public call[13] for occurrence data (usage level and/or analytical data) on esters of mono- and diglycerides of fatty acids (E 472a-f). In response to these calls, information on the actual use levels of all (E 472a-f) in foods was made available to EFSA by industry.

No analytical data on the concentration of esters of mono- and diglycerides of fatty acids (E 472a-f) in foods were made available by the Member States.

Summarised data on reported use levels in foods provided by industry

Industry provided EFSA with data on use levels (n = 664) of esters of glycerides of fatty acids (E 472a-f) at the individual food additive level.

Information on use levels of esters of mono- and diglycerides of fatty acids (E 472a-f) in foods was made available to EFSA by the European Dairy Association (EDA), EFEMA, KRÜGER GmbH & Co. (KRÜGER), Food Drink Europe (FDE), the International Chewing Gum Association (ICGA), Specialised Nutrition Europe (SNE) and the Association of the European Self-Medication Industry.

The Panel noted that 65 use levels in 14 food categories (FCs) referred to niche products. If other use levels referring to widely consumed foods were available for a given food category, the Panel excluded the use levels from further analysis in the refined scenarios and only considered them in the maximum level scenario. Based on this criterion, 13 use levels were excluded from further analysis in the refined scenarios. These use levels were related to FC 5.4 Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4, FC 7.1 Bread and rolls, FC 7.2 Fine bakery wares and FC 16 Desserts excluding products covered in category 1, 3 and 4 (Appendix A).

The Panel noted that one of the data providers (EFEMA) was not a food industry company using food additives in its food products but an association representing food additive producers. Use levels reported by food additive producers should not be considered in the same way as those provided by food industry. Indeed, food additive producers might recommend use levels to the food industry but the final levels in the food products might, ultimately, be different. Because EFEMA declared that the reported levels are suggested amounts and not based on actual use data in final food products, they were not considered in the refined exposure scenarios. These data were, however, used in the maximum level exposure assessment scenario in case of QS authorisation and when no other data were available from food industry (Appendix A). In this way, the most complete exposure estimates were calculated.

[13] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published: 12 October 2015. Available online: https://www.efsa.europa.eu/en/data/call/151012

Two use levels on E 472e in FC 15.1 Potato-, cereal-, flour- or starch-based snacks referred to food products, which are no longer available on the market according to the data provider (FDE). Consequently, these levels were only considered in the maximum level exposure assessment scenario.

For each of the food additives considered in this opinion, the number of use levels and food categories for which usage data were provided out of the total authorised food categories are presented in Table 8.

Table 8: Number of use levels provided by industry and the number of food categories for which usage data were provided out of the total authorised food categories for esters of mono- and diglycerides of fatty acids (E 472a-f)

	Food additive					
	E 472a	**E 472b**	**E 472c**	**E 472d**	**E 472e**	**E 472f**
Use levels (n)	33	37	491	9	89	5
Food categories covered	18	16	17	5	16	5
Authorised food categories	69	68	73	67	67	67

Appendix A provides the data on the use levels of esters of mono- and diglycerides of fatty acids (E 472a-f) in foods as reported by industry.

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

The Mintel's Global New Products Database (GNPD) is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 3 million food and beverage products of which more than 1,100,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 25 out of its 28 Member Countries and Norway presented in the Mintel GNPD.[14] For the purpose of this Scientific Opinion, Mintel's GNPD[15] was used for checking the labelling of food and beverages products and food supplements for esters of mono- and diglycerides of fatty acids (E 472a-f) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to Mintel's GNPD, esters of mono- and diglycerides of fatty acids E 472a-f were labelled altogether on 9,257 products between January 2014 and September 2019, including Bread & Bread Products, Cakes, Pastries & Sweet Goods, Chilled Desserts, Sandwiches/Wraps, Baking Ingredients & Mixes and Sweet Biscuits/Cookies.

Appendix B lists the number and percentage of the food products labelled with E 472a-f out of the total number of food products per food subcategories according to the Mintel's GNPD food classification. The percentages ranged from less than 0.1% in many food subcategories to 28% in Mintel's GNPD food subcategory 'Sandwiches/Wraps'. The average percentage of foods labelled to contain any of the additives E 472a-f was 2%.

Appendix R provides further details on the most relevant subcategories listed E 472a-f.

No use levels were submitted for certain food categories that correspond to the Mintel food subcategories in which esters of mono- and diglycerides of fatty acids E 472a-f are authorised and labelled. These food categories are highlighted in yellow in Appendix B.

3.3.3. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). Consumption surveys added in the Comprehensive database in 2015 were also taken into account in this assessment.[11]

[14] Missing Cyprus, Luxembourg and Malta.
[15] http://www.gnpd.com/sinatra/home/ accessed on 09/09/2019.

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons may not be appropriate. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

Food consumption data from the following population groups were used for the exposure assessment: infants, toddlers, children, adolescents, adults and the elderly. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 9).

Table 9: Population groups considered for the exposure estimates of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acids, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f)

Population	Age range	Countries with food consumption surveys covering more than 1 day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers[a]	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children[b]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly[b]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Netherlands, Sweden, UK

(a): The term 'Toddlers' in the Comprehensive Database (EFSA, 2011a) corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.
(b): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in Comprehensive Database (EFSA, 2011a).

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

Food categories considered for the exposure assessment of esters of mono- and diglycerides of fatty acids (E 472a-f)

The food categories for which MPLs are set and/or use levels of esters of mono- and diglycerides of fatty acids (E 472a-f) were provided by the industry, were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

In general, esters of mono- and diglycerides of fatty acids (E 472a-f) are all allowed in FCs 13.2, 13.3 and 13.4. Food items belonging to these food categories, consumed by population groups children, adolescents, adults and the elderly, may be very diverse and, in addition, there is very limited information on their consumption. Therefore, eating occasions belonging to these food categories were reclassified under FCs in accordance to their main ingredient. The reported use levels available for FCs 13.2, 13.3 and 13.4 for any of the esters of glycerides of fatty acids (E 472a-f) were not considered for the exposure assessment.

Esters of mono- and diglycerides of fatty acids (E 472a-f) are also allowed in FC 18 (Processed foods not covered by categories 1–17, excluding foods for infants and young children). This food category is, however, extremely unspecific. Therefore, the foods belonging to FC 18 (e.g. processed foods, prepared or composite dishes) were reclassified under food categories in accordance with their main ingredient and included as such in the exposure assessment.

Specific information on food categories considered for the exposure assessment per individual food additive (E 472a-f) is described below.

Food categories considered for the exposure assessment of acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

For the following food categories, the restrictions/exceptions, which apply to the use of E 472a, could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to six food categories (Appendix C) and may have resulted in an overestimation of the exposure:

- FC 5.1 Cocoa and Chocolate products as covered by Directive 2000/36/EC, only energy-reduced or with no added sugar – restriction cannot be taken into account, as this information is not always indicated in the Comprehensive Database.
- FC 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC, only biscuits and rusks, cereal-based foods, baby foods. Category only considered in MPL scenario, restriction cannot be taken into account.
- FC 13.1.5.2 Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC, only biscuits and rusks, cereal-based foods, baby foods. Category only considered in Food for Special Medical Purposes (FSMP) consumers only scenario, restriction cannot be taken into account.
- FC 17.1/17.2 Food supplements supplied in a solid form or supplied in a liquid form, excluding food supplements for infants and young children.[16] Food categories are taken into account in the food supplements consumers only scenario altogether as FC 17, as information about the form of the supplement is not always included in the Comprehensive Database.

In the refined scenario, 51 food categories were not taken into account because no use levels were provided (Appendix C). Furthermore, five additional food categories were not taken into account in this scenario, because the use levels were provided by an association representing food additive producers (EFEMA) and not deemed suitable for use in this exposure scenario (see Section 3.3.1). These data were included in the regulatory maximum level exposure scenario. For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

Overall, in the regulatory maximum level exposure scenario, 12 food categories were included, while in the refined scenarios, six food categories were included in the exposure assessment to E 472a. Compared to the refined scenario, two additional food categories were considered (FC 17.1 and 17.2) in the food supplement scenario, while in the FSMP scenario, one additional food category (FC 13.1.5.2) was considered resulting in a total number of food categories of 8 and 7, respectively (Appendix C). Foods belonging to these food categories (FCs 17.1, 17.2 and 13.1.5.2) were not considered in the regulatory maximum level exposure scenario.

Food categories considered for the exposure assessment of lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

For the following food categories, the restrictions/exceptions, which apply to the use of E 472b, could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to three food categories (Appendix D) and may have resulted in an overestimation of the exposure:

- FC 5.1 Cocoa and Chocolate products as covered by Directive 2000/36/EC, only energy-reduced or with no added sugar – restriction cannot be taken into account, as this information is not always indicated in the Comprehensive Database.
- FC 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC, only biscuits and rusks, cereal-based foods, baby foods. Category only considered in MPL scenario, restriction cannot be taken into account.
- FC 13.1.5.2 Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC, only biscuits and rusks, cereal-based foods, baby foods.

[16] Call for data on esters of mono- and diglycerides of fatty acids (E 472(a-f)) was launched during batch 4, with deadline May 2016. At the time, food additives legislation foresaw three food categories of food supplements (17.1, 17.2 and 17.3) depending on their forms. In October 2018, Regulation (EC) No 1333/2008 was modified and food supplements are now subdivided into two food categories of 17.1 and 17.2 (as mentioned in Table 6).

Category only considered in FSMP consumers only scenario, restriction cannot be taken into account.

In the refined scenario, 50 food categories were not taken into account because no use levels were provided (Appendix D). Furthermore, five additional food categories were not taken into account in this scenario, because the use levels were provided by an association representing food additive producers (EFEMA) and not deemed suitable for use in this exposure scenario (see Section 3.3.1). These data were included in the regulatory maximum level exposure scenario. For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

Overall, in the regulatory maximum level exposure scenario, 14 food categories were included, while in the refined scenarios, eight food categories were included in the exposure assessment to E 472b. Compared to the refined scenario, one additional food category (FC 13.1.5.2) was considered in the FSMP scenario resulting in a total number of food categories of 9 (Appendix D). This food category (FC 13.1.5.2) was not considered in the regulatory maximum level exposure scenario.

Food categories considered for the exposure assessment of citric acid esters of mono- and diglycerides of fatty acids (E 472c)

For the following food categories, the restrictions/exceptions, which apply to the use of E 472c, could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to six food categories (Appendix E) and may have resulted in an overestimation of the exposure:

- FC 8.3.1, 8.3.2 Non-heat treated- and Heat-treated meat products – Categories are considered together on higher level as in the Comprehensive Database information on the heat treatment is not always described. Restriction on 8.3.2 '*except foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*' cannot be taken into account.
- FC 13.1.1 Infant formulae as defined by Directive 2006/141/EC, '*only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids*' restriction cannot be taken into account as this specific information is not included in the Comprehensive Database.
- FC 13.1.2 Follow-on formulae as defined by Directive 2006/141/EC, '*only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids*' restriction cannot be taken into account as this specific information is not included in the Comprehensive Database.
- FC 13.1.3 Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC, '*only biscuits and rusks, cereal-based foods, baby foods'* restriction cannot be taken into account. Category only considered in MPL scenario due to the lack of use level data.
- FC 13.1.4 Other foods for young children, '*only sold as liquid where the products contain partially hydrolysed proteins, peptides or amino acids*' restriction cannot be taken into account as this specific information is not included in the Comprehensive Database. Category only considered in MPL scenario due to the lack of use level data.

In the refined scenario, 55 food categories were not taken into account because no concentration data were provided for these food categories to EFSA (Appendix E). Furthermore, three additional food categories were not taken into account in the refined scenario, because the use levels were provided by an association representing food additive producers (EFEMA) and not deemed suitable for use in this exposure scenario (see Section 3.3.1). These data were included in the regulatory maximum level exposure scenario. For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

Overall, for the regulatory maximum level exposure scenario, 14 food categories were included, while for the refined scenarios, nine food categories were included in the present exposure assessment to citric acid esters of mono- and diglycerides of fatty acids (E 472c). Compared to the refined scenario, two additional food categories (FC 13.1.5.1 and 13.1.5.2) were considered in the FSMP scenario resulting in a total number of food categories of 11 (Appendix E). These food categories (FC 13.1.5.1 and 13.1.5.2) were not considered in the regulatory maximum level exposure scenario.

