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SCIENTIFIC OPINION

Scientific Opinion on the re-evaluation of tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308) and δ-tocopherol (E 309) as food additives[1]

EFSA Panel on Food additives and Nutrient Sources added to Food (ANS)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Additives and Nutrient Sources added to Food provides a scientific opinion re-evaluating the safety of tocopherol-rich extract of natural origin (E 306), synthetic α-tocopherol (*all-rac*-α-tocopherol; dl-α-tocopherol; E 307), synthetic γ-tocopherol (dl-γ-tocopherol; E 308) and synthetic δ-tocopherol (E 309). The European Union's Scientific Committee on Food did not set an Acceptable Daily Intake (ADI), but derived a Tolerable Upper Intake Level (UL) for vitamin E of 300 mg/day for adults. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived an ADI of 0.15–2 mg/kg body weight (bw)/day for dl-α-tocopherol. The acute oral toxicity of tocopherols is low. In both a 13-week and a chronic (16-month) oral toxicity study, the No Observed Adverse Effect Level (NOAEL) was 125 mg/kg bw/day. The critical adverse effect is prolonged coagulation time. There is no concern that tocopherols are genotoxic or carcinogenic. There are insufficient data to address the reproduction and developmental toxicity. The Panel concluded that the available data are too limited to establish an ADI for the tocopherols. However, taking into account that vitamin E is widely consumed via human food, it is an essential nutrient and that the ULs are not exceeded in any population group, except in children in one survey from only one country, α-tocopherol, for the reported uses and use levels as a food additive, is not considered to be of safety concern. The Panel considered that the dataset on tocopherol-rich extract, and γ- and δ-tocopherol was too limited to be included in the safety assessment of tocopherols. Moreover, the Panel is aware that much lower concentration levels and fewer uses for γ- and δ-tocopherol are reported in food than for α-tocopherol. Therefore, the Panel concluded that tocopherols (E 306–E 309) are not of safety concern at the levels used in food.

KEY WORDS

[1] On request from the European Commission, Question No EFSA-Q-2011-00475-00478, adopted on 9 September 2015.

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[3] Acknowledgement: The Panel wishes to thank the members of the former Working Group 'B' Food Additives and Nutrient Sources (2011–2014) and the members of the Standing Working Group on the re-evaluation of food colours: Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Maria Jose Frutos, Pierre Galtier, David Gott, Claude Lambré, Jean-Charles Leblanc, Agneta Oskarsson, Jeanne Stadler, Paul Tobback, Ine Waalkens-Berendsen and Rudolf Antonius Woutersen, for the preparatory work on this scientific opinion and EFSA staff members Petra Gergelova, Ana Maria Rincon and Stavroula Tasiopoulou for the support provided to this scientific opinion. The ANS Panel wishes to acknowledge all European competent institutions, Member State bodies and other organisations that provided data for this scientific output.

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tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308), δ-tocopherol (E 309), food antioxidant, vitamin E

SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) was asked to provide a scientific opinion re-evaluating the safety of tocopherol-rich extract of natural origin (E 306), synthetic α-tocopherol (*all-rac*-α-tocopherol; dl-α-tocopherol; E 307), synthetic γ-tocopherol (dl-γ-tocopherol; E 308) and synthetic δ-tocopherol (E 309), which are used as antioxidants in foods to inhibit the peroxidation of fats and lipids.

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that has become available since then and data provided following a public call for data. The Panel noted that not all of the original studies on which the previous evaluations were based were available for re-evaluation by the Panel.

Tocopherols belong to the group of substances named vitamin E. Vitamin E is the collective term for a family of structurally related substances, namely tocopherol- and tocotrienol-derivatives, that exhibit, qualitatively, the biological activity of the naturally occurring d-α-tocopherol. Vitamin E is an essential vitamin and is naturally present in plant-derived foods, particularly fruit and vegetables.

All tocopherols evaluated in this opinion are used as antioxidants in food, either individually or in combination, and are authorised under Annex II of Regulation (EC) No 1333/2008 on food additives.

The Scientific Committee on Food (SCF) has not set an Acceptable Daily Intake (ADI) for tocopherols, but considered the use of tocopherols as antioxidants in food acceptable. The SCF, in its evaluation of vitamins and minerals, established a Tolerable Upper Intake Level (UL) of 300 mg/day for vitamin E (SCF, 2003). Effects on blood clotting were used as the basis for deriving this UL of 300 mg/day for vitamin E. This UL also applies to pregnant and lactating women. The UL was scaled for children in the age ranges 1–3, 4–6, 7–10, 11–14 and 15–17 years to give ULs of 100, 120, 160, 220 and 260 mg/day, respectively.

The current ADI for α-tocopherol, established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), is 0.15–2 mg/kg body weight (bw)/day. The JECFA ADI is based on clinical experience in humans and takes into account the fact that α-tocopherol is an essential nutrient.

Specifications for tocopherol-rich extract of natural origin (E 306) and synthetic α-tocopherol (E 307) have been defined in Commission Regulation (EU) No 231/2012 and by JECFA. Specifications for synthetic γ-tocopherol (E 308) and synthetic δ-tocopherol (E 309) have been defined in only Commission Regulation (EU) No 231/2012.

Tocopherols are relatively stable in foods, but oxidation may occur when exposed to air, heat, acids, alkalis or metal ions. During storage, when peroxyl radicals are formed in oils or in the presence of unsaturated fatty acids, α-tocopherol reacts with these radicals, leading to the formation of tocopheroxyl radicals that further react with other peroxyl radicals to form non-radical products (Burton and Traber, 1990). The non-radical oxidation products of vitamin E have been identified as α-tocopheryl quinone, epoxy-alpha-tocopherylquinones and 8a-(lipid-dioxy)-alpha-tocopherones (Yamauchi et al., 2002). A decrease in tocopherol content occurs during food processing as a result of oxidation or thermal degradation depending on the processing procedures, storage time, conditions and type of food. In sunflower oil heated to 180 °C, α-tocopherol reacts partly to produce oxidation and degradation products, such as α-tocopheryl quinone and α-tocopheryl fatty acids (Kreps et al., 2015).

Based on toxicokinetics data for α-, γ- and δ-tocopherol and tocopherol-rich extract, α-tocopherol is the most biologically active and is, therefore, the form that is most often used in toxicity testing. For the purpose of this opinion, it is assumed that α-tocopherol is representative of the other tocopherols as a worst case, based on the fact that this form of vitamin E is the only form that the liver can re-secrete into the plasma, hence maintaining plasma concentrations and prolonging time in the plasma before

elimination. In testing α-tocopherol, it is likely that the most conservative No Observed Adverse Effect Level (NOAEL) is determined. Therefore, results from toxicity studies on α-tocopherol are assumed to also apply to γ-tocopherol, δ-tocopherol and tocopherol-rich extract.

Absorption of the tocopherols varies with dose, and the efficiency of absorption decreases with increasing intake. Absorption across the gastrointestinal tract occurs along with dietary lipids and is dependent on biliary secretion of bile acids and salts, which aid the emulsification process, to form micelles with the hydrolysed fat. The micelles containing the vitamin E are then absorbed by passive diffusion at the brush border enterocytes of the small intestine. Once absorbed, the tocopherols enter the blood and lymphatics in chylomicrons, and are transported to the tissues. The liver appears to select α-tocopherol using α-tocopherol transport protein, whereas most ingested γ- and δ-tocopherol are eliminated by the liver into the bile and excreted in the faeces.

The acute oral toxicity of α-tocopherol is very low, with LD_{50} values for α-tocopherol reported to be greater than 2 000 mg/kg bw/day for rats.