Food categories considered for the exposure assessment of tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

For FC 5.1 'Cocoa and Chocolate products as covered by Directive 2000/36/EC, only energy-reduced or with no added sugar', the restrictions/exceptions which apply to the use of E 472d could not be taken into account, as this information is not indicated in all cases in the Comprehensive Database, and therefore, the whole food category was considered in the exposure assessment.

In the refined scenario, 60 food categories were not taken into account because no concentration data were provided for these food categories to EFSA (Appendix F). For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

Overall, as the data provider reported the same typical and maximum usage levels for the three food categories, the exposure to E 472d was assessed for one exposure scenario.

Food categories considered for the exposure assessment of mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

The exposure to esters of glycerides of fatty acids (E 472a-f) was estimated for the food additives individually, except for E 472e and E 472f, because it was considered that E 472f is not markedly different from E 472e, when considering the description of their manufacturing processes and their compositions (Sections 3.1.1 and 3.1.3). The Panel considered that E 472e and E 472f are not likely to be used in combination in the same food product and, therefore, the exposure assessment of them was performed considering the highest reported use level for either E 472e or E 472f per food category (Appendix A).

For the following food categories, the restrictions/exceptions which apply to the use of E 472e and E 472f could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to four food categories (Appendix G) and may have resulted in an overestimation of the exposure:

- FC 5.1 Cocoa and Chocolate products as covered by Directive 2000/36/EC, only energy-reduced or with no added sugar – Restriction cannot be taken into account, as this information is not always indicated in the Comprehensive Database.
- FC 7.1 Bread and rolls, 'except products in 7.1.1 and 7.1.2' – Restriction cannot be taken into account, as the specific information on the type of the bread is not always reported in the Comprehensive Database. Reported use levels of FC 7.1 are applied for FC 7.1.1 as well.
- FC 8.3.1, 8.3.2 Non-heat-treated and heat-treated meat products – Categories are considered together on higher level as in the Comprehensive Database information on the heat treatment is not always described. Restriction on 8.3.2 'except foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben' cannot be taken into account. (Applies only to the MPL scenario, as the data is from additive producer.)

In the refined scenario, 46 food categories were not taken into account because no concentration data were provided for these food categories to EFSA (Appendix G). Furthermore, five additional food categories were not taken into account in the refined scenario, because the use levels were provided an association representing food additive producers (EFEMA) and not deemed suitable for use in this exposure scenario (see Section 3.3.1). These data were included in the regulatory maximum level exposure scenario. For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

Overall, for the regulatory maximum level exposure scenario, 17 food categories were included, while for the refined scenarios, 12 food categories were included in the present exposure assessment to E 472e and E 472f (Appendix G).

3.4. Exposure estimates

3.4.1. Exposure to esters of mono- and diglycerides of fatty acids (E 472a-f) from their use as food additives

The Panel estimated the chronic dietary exposure to esters of mono- and diglycerides of fatty acids (E 472a-f) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Dietary exposure to esters of mono- and diglycerides of fatty acids (E 472a-f) was calculated

by multiplying concentrations of the additive per food category (Appendices C–G) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only one day per subject were excluded as they are considered as not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 9). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011a). Therefore, in the present assessment, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain was not estimated.

Exposure assessment to esters of mono- and diglycerides of fatty acids (E 472a-f) was carried out by the Panel based on two different sets of concentration data: (1) MPLs as set down in the EU legislation or maximum reported use levels for food categories with a permitted use at QS (defined as the *maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

These scenarios do not consider the consumption of FSMP. These exposure sources are covered in two additional scenarios detailed below (*foods for special medical purposes consumer only scenario* and *food supplements consumers only scenario*).

A possible additional exposure from the use of esters of mono- and diglycerides of fatty acids (E 472a-f) in accordance with Annex III to Regulation (EC) No 1333/2008 (see in details in Section 3.2) was not considered in any of the exposure assessment scenarios.

Maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008 and listed in Table 7 and/or maximum reported use levels provided by industry for food categories in which the additives are authorised as QS, excluding exposure via FSMP, as described in the approach followed for the refined exposure assessment (EFSA ANS Panel, 2017c) (Appendices C–G).

The Panel considers the exposure estimates derived following this scenario as the most conservative possible since it is assumed that the population will be exposed to the food additive present in food at the MPL or maximum reported use levels over a longer period of time.

Refined exposure assessment scenario

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

Appendices C–G summarise the use levels of esters of mono- and diglycerides of fatty acids (E 472a-f) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on two model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long term to esters of mono- and diglycerides of fatty acids of fatty acids (E 472a-f) present at the maximum reported use for one food category. This exposure estimate was calculated as follows:
  - Combining food consumption with the maximum of the reported use levels for the main contributing food category at the individual level.
  - Using the mean of the typical reported use levels for the remaining food categories.
- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long term to esters of mono- and diglycerides of fatty acids (E 472a-f) present at the mean reported use in food. This exposure estimate was calculated using the mean of the typical reported use levels for all food categories.

Specific exposure assessment scenarios

- 'Food supplement consumers only' scenario:

Esters of mono- and diglycerides of fatty acids (E 472a-f) are authorised in FC 17 (Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children) at QS. As exposure via food supplements may deviate largely from that via food, and the

number of food supplement consumers may be low depending on populations and surveys, an additional scenario was calculated in order to reflect additional exposure from the intake of food supplements. This was done for E 472a since use levels for FC 17 were provided only for this food additive. This additional exposure scenario was estimated assuming that consumers of food supplements were exposed to E 472a present at the maximum reported use level in food supplements on a daily basis. For the remaining food categories, the mean of the typical reported use was used.

As FC 17 does not consider food supplements for infants and toddlers as defined in the legislation, the exposure to E 472a from food supplements was not estimated for these two population groups.

This scenario included nine food categories (Appendix C).

- FSMP scenario consumers only:

As E 472a and E 472b are authorised in FC 13.1.5.2, whereas E 472c is authorised in both FC 13.1.5.1 and FC 13.1.5.2, an additional exposure assessment scenario taking into account the reported use levels for these food categories was performed to estimate the exposure of infants and toddlers who may eat and drink these FSMP.

The consumption of these foods is not reported in the EFSA Comprehensive database. To consider the potential exposure to E 472a, E 472b and E 472c via these foods, the Panel assumed that the amount consumed of FSMP in infants and toddlers resembles that of comparable foods in infants and toddlers from the general population. Thus, the consumed amounts of FSMP categorised as FC 13.1.5 was assumed to equal that of formulae and food products categorised as FCs 13.1.1, 13.1.2, 13.1.3 and 13.1.4.

This scenario was estimated assuming the consumers of FSMP were exposed to E 472a, E 472b and E 472c present at the maximum reported use level on a daily basis via consumption of FCs 13.1.5.1 or/and 13.1.5.2 (infant formulae, follow-on formulas and processed cereal-based foods and baby foods for infants and young children as defined by Commission Directive 2006/125/EC). For the remaining food categories, the mean of the typical reported use levels was used.

This scenario included seven food categories for E 472a (Appendix C), nine for E 472b (Appendix D) and 11 for E 472c (Appendix E).

Dietary exposure to acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Table 10 summarises the estimated exposure to E 472a from its use as a food additive in six population groups (Table 9) according to the different exposure scenarios (Section 3.4.1). Detailed results per population group and survey are presented in Appendix H.

Table 10: Summary of dietary exposure to E 472a from its use as a food additive in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Maximum level exposure assessment scenario												
Mean	2.4	50.0	11.0	97.8	30.7	83.8	12.5	38.4	3.7	25.4	2.9	24.0
95th percentile	8.9	149.9	40.8	185.5	74.7	181.9	28.1	88.7	11.5	60.0	8.4	50.1
Refined estimated exposure assessment scenario												
Brand-loyal scenario												
Mean	0.5	6.9	2.6	41.9	2.7	38.6	1.3	12.5	0.6	6.9	0.4	6.9
95th percentile	7.9	38.7	8.7	130.3	9.0	115.4	4.0	40.3	1.9	24.8	1.2	23.2
Non-brand-loyal scenario												
Mean	0.5	2.5	2.4	29.1	2.5	27.0	1.2	7.9	0.4	3.8	0.2	3.2
95th percentile	5.2	12.4	8.5	81.7	7.9	95.7	3.9	29.5	1.5	13.6	0.9	15.5

In the *FSMP consumers only scenario*, mean exposure to E 472a from its use as a food additive ranged from 99.0 to 340.3 mg/kg bw per day for infants and from 26.7 to 197.5 mg/kg bw per day for toddlers. The corresponding 95th percentiles of exposure were 278.7 and 486.3 mg/kg bw per day, and 1132.9 and 289.5 mg/kg bw per day, respectively.

In the *food supplements consumers only scenario*, mean exposure to E 472a from its use as a food additive ranged from 5.42 to 37.5 mg/kg bw per day for children and from 2.17 to 6.25 mg/kg bw per day for adults. The corresponding 95th percentiles of exposure were 14.76 and 47.68 mg/kg bw per day and between 15.25 and 24.42 mg/kg bw per day, respectively.

Main food categories contributing to exposure to acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

– *using the maximum level exposure assessment scenario*

In the *maximum level exposure assessment scenario*, the main contributing food category to the total mean exposure estimates for all population groups was FC 7.2 Fine bakery wares.

For children, adolescents, adults and elderly also, FC 3 Edible ices contributed largely to the exposure. Furthermore, in toddlers, adults and elderly, FC 2.2 Fat and oil emulsions was an important contributor to the exposure. For infants, FC 13.1.3 Processed cereal-based foods and baby foods was the other main contributor (Appendix I)

– *using the refined exposure assessment scenarios*

FC 7.2 Fine bakery wares was also the main contributing food category in both *refined estimated exposure scenarios (brand-loyal and non-brand loyal scenario)* for all population groups

Furthermore, additional food categories that contributed largely to the exposure in both refined scenarios were FC 14.1.4 Flavoured drinks in all population groups except infants and elderly, and FC 16 Desserts in adults, elderly and infants. For infants, adolescents, adults and elderly also FC 5.1 Cocoa and chocolate products contributed significantly to the exposure (Appendix I).

Dietary exposure to lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

Table 11 summarises the estimated exposure to E 472b from its use as a food additive in six population groups (Table 9) according to the different exposure scenarios (Section 3.4.1). Detailed results per population group and survey are presented in Appendix J.

Table 11: Summary of dietary exposure to E 472b from its use as a food additive in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Maximum level exposure assessment scenario												
Mean	2.4	50.8	28.4	109.4	22.3	97.3	13.0	35.8	2.8	24.4	2.4	23.1
95th percentile	8.5	148.3	84.8	217.6	57.0	195.3	29.0	77.0	8.0	56.0	6.3	49.6
Refined estimated exposure assessment scenario												
Brand-loyal scenario												
Mean	0.5	10.8	3.4	48.0	3.2	46.9	1.4	19.6	1.4	12.3	1.3	11.1
95th percentile	7.9	45.8	10.3	110.3	8.6	114.7	4.2	48.8	5.4	34.4	4.2	28.1
Non-brand-loyal scenario												
Mean	0.5	5.2	2.0	41.3	2.8	38.6	1.2	12.9	0.8	6.9	0.6	6.2
95th percentile	4.4	26.6	6.2	98.2	7.5	102.9	3.8	33.9	2.9	20.2	1.9	17.5

In the *refined estimated exposure scenario taking into account the foods for special medical purposes (FSMP consumers only scenario)*, mean exposure to E 472b from its use as a food additive ranged for infants between 101.6 and 340.1 mg/kg bw per day and between 34.0 and 195.4 mg/kg

bw per day for toddlers. The 95th percentile of exposure to E 472b ranged for infants between 281.2 and 486.3 mg/kg bw per day and for toddlers between 147.9 and 292.0 mg/kg bw per day.