The critical effects on haematology (blood clotting) and clinical chemistry (total cholesterol, total lipids and phospholipids) are not expected to vary qualitatively among the various forms of tocopherols, i.e. prolonged coagulation times are common to all tocopherols and are thought to be due to reduced absorption of vitamin K from the gastrointestinal tract, as supplementation with vitamin K prevents the effects of the tocopherols on blood clotting. The NOAEL for this critical effect observed in a 13-week oral (gavage) toxicity study in rats was 125 mg/kg bw/day.

Studies in humans give conflicting results with respect to the potential of vitamin E to affect the incidence of cardiovascular disease and subsequent mortality. It appears that, as was observed in animal studies, the principal adverse effect of the tocopherols is on prothrombin times and factors related to blood clotting, via an interaction with vitamin K or vitamin K-dependent proteins. However, it does appear that in humans this effect is only observed at high doses, which are not relevant to the use of tocopherols as food additives. Susceptible subgroups appear to be individuals with already compromised blood clotting capacity, and those with low vitamin K status. Although not all studies are consistent, it appears that while cardiovascular disease is not affected by vitamin E in healthy individuals, it has the potential to reduce primary cardiovascular outcomes, such as stroke, in patients with existing cardiovascular disease.

There is no evidence to suggest that α-tocopherol is genotoxic. Well-conducted genotoxicity studies (three Ames tests, an *in vitro* chromosomal aberration test and an *in vivo* mutagenicity study), available through the public call for data, were all negative. There are no *in vitro* mammalian cell gene mutation studies. However, there are *in vitro* and *in vivo* studies that support the antioxidant properties of vitamin E being protective against genetic damage.

In a chronic toxicity study in rats (duration of up to 16 months), a NOAEL of 125 mg/kg bw/day was determined, based on reduced body weight and increased heart and spleen weight.

One limited carcinogenicity study has been performed in rats. A NOAEL for general systemic toxicity of α-tocopherol could not be established in this study due to the effects on blood clotting and the liver. The NOAEL for carcinogenicity was > 2 000 mg/kg bw/day, the highest dose tested. The Panel concluded that there is no concern that α-tocopherol is carcinogenic.

There are insufficient studies to address the reproduction and developmental endpoints, as there are no multigeneration studies conducted in accordance with appropriate test guidelines.

Reported use levels from industry give information on the amount of the food additive added to food. The use of these data results in an estimate of the exposure to α-tocopherol (E 307) at the moment the food was produced. Considering that tocopherols are degraded during processing and storage, the loss of tocopherols in food is very likely to have an impact on the overall exposure estimates calculated

using the reported use levels. Therefore, the Panel calculated additional exposure estimates for the additive itself, including potential loss factors, intended to more closely reflect the exposure to α-tocopherol (E 307) via foods as consumed.

The total exposure to α-tocopherol from all food sources (food additives, enzyme preparations, nutrient as vitamin and from natural sources) would reach up to 6.3 mg/kg bw/day in toddlers at the high level (with the exception of children in one survey from one country, achieving up to 9.7 mg/kg bw/day). From the use of α-tocopherol (E 307) as a food additive itself, the exposure (non-brand loyal scenario, considering loss factors) would range from 0.3 mg/kg bw/day in infants to 2.7 mg/kg bw/day in toddlers at the mean and from 0.9 mg/kg bw/day in adolescents to 5.9 mg/kg bw/day in toddlers at the high level.

The Panel estimated that, when comparing all sources (i.e. from the additive itself, from natural sources and from all food sources), the contribution of α-tocopherol (E 307) from its use as a food additive may represent, on average, approximately 71 % (range 59–80 %) of the overall exposure to α-tocopherol, and around a two- to five-fold higher intake than from natural sources, with the exception of infants whose intake from the use of α-tocopherol (E 307) as a food additive is likely to be 0.9-fold that of the intake from natural sources.

The Panel considered that the uncertainties identified would tend overestimate the actual exposure to α-tocopherol (E 307) as a food additive, particularly for the maximum level scenario, and to underestimate the actual exposure to α-tocopherol from all sources in European countries.

Taking into account that:

- vitamin E is widely consumed via human food;
- it is an essential nutrient;
- there is no indication of genotoxic or carcinogenic potential;
- animal and human studies available have not shown adverse effects, except effects on blood clotting at high levels;
- the exposure to α-tocopherol resulting from all food sources does not exceed the ULs for vitamin E (SCF, 2003) in any population group, except in children in one survey from only one country,

the Panel considered that α-tocopherol (E 307) at the reported uses and use levels as a food additive is not of safety concern.

The Panel noted that the exceedance of the UL observed in children in one survey from one country may be a result of different methodologies used among dietary surveys for reporting the amounts of food supplements consumed.

The Panel considered that the database on γ- and δ-tocopherol was too limited to be included in the safety assessment of tocopherols. However, the Panel is aware that much lower concentration levels and fewer uses for γ- and δ-tocopherols are reported in food than for α-tocopherol. The Panel considered that data on α-tocopherol can be read-across to the other tocopherols, based on the similarities in the chemical structure, and the fact that α-tocopherol represents a worst case, as it is the form which the body selectively retains. The Panel noted that it would be prudent to re-assess the appropriateness of this read-across as new data on γ- and δ-tocopherols become available. Therefore, the Panel considered that, overall, the use of tocopherols (E 306–E 309) as food additives would not be of safety concern at the levels used in food.

The Panel noted that in Annex II of Regulation (EC) No 1333/2008, use levels of tocopherols (E 306–E 309) in food for infants under the age of 12 weeks are included in categories 13.1.1, 13.1.5.1 and 13.1.5.2. The Panel considered that these uses would require a specific risk assessment in line with the recommendations given by JECFA (1978) and the SCF (1998) and endorsed by the Panel. Therefore, the current re-evaluation of tocopherols (E 306–E 309) as food additives is not considered to be applicable to infants under the age of 12 weeks. The Panel concluded that the current re-evaluation of tocopherols (E 306–E 309) as food additives is not applicable to infants under the age of 12 weeks.

The Panel recommended that the maximum limits for the impurities of toxic elements (arsenic, lead and mercury) in the EC specifications for tocopherols should be revised in order to ensure that tocopherols (E 306–E 309) as food additives will not be a significant source of exposure to these toxic elements in food.

The Panel recommended re-assessing the appropriateness of the read-across from α-tocopherol to the other tocopherols as new data on γ- and δ-tocopherols become available.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1333/2008[4] 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[5]. 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[6] of 2001. The report "Food additives in Europe 2000[7]" 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 Reference are replaced by those below.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Commission asks the European Food Safety Authority 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.

INTERPRETATION OF THE TERMS OF REFERENCE

The 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. According to the definition above, the ADI as established for the general population does not apply to infants below 12 weeks of age (JECFA, 1978; SCF, 1998). In this context, the re-evaluation of the use of food additives in food for infants below 12 weeks of age represents a special case for which specific recommendations were given by the Joint FAO/WHO

[4] 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, p. 16.

[5] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up the 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, 26.03.2010, p. 19.

[6] Report from the Commission on Dietary Food Additive Intake in the European Union, Brussels, 01.10.2001, COM (2001) 542 final.

[7] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers. TemaNord 2002:560.

Expert Committee on Food Additives (JECFA) (JECFA, 1972, 1978) and by the SCF (SCF, 1996, 1998). The Panel endorsed these recommendations.

The Panel noted that in Annex II of Regulation (EC) No 1333/2008, use levels of tocopherols (E 306–E 309) in food for infants under the age of 12 weeks are included in categories 13.1.1, 13.1.5.1 and 13.1.5.2. The Panel considered that these uses would require a specific risk assessment in line with the recommendations given by JECFA (1978) and the SCF (1998), and endorsed by the Panel (EFSA ANS Panel, 2012). Therefore, the current re-evaluation of tocopherols (E 306–E 309) as food additives is not considered applicable for infants under the age of 12 weeks.