Main food categories contributing to exposure to lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

– *using the maximum level exposure assessment scenario*

In the *regulatory maximum level exposure assessment scenario*, the main contributing food category to the total mean exposure estimates for all population groups was again FC 7.2 Fine bakery wares. For infants, toddlers, children, adolescents and adults, FC 1.4 Flavoured fermented milk products contributed also largely to the exposure. In addition, for toddlers FC 16 Desserts, and for children and adolescents FC 14.1.4 Flavoured drinks while for adults FC 12.6 Sauces were also important contributors. For elderly, FC 2.2 Fat and oil emulsions and FC 16 Desserts were also important contributors (Appendix K).

– *using the refined exposure assessment scenarios*

FC 7.2 Fine bakery wares was also in both *refined estimated exposure scenarios (brand-loyal and non-brand loyal scenario)* for all population groups the main contributing food category.

Furthermore, the additional main contributing food categories in both of the refined scenarios were FC 14.1.4 Flavoured drinks in all population groups except infants, and FC 16 Desserts in all population groups except adolescents. For adolescents and adults also FC 5.1 Cocoa and chocolate products contributed significantly to the exposure (Appendix K).

Dietary exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c)

Table 12 summarises the estimated exposure to E 472c from its use as a food additive in six population groups (Table 9) according to the different exposure scenarios (Section 3.4.1). Detailed results per population group and survey are presented in Appendix L.

Table 12: Summary of dietary exposure to E 472c from its use as a food additive in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Maximum level exposure assessment scenario												
Mean	316.3	561.8	86.7	228.3	56.9	148.6	30.4	75.6	16.8	51.3	14.4	58.0
95th percentile	852.3	1,220	265.6	650.0	127.5	305.1	67.0	162.7	47.1	123.7	36.2	159.2
Refined estimated exposure assessment scenario												
Brand-loyal scenario												
Mean	24.6	83.2	26.4	103.5	29.7	100.5	14.8	48.0	6.5	38.9	6.8	46.0
95th percentile	65.2	202.2	101.5	216.8	73.1	202.1	38.8	111.2	25.8	104.6	20.3	138.9
Non-brand-loyal scenario												
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

In the *refined estimated exposure scenario taking into account the foods for special medical purposes* (FSMP consumers only scenario), mean exposure to E 472c from its use as a food additive ranged for infants between 157.3 and 547.3 mg/kg bw per day and between 24.7 and 173.8 mg/kg bw per day for toddlers. The 95th percentile of exposure to E 472c ranged for infants between 429.2 and 1561 mg/kg bw per day and for toddlers between 126.6 and 425.0 mg/kg bw per day.

Main food categories contributing to exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c)

– *using the maximum level exposure assessment scenario*

In the *regulatory maximum level exposure assessment scenario*, the main contributing food categories to the total mean exposure estimates for all population groups except infants were FC 7.2 Fine bakery wares, FC 2.2 Fat and oil emulsions and FC 8.3 Meat products. For infants, FC 13.1.1 Infant formulae and FC 13.1.2 Follow-on formulae was the most important contributor (Appendix M).

– *using the refined exposure assessment scenarios*

FC 7.2 Fine bakery wares and FC 2.2 Fat and oil emulsions were the main contributing food categories in both *refined estimated exposure scenarios (brand-loyal and non-brand loyal scenario)* for all population groups.

Furthermore, for toddlers, children and adolescents also FC 14.1.4 Flavoured drinks was an important contributor to the exposure. For infants, FC 13.1.1 Infant formulae and FC 13.1.2 Follow-on formulae were also important contributors (Appendix M).

Dietary exposure to tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

Table 13 summarises the estimated exposure to E 472d from their use as food additives in six population groups (Table 9) (Section 3.4.1). As the data provider reported the same typical and maximum usage levels for the three food categories, the exposure estimates of the regulatory maximum and the refined scenarios were the same. Detailed results per population group and survey are presented in Appendix N.

Table 13: Summary of dietary exposure to E 472d from their use as food additives, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Mean	0.2	2.0	0.7	20.5	1.0	19.2	0.4	6.8	0.1	2.7	0.1	3.0
95th percentile	0.0	7.9	5.4	65.7	5.1	85.3	2.0	27.6	0.7	13.0	0.4	15.4

Main food categories contributing to exposure to tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

As only use levels in three food categories were provided to EFSA, the contributors to the exposure were FC 05.1 Cocoa and Chocolate products, FC 14.1.4 Flavoured drinks and FC 01.8 Dairy analogues in all population groups (Appendix O).

Dietary exposure to mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

As stated in Section 3.3, the exposure to E 472e and E 472f was considered together, because E 472f is not markedly different from E 472e, when considering the description of their manufacturing processes and their compositions (Sections 3.1.1 and 3.1.3).

Table 14 summarises the estimated exposure to E 472e and E 472f from their use as food additives in six population groups (Table 9) according to the different exposure scenarios (Section 3.4.1). Detailed results per population group and survey are presented in Appendix P.

Table 14: Summary of dietary exposure to E 472e and E 472f from their use as food additives in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Maximum level exposure assessment scenario												
Mean	2.8	39.3	10.5	189.8	19.8	152.5	9.6	68.6	17.0	45.3	17.5	46.9
95th percentile	9.3	134.7	32.0	339.7	36.8	316.5	19.2	138.7	35.9	96.3	36.4	98.1
Refined estimated exposure assessment scenario												
Brand-loyal scenario												
Mean	2.4	27.7	8.1	99.6	13.1	78.9	6.7	43.3	12.3	30.0	14.1	30.6
95th percentile	8.3	68.5	26.6	120.4	25.4	159.4	13.4	85.1	25.4	61.2	30.2	61.2
Non-brand-loyal scenario												
Mean	1.9	16.2	6.6	81.5	10.1	62.1	5.7	31.6	4.0	21.4	4.2	24.5
95th percentile	6.6	33.1	22.9	111.6	20.8	147.7	11.5	73.8	8.2	50.4	9.0	54.8

Main food categories contributing to exposure to mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

– *using the maximum level exposure assessment scenario*

In the *regulatory maximum level exposure assessment scenario*, the main contributing food categories to the total mean exposure estimates for all population groups were FC 7.2 Fine bakery wares, FC 7.1 Bread and rolls and FC 16 Desserts, followed by FC 12.5 Soups and broths and FC 12.6 Sauces (Appendix Q).

– *using the refined exposure assessment scenarios*

FC 7.2 Fine bakery wares and FC 7.1 Bread and rolls were the main contributing food categories in both *refined estimated exposure scenarios (brand-loyal and non-brand loyal scenario)* for all population groups.

Additionally, FC 14.1.4 Flavoured drinks in children and adolescents, FC 12.5 soups and broths in elderly and toddlers, FC 12.6 Sauces in adults and FC 2.2 Fat and oil emulsions in elderly contributed significantly (Appendix Q).

3.4.2. Uncertainty analysis

Potential sources of uncertainty in the exposure assessment of esters of mono- and diglycerides of fatty acids (E 472a-f) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 15.

Table 15: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate of esters of mono and diglycerides of fatty acids (E 472a-f)

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/–
Methodology used to estimate high percentiles (95th) of long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Usage level data: – Not fully representative of foods on the EU market – Foods which may contain the food additives according to Annex III to Regulation (EC) No 1333/2008 not taken into account – Use levels considered applicable to all foods within the entire food category, while the average percentage of the foods labelled with the additives in Mintel was maximally 1.6%	+/– – +
Maximum level exposure assessment scenario: – Exposure calculations based on the MPL or the maximum reported use levels (reported use from industries and food additive producers)	+
Refined exposure assessment scenarios: – Exposure calculations based on the maximum or mean levels (reported use from industries)	+/–
Number of Mintel GNPD subcategories in which esters of glycerides of fatty acids (E 472af) were labelled and which were included in the current exposure assessment: E 472a: 30 out of 42 subcategories, representing 93% of the products E 472b: 29 out of 43 subcategories, representing 89% of the products E 472c: 33 out of 68 subcategories, representing 84% of the products E 472d: use level data did not cover the subcategories in Mintel E 472ef: 47 out of 79 subcategories, representing 95% of the products	+/–
Food categories selected for the exposure assessment: inclusion of food categories without considering the restriction/exception E 472a: n = 2 MPL scenario/n = 1 refined scenarios out of 69 food categories E 472b: n = 2 MPL scenario/n = 1 refined scenarios out of 68 food categories E 472c: n = 6 MPL scenario/n = 4 refined scenarios out of 73 food categories E 472d: n = 1 out of 67 food categories E 472ef: n = 4 MPL scenario/n = 2 refined scenarios out of 67 food categories	+
Food categories included in the exposure assessment: no data for certain food categories which were therefore not considered in the exposure estimates E 472a: n = 12 MPL scenario/n = 6 refined scenarios out of 69 food categories E 472b: n = 14 MPL scenario/n = 8 refined scenarios out of 68 food categories E 472c: n = 14 MPL scenario/n = 9 refined scenarios out of 73 food categories E 472d: n = 3 out of 67 food categories E 472ef: n = 17 MPL scenario/n = 12 refined scenarios out of 67 food categories	–

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

Esters of mono and diglycerides of fatty acids (E 472a-f) are all authorised as a Group I food additive in 67 food categories and have a specific authorised use in some other food categories (Table 7). Since, the majority of food categories correspond to the general Group I food additives authorisation, the food additives may not necessarily be used in these food categories. This may explain why reported use levels of esters of mono and diglycerides of fatty acids (E 472a-f) were available for much less food categories than in which they are authorised (See last row of the uncertainty table). This observation was supported by the information from Mintel's GNPD (Appendix B).

Given their authorised use as Group I food additives and the uncertainties listed in Table 15, the Panel considered overall that the exposure to esters of mono and diglycerides of fatty acids (E 472a-f) from their use as food additives according to Annex II was overestimated in the maximum level exposure scenario and the refined exposure scenario.

The Panel noted that food categories which may contain food additive esters of mono and diglycerides of fatty acids (E 472a-f) due to carry-over (Annex III, Part 1, 3, 5) were not considered in the current exposure assessment.

3.4.3. Exposure to tartaric acid from E 472d, E 472e and E 472f

The Panel noted that tartaric acid released from E 472d, E 472e and E 472f would add to the exposure to tartaric acid-tartrates (E 334-337, E 355) previously re-evaluated by EFSA (EFSA FAF Panel, 2020).

The total amount of tartaric acid in E 472d amount up to a maximum of 40% by weight and up to a maximum 50% in E 472fe and E 472f according to the EU specifications for these food additives (Commission Regulation (EU) No 231/2012). The Panel considered these amounts releases as a worst case on which exposure to tartaric acid was estimated. Tables 16 and 17 summarise the estimated exposure to tartaric acid from the use of E 472d and E 472e,f as food additives, respectively.

Table 16: Summary of dietary exposure to tartaric acid from the use of E 472d as a food additive in the maximum level exposure assessment scenario, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Mean	0.09	1.02	0.34	10.24	0.50	9.60	0.22	3.41	0.06	1.33	0.03	1.48
95th percentile	0.00	3.95	2.68	32.85	2.57	42.63	1.00	13.81	0.36	6.50	0.18	7.69

Table 17: Summary of dietary exposure to tartaric acid from the use of E 472e and E 472f as food additives in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)		Toddlers (12–35 months)		Children (3–9 years)		Adolescents (10–17 years)		Adults (18–64 years)		The elderly (≥ 65 years)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Maximum level exposure assessment scenario												
Mean	1.1	15.7	4.2	75.9	7.9	61.0	3.9	27.4	6.8	18.1	7.0	18.8
95th percentile	3.7	53.9	12.8	135.9	14.7	126.6	7.7	55.5	14.4	38.5	14.6	39.3
Refined estimated exposure assessment scenario												
Brand-loyal scenario												
Mean	0.9	11.1	3.2	39.8	5.2	31.5	2.7	17.3	4.9	12.0	5.6	12.2
95th percentile	3.3	27.4	10.6	48.2	10.2	63.8	5.4	34.1	10.1	24.5	12.1	24.5
Non-brand-loyal scenario												
Mean	0.7	6.5	2.6	32.6	4.0	24.8	2.3	12.6	1.6	8.6	1.7	9.8
95th percentile	2.7	13.2	9.1	44.7	8.3	59.1	4.6	29.5	3.3	20.2	3.6	21.9

Overall, the Panel considered that an accurate exposure assessment for tartaric acid released from E 472d, E 472e and E 472f was influenced by the same uncertainties as mentioned in Section 3.4.2, as well as the uncertainty of the amount of tartaric acid present in the food additives.