ASSESSMENT

1. Introduction

The present opinion deals with the re-evaluation of the safety of tocopherol-rich extract of natural origin (E 306), synthetic α-tocopherol (*all-rac*-α-tocopherol; dl-α-tocopherol; E 307), synthetic γ-tocopherol (dl-γ-tocopherol; E 308) and synthetic δ-tocopherol (E 309), which are used as antioxidants in foods to inhibit the peroxidation of fats and lipids. These tocopherols are authorised as food additives under Annex II of Regulation (EC) No 1333/2008[8] on food additives.

The food additives E 306, E 307, E 308 and E 309 belong to a family of structurally related chemical substances bearing the collective term vitamin E, which comprises all tocopherol- and tocotrienol-derivatives that exhibit, qualitatively, the biological activity of naturally occurring d-α-tocopherol.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived an Acceptable Daily Intake (ADI) for dl-α-tocopherol of 0.15–2 mg/kg body weight (bw) based on clinical experience in humans (JECFA, 1987). The Scientific Committee on Food (SCF) concluded that the use of α-, β-, γ- and δ-tocopherols and α-tocopheryl acetate as antioxidants was acceptable, but considered that the available data were not appropriate for establishing an ADI (SCF, 1989). Later, the SCF (2003) did not set an ADI, but considered the available data and derived a Tolerable Upper Intake Level (UL) of 300 mg/day for vitamin E for adults, with scaling for children of various ages.

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that has become available since then and data provided following public calls for data[9,10]. The Panel noted that not all of the original studies on which the previous evaluations were based were available for the present re-evaluation.

2. Technical data

2.1. Identity of the substances

Tocopherols belong to the group of substances named vitamin E. All tocopherols evaluated in this opinion are used as antioxidants in food, either individually or in combination.

According to the International Union of Pure and Applied Chemistry (IUPAC): "*The term vitamin E should be used as the generic descriptor for all tocol and tocotrienol derivatives exhibiting qualitatively the biological activity of α-tocopherol. The term tocol is the trivial designation for 2-methyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol). The term tocopherol(s) should be used as a generic descriptor for all mono, di, and trimethyltocols*" (IUPAC–IUB, 1981).

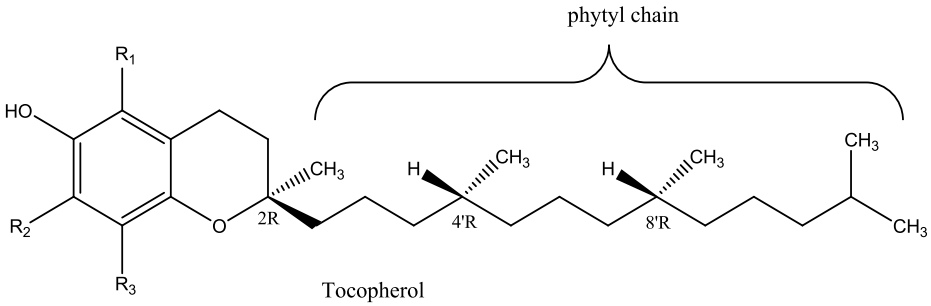
Vitamin E occurs naturally as eight different substances: four tocopherols (d-α-, d-β-, d-γ- and d-δ-tocopherol) and four tocotrienols (d-α-, d-β-, d-γ- and d-δ-tocotrienol). The molecular formulae of these compounds have in common a polar chromanol ring. In the case of tocopherols, it is linked to a phytyl chain, and in the case of tocotrienols it is linked to an isoprenoid chain. The structure of the natural tocotrienols differs from that of the tocopherols by the presence of three *trans* double bonds in the hydrocarbon chain. In addition, α, β, γ and δ species of both tocopherols and tocotrienols differ with regard to the number and position of the methyl groups on the chromanol ring.

[8] 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, p. 16.