3.5. Exposure via other sources

Citric acid esters of mono-glycerides of fatty acids are used as emulsifier in various pharmaceutical, cosmetic and body care lotions according to Palsgaard (2010 (Documentation provided to EFSA n. 23)).

Quantification of exposure via all these sources is not known and could therefore not be taken into account in this opinion.

3.6. Biological and Toxicological studies

The test materials used in the biological and toxicological studies fall under the definition of the food additives esters of mono- and diglycerides of fatty acids (E 472a-f). Although a test material may not have fully conformed to the specifications of the food additives E 472a-f, the Panel considered them sufficiently similar to the food additives E 472a-f and included those studies for the safety assessment.

3.6.1. Absorption, distribution, metabolism and excretion

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Groups of 10 mature male albino fasted rats were fed diets containing 20% of different acetooleins or acetostearins (fully acetylated acetoolein from cottonseed oil, fully acetylated acetoolein from prime steamed edible lard, partially acetylated acetostearin from hydrogenated lard or fully acetylated acetostearin from hydrogenated lard) (Ambrose and Robbins, 1956a). After 4 hours, the amount of ether soluble residue (fat) was determined in the contents of the oesophagus, stomach and small intestine, which were removed surgically. Rats fasted for 48 hours but fed no fat or acetoglycerides served as control. The amount of fat absorbed was higher for the acetooleins (77%) compared with the acetostearins (68%).

The digestibility (coefficient indicating the percentage of the absorbed compared to the fed fat) of acetoglycerides was studied in groups of five male and five female albino rats. Another group of 10 rats was fed the control diet. All other rats in groups of 10 were placed on the experimental diets containing 20% of one of the acetoglycerides or mixtures of acetoglycerides. The digestibility over a 7-day period was shown to be up to 99% for acetooleins and up to 85% for acetostearins. (Ambrose and Robbins, 1956a).

In another study, groups of 10 male albino rats were dosed via diet over 20 weeks with 0 or 30% of two different acetostearins: I.) 14.6% monoglycerides (monostearins), 47.4% 'diglycerides' (42% monoacetomonostearin) and 38% 'triglycerides' (29,9% diacetomonostearin and 7,7% monacetodistearin); II.) 20% monostearin, 50% monoacetomonostearin and 30% diacetomonostearin. The digestibility was given with up to 53% for diet I and with up to 61% for diet II (Coleman et al., 1963).

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

One male mongrel dog and groups of male or female albino Wistar rats were dosed with ^{14}C-labelled glycerol lactate in olive oil by gavage. In rats, the expired CO_2 and the faecal and urinary radioactivity was determined, in the dog lymph and blood samples were examined. In the dog (20 kg) dosed with 10 g of glyceryl lacto-2-^{14}C-palmitate in 30 g of olive oil, the presence of radioactive lactate in lymph within 0.5 hour after administration indicated absorption of lactate, possibly after hydrolysis in the gut and/or gut wall. In eight female rats dosed with glyceryl lacto-2-^{14}C-palmitate (dose level was given with 3–4.7 mL of a solution containing 10 g of glyceryl lacto-2-^{14}C-palmitate dissolved in 30 g olive oil), up to 55% of the dose was expired as CO_2, 17% was excreted via urine and 1.4% via faeces within 48 hours. After dosing of four male rats with glyceryl-1,3-^{14}C-lactopalmitate (exact dose not specified), also most of the applied dose was eliminated within 48 hours (up to 75% via expired CO_2, 6.2% via urine and 1.7% via faeces). Since both glycerol and lactic acid were metabolised following the administration of glyceryl lactopalmitate, it was presumed that hydrolysis of the ester linkages from both acids had taken place (McKennis et al., 1958).

In an *in vitro* study with non-labelled glycerol lactate palmitate, the test substance was split by a lipase enzyme (whole hog pancreas preparation) in the presence of sodium taurocholate: 42% at 1 hour, 48% at 2 hours, 58% at 4 hours, 60% at 6 hours and 68% at 22 hours. In a replicate study, the values were confirmed (Treon et al., 1962).

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

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. 1,500 or 3,000 mg/rat per day) and 16.7 or 33.3% for lard (ca. 1,000 or 2,000 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, 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.

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

No data available.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

Groups of six male and six female rats (not further specified) were dosed with 50 mg/kg bw by gavage with diacetyltartaric acid ester of a monoglyceride, which was ^{14}C-labelled in the acetyl moiety. A further group of six rats were dosed with 15 mg/kg bw ^{14}C-acetic acid. Forty-eight hours after dosing with ^{14}C-acetic acid, the ^{14}C was mainly found in expired air (80%) with only minor amounts in urine (4%), faeces (1.6%) and carcass (7%). After dosing with ^{14}C-labelled E 472e only 47–56% of the ^{14}C recovered was as exhaled $^{14}CO_2$, 5% was in urine, 7.5% in carcass and 30–40% were found in faeces. The rate of $^{14}CO_2$ exhalation in rats dosed with ^{14}C-labelled E 472e was slower compared to the exhalation of $^{14}CO_2$ in ^{14}C-acetic acid dosed rats. An analysis of the ^{14}C in the stomach, small and large intestines and in the faeces showed degradation of the E 472e to polar compounds in the small intestine. No unchanged E 472e was found in the faeces but polar ^{14}C-material was detected, and the authors assumed this was due to the presence of mono- or diacetyltartaric acid. The levels of ^{14}C measured (7.5%) in the tissues and carcasses of the rats dosed with ^{14}C-labelled E 472e were similar to the ones of rats dosed with the equivalent molar dose of ^{14}C-acetic acid (7%).The authors concluded that E 472e was extensively but not completely digested in the GI tract (Unilever, 1988 (Documentation provided to EFSA n. 27)).

As described in an unpublished study, six male rats were fed 530–810 mg/kg bw of an oily solution of [^{14}C]acetyltartaric acid ester of mono- and diglycerides (labelled in the two carboxyl groups of tartaric acid). Within 24 hours, 26–31% of the radiolabel had been absorbed, 12–20% was eliminated as $^{14}CO_2$ and 8–13% via urine. Only 2% was found in the carcass (Lang and Schmidt, 1967, as referred to by JECFA, 2001).

In a study with eight dogs, the animals were dosed once by gavage with tartaric acid, diacetyl tartaric acid or with diacetyltartaric acid esters of mono- and diglycerides obtained from natural fats. Doses were 500 mg tartaric acid/kg bw in one dog, 729 mg diacetyl tartaric acid/kg bw in three dogs, and 2,700 mg mono- and diacetyltartaric esters of mono- and diglycerides/kg bw in four dogs. Within 12 hours, about 50% of the administered tartaric acid was excreted via urine and 31.8–58.6% of the administered diacetyl tartaric acid was excreted via urine. In contrast, in dogs dosed with diacetyl tartaric acid esters of mixed mono- and diglycerides only 6.7–18.8% of available tartaric acid was excreted via urine. At the end of the study, the intestinal contents of two dogs dosed with diacetyl tartaric acid esters of mixed mono- and diglycerides were collected and the ether-soluble residue was weighed and found to be equivalent to 12.6% and 11.4%, respectively, of the weight of diacetyl

tartaric acid esters of mixed mono- and diglycerides administered. According to the authors, if the ether-soluble residue consisted of diacetyl tartaric acid esters of mixed mono- and diglycerides alone, then 88% of the diacetyl tartaric acid esters of mixed mono- and diglycerides administered could be accounted for by intestinal absorption (Sourkes and Koppanyi, 1950).

In another study with dogs fed diets containing up to 20 % diacetyltartaric acid esters of mono- and diglycerides obtained from natural fats (ca. 5,000 mg/kg bw) for 22 months, the digestibility of the test substance was > 90 %. No traces of either free tartaric acid or tartaric acid containing fat-soluble derivative were detected in the depot fat (Koppanyi and Dardin, 1950 (Documentation provided to EFSA n. 16)).

In an aqueous medium, diacetyltartaric ester of mono- and diglycerides was hydrolysed spontaneously to mono- and diglycerides and acetylated tartaric acid, the hydrolysis being accelerated by pancreatic lipase (Lang & Schmidt, 1965, as referred to by JECFA, 2001).

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

No studies specifically performed with E 472f were available. However, the Panel considered that the results of the studies described above for E 472e are also relevant for E 472f.

Overall, the Panel considered 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. The Panel considered that E 472d would behave similar to E 472e. The hydrolysis products are known to be either readily metabolised or excreted intact.

3.6.2. Acute toxicity

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

The acute oral toxicity of acetostearin or acetoolein was determined in 10 male and 10 female mature rats. The single dosing with 4,000 mg/kg bw by gavage caused no obvious adverse effects (Ambrose and Robbins, 1956b; Alfin-Slater et al., 1958).

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

In an unpublished study, two groups of six male rats each were given glycerol lactopalmitate suspended in water by gavage in doses of 8,650 and 5,750 mg/kg bw, respectively. All animals survived without adverse effects other than those attributable to mechanical distension (Gongwer, 1959; as referred to by JECFA, 1967).

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

No data available to the Panel.

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

No data available to the Panel.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

Groups of six rats and six rabbits were dosed by gavage with 30,000 mg/kg bw of diacetyltartaric acid esters of mono- and diglycerides obtained from natural fats. The animals did not show any adverse effects. In the same study, the acute toxicity was studied in dogs. The dogs received 27,000 mg/kg bw administered by stomach tube as a solution or slurry in water. No adverse effects were observed. (Koppanyi and Dardin, 1950 (Documentation provided to EFSA n. 16)).

In another study, four dogs were dosed once by gavage with diacetyl tartaric acid esters of mono- and diglycerides obtained from natural fats at doses of 2,700 mg/kg bw. No adverse effects were observed (Sourkes and Koppanyi, 1950).

For mice an oral median lethal dose (LD_{50}) value of 20,000 mg/kg bw was reported (Kieckebusch et al., 1967; as referred to in JECFA, 2001).

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

No studies specifically performed with E 472f were available. However, the Panel considered that the results of the studies described above for E 472e are also relevant for E 472f.

Overall, the available data indicated that E 472a, E 472b, E 472e and E 472f have a low acute oral toxicity.

3.6.3. Short-term and subchronic toxicity

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Groups of 10 male weanling rats of the Holtzman strain were fed diets containing 25% of stearin, olein, diacetostearin or diacetoolein, respectively (equivalent to 20,250 mg/kg bw per day), and additional groups were dosed with 50% oil (75/25 mixture of hydrogenated soybean oil with cottonseed oil) or diacetin of the oil (equivalent to 40,500 mg/kg bw per day) for 8 weeks or with 15% oil or monoacetin of the oil (equivalent to 10,150 mg/kg bw per day) for 12 weeks (Mattson et al., 1956). No modification of body weight gain or food consumption was observed. Blood chemistry and urine analysis were similar across all groups.

In a 14-week study, five weanling female albino rats were fed a diet containing 0, 5, 10 or 20% of acetostearin (equivalent to 0, 4,550, 9,100, 18,200 mg/kg bw per day) (Ambrose and Robbins, 1956b). Body weights and food consumption were recorded weekly. At termination, all rats were autopsied. There were no effects on growth, food intake and mortality. At necropsy, no gross post-mortem changes were observed.

Groups of 10 male albino rats were fed diets during 20 weeks to 0 or 30% (equivalent to 33,500 mg/kg bw per day) of two different commercial acetostearin (Coleman et al., 1963). The dose tested induced a decrease in body weight gain compared with rats fed with normal diet. The retarded growth and poor survival of acetostearin-fed animals is considered by the authors as an antagonism of the acetostearins to essential fatty acid utilisation.

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

No studies were available.

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

In a 10-day study, groups of 10 male and 10 female Sprague-Dawley rats were fed a calorie-restricted basal diet (Huntingdon Research Centre, 1966 (Documentation provided to EFSA n. 12)). The dietary levels for citric acid esters of mono- and diglycerides were 0, 23.1 or 37.5% (equivalent to 20,790 and 33,750 mg/kg bw per day). After 10 days, all rats were killed and samples of depot fat were removed. The following organs were weighed: kidneys, liver, gonads and thyroid gland. Histopathological examination included the liver, kidneys, heart, spleen, gonads, brain thyroid and GI tract. Apart from a dystrophic lower nephron calcification in animals of both sexes of the high-dose group, no other adverse findings were reported.

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

No studies were available to the Panel.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

In a study performed in compliance with good laboratory practice (GLP), groups of five male Han Wistar rats were fed 0, 3 or 10% E 472e (equivalent to 0, 3,540 or 11,800 mg/kg bw per day) for 2 weeks (Reynolds and Britton (1999 (Documentation provided to EFSA n. 24)) In addition, groups of five male rats received Dimodan PM (a distilled monoglyceride of fatty acids) in order to obtain diets with comparable caloric values. Over the complete treatment period, all groups to which E 472e was administered in the diet, showed a lower body weight gain compared to the one with the diet containing monoglycerides of fatty acids. For effects of E 472e on the diet palatability, diets containing 30% freeze-dried paste with 10% E 472e, 30% freeze-dried paste with 10% acid neutralised E 472e, 30% bread without any E 472e and 30% bread with 10% acid neutralised E 472e were also administrated to groups of five male rats. Over the complete treatment period, rats dosed with 30% freeze-dried paste containing 10% E 472e, 30% freeze-dried paste containing 10 % acid neutralised E 472e or 30% bread containing 10% acid neutralised E 472e had lower body weight gain compared with control rats or rats dosed with 30% bread without E 472e. The Panel considered that reduced food consumption was due to diet palatability which likely gave rise to lower body weight gain. The haematological examination gave no indications for adverse effects caused by feeding the different diets.

Four groups of two dogs (3 years old; sex not specified) were fed diets containing 0, 5, 10 or 20 % E 472e (equivalent to 1,500, 3,000 and 6,000 mg/kg bw). After a 3-month feeding period, 1 dog in

each group was sacrificed. No adverse effects attributable to the test substance were observed. Gross and macroscopic examination of livers and kidneys in all dogs gave no evidence for adverse effects (Koppanyi and Dardin, 1950 (Documentation provided to EFSA n. 16)).

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

No studies specifically performed with E 472f were available. However, the Panel considered that the results of the studies described above for E 472e are also relevant for E 472f.

Overall, from the limited available data with E 472a,b,c,e, no significant adverse effects were noted, except kidney effects at very high doses (33,750 mg/kg bw per day) in a study with citric acid esters of mono- and diglycerides in rats.

3.6.4. Genotoxicity

In vitro *studies*

E 472e was tested in a bacterial reverse mutation assay with the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 in compliance with GLP. Two separate trials were performed using the plate incorporation method both with and without metabolic activation. In the first experiment, two different concentrations of S9 fraction (10% and 30%) were used, while in the second experiment, only 10% S9 fraction was employed. In a preliminary test, no toxicity was observed at concentrations of up to 5,000 μg/plate and so for the main study dose levels of 50–5,000 μg/plate were used. The results of this study gave no indications for a mutagenic activity at any dose level neither with nor without metabolic activation (Jones, 1996 (Documentation provided to EFSA n. 15)). The study complies with the current OECD Guideline no. 471 with the exception that the tester strains S. typhimurium TA102 or *E. coli* WP2uvrA, bearing AT mutations were not used. However, the Panel noted that no oxidising or cross-linking activities are expected to occur and considered the negative results observed as reliable.

E 472e (DATEM 900339-2), was also tested in a chromosomal aberration assay with human lymphocytes in compliance with GLP. In the first trial, concentrations of 39.1–156.3 μg/mL (without S9-mix; 21 hour harvest) or 78.1–312.5 μg/mL (with S9-mix; 21 hour harvest) were selected for the metaphase analysis. In the second trial, concentrations of 117.2–234.4 μg/mL (without S9-mix; 21 hour harvest), 78.1–234.4 μg/mL (with S9-mix; 21-hour harvest) or 234.4 μg/mL (both with and without S9-mix; 45-hour harvest) were selected for the metaphase analysis. There was no statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations at any concentration when compared with the solvent control (tissue culture medium), while positive controls (mitomycin C or cyclophosphamide) caused large and statistically significant increases in the proportion of aberrant cells (Akhurst, 1996 (Documentation provided to EFSA n. 1)). The study essentially complies with the current OECD Guideline 473, with the exception that the short treatment (3–6 hours) in the absence of S9 metabolism was not performed and that 100 and not 150 metaphases were scored per individual culture. The Panel, therefore, considered that the reliability of the study was somewhat limited.

In silico *evaluations*

Acetic acid monoester of monopalmitin (representative for (E 472a)), lactic acid monoester of monopalmitin (representative for (E 472b)), citric acid monoester of monopalmitin (representative for (E 472c), tartaric acid monoester of monopalmitin (representative for (E 472d)) diacetyltartaric acid monoester of monopalmitin (representative for E 472e and E 472f), but also two other substances i) tartaric acid monoester of dipalmitin and ii) tartaric acid diester of monopalmitin (expected to be present in E 472d-f) were analysed for potential structural alerts for genotoxicity using the OECD (Q) SAR Toolbox (version 4.2-2, 2018). No structural alerts were found except an alert for 'Hacceptor-path3-Hacceptor' in the *in vivo* micronucleus test. However, the Panel considered this alert not relevant based on the consideration that 'Hacceptor-path3-Hacceptor' refers to non-covalent binding to DNA or proteins as a result of the presence of two bonded atoms connecting two hydrogen bond acceptors and its positive predictivity is quite low, ranging from 'none' (34%) to just 63% depending on the database, with a high incidence of false positives (Benigni et al., 2010, 2012).

Overall, *in vitro* genotoxicity studies were only available for E 472e. In these experiments, the compound did not show any genotoxic potential. In silico evaluation of substances representative of E 472a-f did not identify any relevant structural alert for genotoxicity. Therefore, the Panel considered that the food additives E 472a-f did not raise a concern with regard to genotoxicity.

3.6.5. Chronic toxicity and carcinogenicity

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

Groups of five weanling male albino rats were fed diets containing 0, 0.25, 0.5, 1, 2 or 4% acetostearin (equivalent to, 125, 250, 500, 1,000 and 2,000 mg/kg bw per day) and 0, 0.25, 0.5 or 1% acetoolein (equivalent to 112.5, 225 and 450 mg/kg bw per day) during 57 weeks (Ambrose and Robbins, 1956b). Mortality and growth rate in all treated groups was comparable to controls and no effects on organ weights, except for testes, were observed. According to the authors, no treatment-related gross or histopathological changes were observed in any organ investigated except for hypoplasia of the testes. Hypoplasia of the testes was observed in rats dosed with 0.25 and 0.5% acetostearin but not at the higher doses and with 0.25–1% acetoolein. Mild to moderate suppression of spermatogenesis was observed to varying degree in all dose groups as well as in the control group. Overall, it is difficult to interpretate the results of this study with regard to testicular effects due to the lack of dose response and apparent effect also in the control groups. Furthermore, in a more extensive study by the same authors (Ambrose et al., 1958a; see description below), acetooleines were found not to induce testicular effects at doses up to 10,000 mg/kg bw per day which further questions the validity of this study.

Groups of 10 male and 10 female weanling albino rats were fed diets containing 0, 5, 10 or 20% (approximately 0, 2,500, 5,000 and 10,000 mg/kg bw per day) of different acetostearins or acetooleins (fully acetylated acetostearin from hydrogenated lard (two different batches), partially acetylated acetostearin from hydrogenated lard, fully acetylated acetoolein from cottonseed oil or fully acetylated acetoolein from prime steamed edible lard) (Ambrose et al., 1958a). All rats exposed to the highest dose of acetoglycerides and an appropriate number of control rats were sacrificed at the end of 400 days, while rats of the two lowest doses of fully acetylated acetostearin from hydrogenated lard were sacrificed at 600 days. All surviving rats from the two lowest doses of the other acetoglycerides were sacrificed at around 709 days. In none of the different dose groups, an increased mortality rate was seen in the first 400 days. At the two lowest doses, most of the deaths occurred during the last 100 days of the 709-day test period. The highest dose induced a slight depression in body weights in male and female rats. The only organ weights consistently affected at the highest dose were those of the testes and liver from rats treated with two of the acetostearins, one of the fully acetylated acetostearin batches and the partially acetylated acetostearin. At the lower doses, only testes were affected. The liver effects seen at the highest dose which included fatty deposits was variable within the animals even in the same group and is probably due to fat storage phenomenon. Pathological examination of livers revealed no signs of any cellular damage.

The testes of rats exposed to one of fully acetylated batches and the partially acetylated acetostearin were significantly smaller compared to control rats or rats exposed to the acetoolein diets. A severe degree of testicular atrophy was present in rats exposed to the highest dose of fully acetylated acetostearin from hydrogenated lard or partially acetylated acetostearin for 400 days, and the same lesion was seen in animals exposed to the lowest doses of partially acetylated acetostearin from hydrogenated lard for 700 days. Well-developed testicular atrophy was observed in all animals exposed to the middle dose of fully acetylated acetostearin for 600 days, whereas the degree of atrophy was moderate in four of six animals of the lowest dose for 600 days. The testes of animals exposed to the second batch of the fully acetylated acetostearin or the fully acetylated acetooleins were not distinctly different from those of the controls. The testicular effects caused by the acetylated acetostearins resemble those caused by vitamin E deficiency and the authors suggested that the effects are due to an increased requirement for vitamin E.

Furthermore, there was some discolouration of the uteri in about 50% of the rats fed the acetostearin and one of the acetooleins.

Changes in kidneys such as focal deposits of basophilic material, presumably calcium, occurred especially in rats exposed to the highest dose of the acetylated acetostearins. In rats exposed to the acetylated acetooleins, essentially no calcification or scarring of the kidneys at any dose levels occurred. Changes in the female kidneys were most severe after exposure to fully acetylated acetostearin from hydrogenated lard, while the most prominent lesions in the male kidneys were seen after exposure to fully acetylated acetostearin or to partially acetylated acetostearin. Fatty tissue changes reminiscent of sclerema adiposum neonatorum (foci of foreign body reactions) especially near the gut were seen in many rats dosed with all acetostearins at the highest dose. The other organs of the dosed animals showed no changes.

The incidence of tumours was not higher in the experimental groups compared to controls.

Overall, acetylated acetostearins at doses of 10,000 mg/kg bw per day caused effects in the liver, kidney and fatty tissue. Acetostearins (one batch of fully acetylated acetostearin and partially acetylated acetostearin) at all doses induced testicular atrophy whereas the acetooleins did not. This effect was suggested by the authors to be due to an increased requirement for Vitamin E. The Panel noted limitations in the study design, composition of the test material (purity) and in the reporting of the results.

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

No studies were available to the Panel.

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

No studies were available to the Panel.

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d).

No studies were available to the Panel.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

Rats

In a 2-year study with rats, groups of eight male or eight female Wistar rats were fed diets containing 0, 5, 10 or 20% (equivalent to 2,500, 5,000 and 10,000 mg/kg bw per day) of diacetyltartaric esters of mixed mono- and diglycerides obtained from natural fats (Koppanyi and Dardin, 1950 (Documentation provided to EFSA n. 16)). Two additional groups of eight male or eight female rats were fed a diet containing 50% white bread ('bread control group') or 50% bread baked with 10% of test substance in terms of flour weight ('bread test group'). No adverse effects in survival rates, body weight, external appearance, behaviour, and liver or kidney weights were reported. Necropsy and histopathological examination of the major organs revealed no indications for adverse effects induced by test substance. In a follow-up study over 22 months with the second generation of rats, groups of eight male or eight female rats were exposed via diet to 0 or 20% test substance or with diets containing 50% white bread ('bread control group') or 50% bread baked with 10% of test substance in terms of flour weight ('bread test group'). Adverse effects were not described. The Panel did not consider this study for the hazard characterisation due to limitations including limited reporting.

Two long-term studies in rats were described by JECFA (Mosinger, 1965 and Kieckebusch et al., 1967 as referred to in JECFA, 2001) with low doses of mixed tartaric, acetic and fatty acid esters of glycerol. No adverse effects were attributed to the test substance.

In a combined chronic toxicity/carcinogenicity study performed according to OECD Guideline 453 and in compliance with GLP (Meyer, 1992 (Documentation provided to EFSA n. 20)), groups of 50 SPF Wistar rats (Mol:WIST) of both sexes were dosed via diet with 0, 3, 6 or 10% mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (equivalent to 0, 1,500, 3,000 and 5,000 mg/kg bw per day) for 2 years. A reference substance, Dimodan PM, a distilled monoglyceride of fatty acids, was included in diet for at dose levels of 0, 4, 7 and 10% in order to obtain diets with comparable caloric values. In addition, groups of 50 rats of both sexes were dosed with basal diet only. In males exposed to the two highest doses and in female exposed to the highest dose, a decrease in body weights was recorded. The Panel considered that this was likely due to decreased food consumption. A dose-related and statistically significant decrease in lymphocytes number and an increase in neutrophil count was significantly lower in weeks 12 and 52. In female rats exposed to the highest dose, similar changes were observed in week 25. The urine analysis showed a dose-dependent decrease in pH values both in male and female rats and the clinical biochemistry demonstrated a statistically significant and dose-related decrease in triglycerides in male rats. Male rats exposed to the highest dose for one year showed a statistically significant increase in absolute and relative adrenal weights and in relative kidney and spleen weights, while in female exposed at the same dose, an increase in the relative spleen weights was observed. A dose-dependent increase in adrenal medullary adenomas in males (statistically significant at 10%) and a statistically significantly higher incidence of focal medullary hyperplasia in all dosed male was observed. In females, a statistically significant increase in focal medullary hyperplasia was seen at the highest dose tested. In males exposed to the highest dose, a statistically significant increase in incidence of haemangiomas in the mesenteric lymph nodes, a statistically significant increase in sinus histiocytosis and haemorrhages in the mesenteric lymph nodes and in focal fibrosis in the heart was observed. Furthermore, a statistically significant higher incidence and degree of mineralisation in the

papilla and pelvis of the kidney were observed. In females, the highest dose induced a statistically significantly increase in incidence of endometrial hyperplasia.

According to a new assessment of the carcinogenicity part of the above study (Mitchell, 1999 (Documentation provided to EFSA n. 22)), females exposed to the highest dose showed a marked reduction in overall bodyweight gain when compared with basal diet controls and the absolute bodyweights for this group in weeks 91 and 104 were also lower than those of basal diet or Dimodan PM controls. Further changes occurring in rats exposed to the highest dose, particularly in females, were according to the authors attributed to a nutritional imbalance rather than to direct toxicity of the test substance. The minor inter-group differences in the incidences of changes in lymphocytes and neutrophils levels were not clearly attributable to the dosing with E 472e. Lymphocyte and neutrophil numbers were within normal ranges for rats of comparable age and strain and none of the differences was considered of toxicological significance by the authors. There was exacerbation of normal ageing changes in the kidneys of male rats related to dietary exposure to the highest dose, but this was not of toxicological significance according to the authors. In rats exposed to the highest dose, there was a slight increase in the incidence of benign adrenal medulla tumours (pheochromocytomas) when compared with Dimodan PM controls. However, this was considered by the authors as a rodent-specific finding and of no toxicological significance to humans. Moreover, the slightly increased incidence of haemangiomas in the mesenteric lymph nodes of males exposed to the highest dose was similarly not considered by the authors to be of toxicological relevance to humans. The authors identified an NOAEL of 6% (equivalent to 3,000 mg/kg bw per day).

The results of the original study (Meyer, 1992 (Documentation provided to EFSA n. 20)) were also evaluated by JECFA in 2004 (JECFA, 2004) based on the information provided on the reassessment of the histopathological data related to adrenal and cardiac lesions from the 2-year study (Mitchell, 1999 (Documentation provided to EFSA n. 22)). JECFA noted that higher incidences of these lesions were observed in all groups in the reassessment compared with the earlier analysis, with the exception of adrenal medullary tumours (designated as phaeochromocytomas) in male. JECFA also noted the incidence of adrenal medullary hyperplasia and adrenal medullary tumours in treated rats was not higher than in untreated controls. JECFA noted the reassessment indicated that exposure to E 472e over 2 years did not affect the incidence of myocardial fibrosis. There was an increased incidence of myocarditis in groups exposed to 10% Dimodan PM (distilled monoglycerides of fatty acids) or 10% E 472e (the highest dose tested) compared with untreated controls, which was considered to reflect an earlier step in the process leading to myocardial fibrosis. JECFA noted that no difference in the incidence of myocarditis was observed between the reference control group and the highest dose group and identified an NOAEL of 10% mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids in the diet (equivalent to 5,000 mg/kg bw per day). The Panel agreed with this conclusion.

In a 6-month study, the role of nutrients in the aetiology of the haematological changes seen in the combined toxicity and carcinogenicity study (Meyer, 1992 (Documentation provided to EFSA n. 20)) was investigated (Meyer, 1994 (Documentation provided to EFSA n. 21)). Wistar rats were assigned to groups of 20 animals. The diets were composed of natural ingredients, which were comparable to those used in the long-term study and contained 10% Dimodan PM as reference substance) as control, 10% E 472e or 10% E 472e supplemented with protein, magnesium, and vitamins B6 and B12. The effect on the circulating white blood cells in this 6-month study was less pronounced than that found in the long-term study (Meyer, 1992 (Documentation provided to EFSA n. 20)). The shift in circulating white blood cells showed a considerable variation, which appeared to be highly influenced by the diet. Therefore, the authors concluded that changing the type of diet resulted in a more pronounced effect on the white blood cells than did the inclusion of E 472e in the different diets.

Overall, long-term studies were available for E 472e. There was no evidence for carcinogenicity or any other substance-related gross or histopathological changes that are considered relevant for humans. An NOAEL of 5,000 mg/kg bw per day mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids, the highest dose tested, was identified.

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

No studies specifically performed with E 472f were available. However, the Panel considered that the results of the studies described above for E 472e are also relevant for E 472f.

3.6.6. Reproductive and developmental toxicity

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a)

In a study investigating effects of acetostearin (fully acetylated acetostearin from hydrogenated lard) on reproduction, a number of weanling male and female rats (not further specified) was dosed via diet with 0 or 10% of acetostearin (equivalent to 5,000 mg/kg bw per day) (Ambrose et al., 1958b). After 50 days, the rats on the acetostearin diets were divided into four groups of 5 males and 10 females each. One of the four groups was placed on unmodified acetostearin diet and the other three groups on acetostearin diets supplemented with either 200 mg vitamin E, 20 g of soybean oil or with 0.25 g of methylene blue. The male and female rats of each group were kept separate on their respective diets until 100 days of age at which time they were mated. All rats were then kept on their respective diets for approximately 7 months, during which time they were mated four times. Records were kept of the size of litters produced and the number of young weaned on each diet. A decreasing number of litters, total number of pups, and diminishing success in weaning were observed over four successive matings in the group fed diet containing 10% acetostearin. In females of this group, a brown discoloration of the uterus was observed. The addition of vitamin E to the acetostearin diet improved reproductive performance. This suggests that while analysis showed an amount of vitamin E comparable to that in the control diet, this amount was inadequate in the presence of a high concentration of acetostearin and that body stores of vitamin E were depleted in successive matings. The addition of soybean oil to the acetostearin diet practically eliminated reproduction. This observation is in concordance with the assumption that oxidation of the unsaturated fatty acids facilitates destruction of vitamin E and raises requirements for this vitamin. No brown discolorisation of the uteri and a restored reproductive performance was observed when methylene blue was added to the diet containing 10% acetostearin.

Overall, the data suggested that a diet containing 10% acetostearin and having a vitamin E content normally adequate for satisfactory reproductive performance failed primarily because of an increased vitamin E requirement. Moreover, the beneficial effect obtained by adding the antioxidant methylene blue to the acetostearin diet suggests that the acetostearin raised the vitamin E requirements.

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b)

No data available.

Citric acid esters of mono- and diglycerides of fatty acids (E 472c)

No data available.

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d)

No data available.

Mono- and diacetyltartaric acid esters of mono- and diglycerides of fatty acids (E 472e)

In a two-generation reproductive toxicity study performed according to OECD Guideline 416 and in compliance with GLP, groups of 30 male and 30 female young SPF Wistar rats (Mol:WIST) were dosed via diet with E 472e (DATEM) and/or the reference substance Dimodan PF (monoglycerides of fatty acids) used for obtaining diets of comparable caloric values (Hansen, 1995a (Documentation provided to EFSA n. 10)). The different groups were dosed as follows: a) 0% of E 472e and 0% of Dimodan PF (monoglycerides of fatty acids) (basic control group fed with IT chow 101), b) 0% of E 472e and 10% of Dimodan PF, c) 3% of E 472e and 7% of Dimodan PF, d) 6% of E 472e and 4% of Dimodan PF, or e) 10% of E 472e and 0% of Dimodan PF. The animals were dosed from 10 weeks before mating of the F_0-generation until section of the F_2-generation. Blood samples for a haematological examination were taken from 20 F_1 males (age of 26–27 weeks) dosed with 0 or 10% E 472e. In males of the F0-generation, the administration of 10% E 472e (equal to 5700 mg/kg bw per day) and to a minor degree with 6% E 472e (equal to 3300 mg/kg bw day) caused a decrease in body weight, body weight gain and food consumption especially during the last part of the premating period. These effects were not observed in the F0- and F1-females. The effects were considered weak by the authors. In the F0 generation, litter weight and litter weight gain was decreased in rats dosed with 6 or 10% E 472e on postnatal day (PND) 13 and 21 and in rats of the second generation dosed with 10% E 472e on PND 7, 13 and 21. Since food consumption was not mentioned during lactation period and effects of food consumption in the dams and later during lactation of the pups cannot be excluded. Apart from a

marginal increase in pups found dead from F_1 generation rats dosed with 10% E 472e, no other adverse effects on reproduction were found. During section and macroscopic examination of the males, females and pups no treatment-related abnormalities were found. As all data from this study indicated no adverse effects on reproduction, a final histological examination on reproductive organs was not done. There were no adverse effects on reproduction after administration in the diet of up to 10 % (equal to 5,700 mg/kg bw per day). The authors identified a no-observed effect level (NOEL) for parental and developmental toxicity of 3% (equal to 1,600–2,100 mg/kg bw per day).

E 472e (DATEM) was tested in a prenatal developmental toxicity study with rats performed according to OECD Guideline 414 and in compliance with GLP (Hansen, 1995b (Documentation provided to EFSA n. 11)). Groups of 23–25 female SPF Wistar rats (Mol:WIST) were administrated via diet with E 472e and/or the Dimodan PF. E 472e was given at dietary levels of 0, 3, 6 or 10% (equal to 0, 2,380, 4,530 and 8,060 mg/kg bw per day) from gestational day (GD) 6–15, while Dimodan PF was included in the diet at levels of 10, 7, 4 or 0%. Maternal body weight, body weight gain and food consumption were comparable in all groups. E 472e had no effect on fetal survival or the incidence of fetal skeletal and soft-tissue anomalies. The NOAEL both for maternal and developmental toxicity was 8,060 mg/kg bw per day, the highest dose tested.

Mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f)

No studies specifically performed with E 472f were available. However, the Panel considered that the results of the studies described above for E 472e are also relevant for E 472f.

Overall, in a multigeneration reproductive study rats were dosed via the diet with 0 or 10% acetostearin (E 472a) (equivalent to 5,000 mg/kg bw per day) (Ambrose et al., 1958b). The reproductive performance was progressively decreased over the generations when rats were administered 10% acetostearin. When vitamin E was added to the diet in addition to acetostearin, the reproductive performance improved compared with animals receiving acetostearin alone. E 472e was tested in a dietary two-generation reproductive toxicity in rats (Hansen, 1995a (Documentation provided to EFSA n. 10)). There were no adverse effects on reproduction after administration in the diet of up to 10 % (equal to 5,700 mg/kg bw per day). The NOEL for parental and developmental toxicity was 3% (equal to 1,600–2,100 mg/kg bw per day E 472e also was tested in a dietary prenatal developmental toxicity study in rats at dose levels of 0, 3, 6 or 10% (equal to 0, 2,380, 4,530 and 8,060 mg/kg bw per day) from GD 6–15 (Hansen, 1995b (Documentation provided to EFSA n. 11)). The NOAEL both for maternal and developmental toxicity was 10% E 472e (equal to 8,060 mg/kg bw day), the highest dose tested.

3.6.7. Other studies

Human studies

In the JECFA monograph (2015), it is reported that CITREM (synonym of E 472c) has been investigated in children (Vandenplas et al.,1993; Isolauri et al.,1995; Mabin et al.,1995; Verwimp et al., 1995; De Boissieu and Dupont, 2000, 2002; Giampietro et al., 2001; Niggemann et al., 2001; Evans et al., 2006; Clarke et al., 2007; Harvey et al., 2014).

Details on the recording of side effects (e.g. spontaneous reporting of the care-givers; 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 (Vandenplas et al.,1993; Isolauri et al., 1995; Verwimp et al., 1995; Giampietro et al., 2001; Niggemann et al., 2001; Harvey et al., 2014), 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.[17] 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 urticarial 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

[17] https://world.openfoodfacts.org/

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 JECFA (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.

Other studies on emulsifiers

In several recent studies, some other emulsifiers have been reported in mice to alter the gut microbiota, to promote gut inflammation, obesity and to impair glycaemic control (Swidsinski et al., 2009a,b; Renz et al., 2012; Merga et al., 2014; Cani and Everard, 2015; Chassaing et al., 2015, 2017; Romano-Keeler and Weitkamp, 2015; Lecomte et al., 2016; Nejrup et al., 2017; Holder and Chassaing, 2018; Jiang et al., 2018; Viennois and Chassaing, 2018; Marion-Letellier et al., 2019). No such data are available for the esters of mono- and diglycerides of fatty acids (E 472a-f).

3.7. Discussion

All the esters of mono- and diglycerides of fatty acids E 472a-f have been evaluated by the SCF (SCF, 1978, 1998b). Only for E 472e an ADI of 0–50 mg/kg bw has been allocated, while for the other substances, E 472a,b,c,d,f ADI 'not specified' was established (SCF, 1978). Regarding tartaric acid esters of mono- and diglycerides (E 472d), the ADI of 'not limited' 'was withdrawn at the JECFA fifty-seventh meeting (2001))'.

Depending on the starting materials for the manufacturing process of E 472a-f, potential toxic impurities such as glycidol, erucic acid or trans-fatty acids may be present in these food additives. Therefore, maximal levels for those impurities should be included in the specifications for E 472a-f.

Commission Regulation 231/2012 does not stipulate which isomer of tartaric acid should be used for the manufacturing process of the food additives E 472d,e,f, and, therefore, currently any isomer of tartaric acid can be used. The Panel considered that only L(+)-tartaric acid should be used in the manufacturing process of E 472d,e,f.

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, given the structure of these compounds, the Panel assumes 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. The Panel considered that E 472d would behave similar to E 472e. The hydrolysis products are known to be either readily metabolised or excreted intact. The hydrolysis products are all normal dietary constituents (considering that only L(+)-tartaric acid is used for the manufacturing process of E 472d,e,f) which are metabolised or excreted intact.

From the available data on acute toxicity with E 472a,b,e, the Panel considered that E 472a-f have very low acute oral toxicity.

There were only a limited number of short-term and subchronic toxicity studies with E 472a,b,c,e available. No significant adverse effects were noted, except some calcification of the kidneys at a dose of more than 30,000 mg/kg bw per day of citric acid esters of mono- and diglycerides (E 472c). Given the excessive concentration used (which will cause fatty acid overload etc.), the Panel considered this effect irrelevant.

Genotoxicity studies were only available for E 472e and only *in vitro*. In these experiments, the compound did not show any genotoxic potential. Furthermore, taking into account the information on structure–activity relationships from in silico evaluation of E 472a-f and the observation that fatty

acids, glycerol and tartaric acid do not raise concern with respect to genotoxicity, the Panel considered that E 472a-f are not of concern with regard to genotoxicity.

Long-term studies on chronic toxicity and carcinogenicity are available for E 472a in rats and E 472e in rats and dogs. There was no evidence of any relevant carcinogenic effects for any of the compounds. There were, however, substance-related gross and histopathological changes observed in studies with E 472a. Effects on liver (including fatty deposits), kidney and fatty tissue occurred only at a dose of 10,000 mg/kg bw per day acetostearin. These effects are most likely due to an overload of fatty acids resulting in effects on foreign body reactions in adipose tissues and on other cellular processes and overall homoeostasis. Such effects are likely to be irrelevant considering the levels of these compounds.

Testicular effects including testicular atrophy occurred at all doses (2,500, 5,000 and 10,000 mg/kg bw per day) of two out of three acetostearin batches tested. No effects, even at high doses, were observed with acetooleins. The effects on the testis closely resembled those seen after feeding rats vitamin E deficient diet (Woldemeskel, 2017; Zubair, 2017). The authors thus concluded that the acetostearin effects were due to an effect on vit E levels rather than a direct toxic effect. This hypothesis was supported by results from a multigeneration reproductive toxicity study performed by the same authors (Ambrose et al., 1958b). In this study, 5000 mg/kg per day acetostearin was shown to progressively decrease the reproductive performance over the generations. Addition of vitamin E to this diet improved the reproductive performance. This thus showed that the amount of vitamin E in the diet was inadequate in the presence of high concentrations of acetostearin and that body stores of vitamin E were depleted in successive matings. The mechanism of such an effect on vit. E depletion in the testis most likely involves lipid peroxidation. This is supported by the lack of effects of the acetooleines which contains mono unsaturated oleic acid not prone to peroxidation and by the fact that addition of soyabeen oil, which contains primarily polyunsaturated fatty acids and thus readily undergo peroxidation, to the acetostearin diet practically eliminated reproduction. Furthermore, addition of the antioxidant methylene blue to the actostearin diet prevented the brown discoloration of the uterus and restored reproductive performance. On the other hand, the fact that acetostearin contains stearic acid which is fully saturated and does not readily undergo peroxidation is not in concordance with this mechanism. The most plausible explanation for this discrepancy is that the acetostearin batches which caused the testicular effects also contained polyunsaturated fatty acids. It is also interesting to note that one of the acetostearin batches tested was without effect. Possibly this batch did not contain any poly unsaturated fatty acids. This apparent lack of control of the composition of the substances used in the studies of Ambrose et al. makes the evaluation and interpretation of the results difficult. The fact that testicular effects also could occur in control animals, inconsistency of results with acetooleins and use of diets with an apparent limited concentration of vitamin E further question the reliability of the results of studies from these authors. In addition, the testicular effects occurred at very high doses and have not been seen with other stearic acid esters. Furthermore, with a diet with adequate Vit E levels, testicular effects of this sort are unlikely to occur.

Overall the results from Ambrose et al. demonstrated that high concentrations of one batch of acetylated acetostearins with unknown composition could cause testicular effects resulting from depletion of vit. E. The Panel considered the studies unreliable and the results thus not relevant for risk assessment of acetic acid esters of mono and diglycerides of fatty acids used as food additive.

E 472e was tested in a dietary two-generation reproductive toxicity in rats (Hansen, 1995a (Documentation provided to EFSA n. 10)). There were no adverse effects on reproduction after administration in the diet of up to 10% of E 472e in the diet (equal to 5,700 mg/kg bw per day). The authors identified an NOEL for maternal and developmental effects of 3% E 472e in the diet (equal to 1,600 -2,100 mg/kg bw per day). The Panel noted that effects on maternal and pup body weights may be related to diet palatability and a decrease of food consumption during lactation of the pups. E 472e was also tested in a dietary prenatal developmental toxicity study in rats up to 10% of E 472e in the diet (equal to 8,060 mg/kg bw per day) and no adverse effects were observed (Hansen, 1995b (Documentation provided to EFSA n. 11)).

An extensive hydrolysis of E 472a-f is assumed to occur either in the GI tract or (pre-)systemically after absorption into their individual components resulting in acetic acid (from E 472a, E 472e and E 472f), lactic acid (from E 472b), citric acid (from E 472c) and tartaric acid (from E 472d,e and f), as well as to the relevant free fatty acids and glycerol. All these hydrolysis products are authorised as food additives. Glycerol (E 422) and fatty acids (E 570) were re-evaluated by the ANS Panel with the conclusion that there

were no safety concerns and no numerical ADIs were needed (EFSA ANS Panel, 2017a). Acetic acid[18] (E 260), lactic acid[19] (E 270) and citric acid[20] (E 330) will be re-evaluated by EFSA. However, an ADI 'non specified' was established by the SCF for these food additives (SCF, 1991). L(+)-tartaric acid (E334) has been re-evaluated by the FAF Panel and a group ADI of 240 mg/kg bw per day, expressed as tartaric acid, for L(+)-tartaric acid-tartrates (E334-337, 354) was established (EFSA FAF Panel, 2020).

The Panel considered that as there is no relevant adverse effects reported for E 472a,b,c and since none of their hydrolysis products raise any safety concerns, presently there is no need for a numerical ADI for E 472a,b,c.

The Panel noted that the group ADI of 240 mg/kg bw per day, expressed as tartaric acid, for L(+)-tartaric acid-tartrates (E334-337, 354) was established and this health-based guidance value should be considered for the risk assessment of food additives E 472d,e,f. Therefore, ADIs for E 472d,e,f were determined on the basis of the total amount of L(+)-tartaric acid released from the food additives and considering that only L(+)-tartaric acid and not DL- or D(-)-tartaric acid is used for the manufacturing of these food additives. According to the EU specifications, the total amount of L(+)-tartaric acid constitutes a maximum of 50% by weight for E 472d and 40% for E 472e,f. On the worst-case assumption that L(+)-tartaric acid is present at its maximum level in the food additives and all L(+)-tartaric acid would be released and considering the group ADI of 240 mg/kg bw per day for L(+)-tartaric acid-tartrates (E334-337, 354), an ADI of 480 mg/kg bw per day can be established for E 472d and an ADI of 600 mg/kg bw per day for E 472e,f.

The Panel noted that in Annex II of Regulation (EC) No 1333/2008 use levels of citric acid esters of mono- and diglycerides of fatty acids (E 472c) in food for infants under the age of 12 weeks are included in category 13.1.1 and 13.1.5.1. The Panel considered that these uses for infants under the age of 12 weeks would require a specific risk assessment in line with the recommendations given by JECFA (1978), the SCF (1998a) and EFSA (EFSA Scientific Committee, 2017). Therefore, the current re-evaluation of citric acid esters of mono- and diglycerides of fatty acids (E 472c) as a food additive is not applicable for infants under the age of 12 weeks.

The exposure to esters of glycerides of fatty acids (E 472a-f) was estimated according to different exposure scenarios. The exposure was estimated for all food additives individually, except for E 472e and f. The Panel performed an exposure assessment to these food additives considering the highest reported use levels for either E 472e or E 472f per food category, because E 472f is not markedly different from E 472e, when considering the description of their manufacturing processes and their composition. Furthermore, the Panel noted that these food additives are not likely to be used together in the same food according to information from Mintel's GNPD.

The Panel considered that the exposure to E 472a-f from their use as food additives according to Annex II was overestimated, given that all these additives are authorised as a Group I food additive and because of the conservative approach taken to address the uncertainties in the exposure assessment (Section 3.4.2). The Panel noted that food categories which may contain the food additives due to carry-over (Annex III) were not considered in the current exposure assessment. Furthermore, the Panel noted that no use levels were submitted for several authorised food categories with food products labelled to contain the additives according to Mintel's GNPD.

The Panel also noted that the refined exposure estimates are based on reported levels of use of these food additives. If actual practice changes, these refined estimates may no longer be representative and should be updated.

Considering that E 472d,e,f are expected to be hydrolysed and tartaric acid will be realised, the exposure to tartaric acid from the use of E 472d,e,f and other food additives from which tartaric acid is released is addressed in the Scientific Opinion on the re-evaluation of tartaric acid-tartrates (E 334-337, 354) (EFSA FAF Panel, 2020).

4. Conclusion

The Panel considered that:

- E 472a-f are extensively hydrolysed in the GI tract and/or (pre-)systemically after absorption into their individual hydrolysis products which are all normal dietary constituents and are metabolised or excreted intact.

[18] EFSA-Q-2011-00592.
[19] EFSA-Q-2011-00596.
[20] EFSA-Q-2011-00603.

- no adverse effects relevant for humans have been identified from the toxicological database available for E 472a-f.
- only L(+)-tartaric acid has to be used in the manufacturing process of E 472d,e,f.

and concluded that:

- for E 472a,b,c presently there is no need for a numerical ADI.
- an ADI of 480 mg/kg bw per day can be established for E 472d and an ADI of 600 mg/kg bw per day for E 472e,f based on the group ADI of 240 mg/kg bw per day, expressed as tartaric acid, for L(+)-tartaric acid-tartrates (E334-337, 354) and considering that the total amount of L(+)-tartaric acid constitutes a maximum of 50% by weight for E 472d and 40% for E 472e,f.
- considering the exposure estimates, there is no safety concern at their reported uses and use levels.

5. Recommendations

The Panel recommended that the European Commission:

- revises the EU specifications for E 472d,e,f by specifying that only L(+)-tartaric acid can be used in the manufacturing process
- setting lower limits for toxic elements (arsenic, lead, mercury and cadmium) in the EU specifications for E 472a,b,d,e,f in order to ensure that the food additives will not be a significant source of exposure to those toxic elements in food and includes maximum limits for mercury, arsenic and cadmium, in addition to lead, in EU specifications for E 472c.
- revises the EU specifications for E 472a-f 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 et al., 2017a).
- revises the EU specifications for E 472a-f 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 472a-f:
- revises the EU specifications for E 472a-f including maximum limits for glycidyl esters/glycidol and 3-MCPD esters, because it is likely that residues of those substances occur in the food additives E 472a-f, if they were present in the raw materials used in the manufacturing process of these food additives or formed during the manufacturing process.
- revises the EU specifications for E 472a-f 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 472a-f.
- includes maximum limits for oxalates in the EU specifications for E 472c,d,e,f, since oxalate can be present in citric acid and L(+)-tartaric acid that are used in manufacturing process of these food additives.
- considers to merge specifications of E 472e and 472f, since E 472f is not markedly different from E 472e, when considering the description of their manufacturing process and their composition.

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3) European Dairy Association (EDA) Data on usage levels 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) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 4), Published 12 October 2015. Submitted to EFSA on 30 May 2016.

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Abbreviations

ADME	absorption, distribution, metabolism, excretion
ADI	acceptable daily intake
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food

Bw	body weight
CAS	Chemical Abstracts Service
CONTAM	EFSA Panel on Contaminants
EDA	European Dairy Association
FAF	EFSA Panel on Food Additives and Flavourings
FC	food category
FCS	food categorisation system
FDE	Food Drink Europe
FSMP	food supplements and foods for special medical purposes
GC/FID	gas chromatography–flame ionisation detector
GD	gestational day
GI	gastrointestinal
GLP	good laboratory practice
GNPD	Global New Products Database
ICGA	International Chewing Gum Association
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KRÜGER	KRÜGER GmbH & Co.
LC–APCI-MS	atmospheric-pressure chemical ionisation mass spectrometry
LD_{50}	lethal dose, median
MPL	maximum permitted level
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PND	postnatal day
QS	*quantum satis*
SCF	Scientific Committee on Food
SNE	Specialised Nutrition Europe
SPF	specific pathogen-free
TDI	tolerable daily intake
TemaNord	is a publishing series for results of the often research-based work that working groups or projects under Nordic Council of Ministers have put in motion
TLC	Thin-layer chromatography
WHO	World Health Organization

Appendix A – Summary of the reported use levels (mg/kg) of E 472a-f provided by industry

Appendix B – Number and percentage of food products labelled with E 472a-f out of the total number of food products present in Mintel GNPD per food subcategory between 2012 and 2019

Appendix C – Concentration levels of acetic acid esters of mono- and diglycerides of fatty acids (E 472a) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix D – Concentration levels of lactic acid esters of mono- and diglycerides of fatty acids (E 472b) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix E – Concentration levels of citric acid esters of mono- and diglycerides of fatty acids (E 472c) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix F – Concentration levels of tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix G – Concentration levels of mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acid and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids E 472e and E 472f used in the refined exposure scenarios (mg/kg or mL/kg as appropriate)

Appendix H – Summary of total estimated exposure of acetic acid esters of mono- and diglycerides of fatty acids (E 472a) from their use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix I – Main food categories contributing to exposure to acetic acid esters of mono- and diglycerides of fatty acids (E 472a) using the maximum level exposure scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix J – Summary of total estimated exposure of lactic acid esters of mono- and diglycerides of fatty acids (E 472b) from their use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix K – Main food categories contributing to exposure to lactic acid esters of mono- and diglycerides of fatty acids (E 472b) using the maximum level exposure scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix L – Summary of total estimated exposure of citric acid esters of mono- and diglycerides of fatty acids (E 472c) from their use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix M – Main food categories contributing to exposure to citric acid esters of mono- and diglycerides of fatty acids (E 472c) using the maximum level exposure scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix N – Summary of total estimated exposure of tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) from their use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix O – Main food categories contributing to exposure to tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) using the maximum level exposure scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix P – Summary of total estimated exposure of (E 472e and f) from their use as a food additive for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix Q – Main food categories contributing to exposure to (E 472e and f) using the maximum level exposure scenario and the refined exposure assessment scenarios (> 5% to the total mean exposure)

Appendix R – Information on summarised data extracted from the Mintel's Global New Products Database

Acetic acid esters of mono- and diglycerides of fatty acids (E 472a) were labelled on 753 products in the indicated period, mostly in Gums (n = 59, 5.1% of all products in subcategory), Shelf stable desserts (n = 91, 3.2% of all products in subcategory), Frozen and chilled desserts (n = 30 and n = 151, 2.1% and 2.4% of all products in subcategory, respectively) and Baking Ingredients & Mixes (n = 169, 1.6% of all products in subcategory).

Lactic acid esters of mono- and diglycerides of fatty acids (E 472b) was labelled on 2,038 products in the indicated period, mostly in Chilled and Frozen desserts (n = 764 and n = 149, 12.1% and 10.5% of all products in subcategory respectively), Cakes, Pastries & Sweet Goods (n = 400, in 2.7% of all products in subcategory), Baking Ingredients & Mixes (n = 192, 1.9% of all products in subcategory) and Cream (n = 116, 7.3% of all products in sub-category).

Citric acid esters of mono- and diglycerides of fatty acids (E 472c) was labelled on 1,076 products in the indicated period, mainly in Meat Pastes & Pates and Meat Products (n = 216 and n = 70, 7.2% and 0.3% of all products in subcategory), Margarine and other blends (n = 47, 4.21% of all products in subcategory) and Cakes, Pastries & Sweet Goods and Baking Ingredients & Mixes (n = 81 and n = 63, 0.5% and 0.6% of all products in sub-category). It was also labelled on 35 Baby Formula (0–6 months) and 11 Baby Formula (6-12 months) products (9.75% and 3.8% of the corresponding subcategory).

Tartaric acid esters of mono- and diglycerides of fatty acids (E 472d) was labelled on only 57 products in the indicated period with 11 products in subcategory Bread & Bread Products and 28 products in subcategory Cakes, Pastries & Sweet Goods (which means 0.1–0.2% of all products in the corresponding subcategory).

Mono- and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids (E 472e) and mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472f) are both referred to 'Diacetyltartaric and Fatty Acid Esters of Glycerol' in the Mintel's GNPD. E 472e or f was labelled on 5,333 products, where the most important subcategories were Bread and bread products (n = 1,715, 14.8% of all products in subcategory), Cakes, Pastries & Sweet Goods (n = 870, 5.8% of all products in subcategory) and Sandwiches/Wraps (n = 630, 27.1% of all products in subcategory).

Appendix S – Description of the studies with formula which contain E 472c in unknown quantities

Details of the studies with formula which contain E 472c in unknown quantities are presented in Table S.1.

Table S.1: Detailed description of the studies with formula which contain E 472c in unknown quantities

Reference	No. of children	Age	Diagnoses	Aim-Endpoints	Product tested	Duration	Results
Giampietro et al. (2001)	32	Range 11–129 months; median: 29 months	Atopic dermatitis 29 Urticaria 3	Hypoallergenicity of an extensive whey protein hydrolysate (Nutrilon Pepti) and tolerance	Extensive hydrolysate whey formula Nutrilon Pepti, vs. Profylac (extensive) and Nan HA (partial) whey hydrolysate products	1 week	Allergenic reaction: Cow's milk 32/32 (100%) Nutrilon Pepti 1/31 (3%) Profylac (e) 2/26 (8%) Nan HA (p) 9/25 (36%), no side effects
Harvey et al. (2014) (Study 1)	115	3–16 weeks	Healthy	Weight, length and head circumference Stool characteristics and gastrointestinal and tolerance	Neocate Infant DHA vs. Neo-Syn	16 weeks	45 subjects (39.1%) withdrew due to the occurrence of an adverse event (n = 22) comparable results in growth parameters and tolerance in both groups. Minimal differences in stool characteristics and GI symptoms
Harvey et al. (2014) (Study 2)	30	Birth to 3 years	CMA	Hypoallergenicity and tolerance	Neosyn Infant DHA vs. placebo	1 week	At least 90% of children with CMA no reaction to Neo-Syn (95% confidence) no side effects

Reference	No. of children	Age	Diagnoses	Aim-Endpoints	Product tested	Duration	Results
Isolauri et al. (1995)	22 vs. 23	4–8 months	Atopic disease, CMA	Antigenicity, nutritional adequacy, and growth-promoting efficacy of protein hydrolysate or amino acid-derived formulas in infants and tolerance	Extensively hydrolysed whey formula vs. formula composed of individual amino acids	9 months	Comparable results in growth parameters and tolerance in both groups
Niggemann et al. (2001)	73	1.5–9 months, median 5.7 months	CMA	Growth and clinical symptoms (SCORAD-test) and tolerance	Extensively hydrolysed cow's milk formulae vs. amino-acid-based formulae	6 months	Comparable results in growth parameters and tolerance in both groups
Vandenplas et al. (1993)	20 vs. 25	Newborn	Healthy	Growth and tolerance	Nutrilon (whey predominant formula) vs. Nutrilon Pepti (100% hydrolysed whey)	13 weeks	Comparable results in growth parameters and tolerance in both groups
Verwimp et al. (1995)	275 vs. 280	2–17 weeks	CMA	Growth and tolerance	Nutrilon Pepti vs. Pepti junior (50% fat from medium chain triglycerides)	10 weeks	Comparable results in growth parameters and tolerance in both groups

CMA: cow's milk allergy.