[9] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of preservatives and antioxidants. Published: 23 November 2009. http://www.efsa.europa.eu/en/dataclosed/call/ans091123a.pdf

[10] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published 27 March 2013. http://www.efsa.europa.eu/en/dataclosed/call/130327.htm

Tocopherols have three chiral centres at positions 2, 4′ and 8′. Thus, for each tocopherol, eight stereoisomers exist. The natural tocopherols possess the stereochemical configuration 2*R*, 4′*R*, 8′*R* (Figure 1).



Compound	R_1	R_2	R_3	Stereochemical configuration
d-α-tocopherol	CH_3	CH_3	CH_3	2*R*, 4′*R*, 8′*R*
d-β-tocopherol	CH_3	H	CH_3	2*R*, 4′*R*, 8′*R*
d-γ-tocopherol	H	CH_3	CH_3	2*R*, 4′*R*, 8′*R*
d-δ-tocopherol	H	H	CH_3	2*R*, 4′*R*, 8′*R*

Figure 1: Structural formulae of the natural tocopherols

Information on the identity of the tocopherols authorised as food additives is presented in Table 1.

Table 1: General information on the tocopherols used as food additives (E 306–E 309)

Food additive	Synonyms	EINECS number	CAS Registry Number [(a)]	Name according to CAS number [(b)]
E 306 "Tocopherol-rich extract" [(c)]	–	–	–	–
E 307 "*alpha*-Tocopherol"	dl-*α*-Tocopherol; (all *rac*)-*α*-tocopherol [(d)]	233-466-0	10191-1-0	(±)-*α*-Tocopherol; dl-*α*-tocopherol; *all-rac-α*-tocopherol
E 308 "*gamma*-Tocopherol"	dl-*γ*-tocopherol	231-523-4	7616-22-0	(±)-*γ*-Tocopherol; dl-*γ*-tocopherol; *all-rac-γ*-tocopherol
E 309 "*delta*-Tocopherol"	–	204-299-0	119-13-1	d-δ-Tocopherol; (*R*,*R*,*R*)-δ-tocopherol

(a): Corresponding to the EINECS numbers (EC Inventory, online) indicated in Commission Regulation (EU) No 231/2012.
(b): From SciFinder.
(c): According to Commission Regulation (EU) No 231/2012, tocopherol-rich extract (E 306) contains tocopherols, such as d-*α*-, d-*β*-, d-*γ*- and d-*δ*-tocopherols, and tocotrienols.
(d): The composition of E 307, as defined in Regulation 231/2012 "(all *rac*)-*α*-tocopherol" means a mixture, not necessarily equimolecular, of all four possible racemates (i.e. of all the four pairs of enantiomers) (IUPAC-IUB, 1981). EINECS (EC) number and CAS Registry Number correspond with this definition.
CAS, Chemical Abstract Service; EINECS, European Inventory of Existing Commercial chemical Substances.

2.1.1. Tocopherol-rich extract (E 306)

Tocopherol-rich extract (E 306) is defined in Commission Regulation (EU) No 231/2012[11] as a "*product obtained by the vacuum steam distillation of edible vegetable oil products, comprising concentrated tocopherols and tocotrienols*". It contains tocopherols such as d-α, d-β-, d-γ- and d-δ-tocopherols.

The Panel noted that JECFA (JECFA, 2006) uses a very similar definition for a tocopherol preparation named "Tocopherol Concentrate, mixed (INS No 307b)". This preparation is defined by JECFA as "*a form of Vitamin E obtained by the vacuum steam distillation of edible vegetable oil products, comprising concentrated tocopherols. It may contain an edible vegetable oil added to adjust the required amount of total tocopherols, and the tocopherol forms may be adjusted by suitable physical and chemical means.*" JECFA stated that no single Chemical Abstract Service (CAS) Registry Number applies to this substance.

The Panel noted that, in 2007, JECFA (JECFA, 2007) used the following definition for both "d-alpha-tocopherol, concentrate (E 307)" and "d-alpha-tocopherol, concentrate (INS No 307a)" (i.e. 5,7,8-trimethyltocol): "*a form of Vitamin E obtained by the vacuum steam distillation of edible vegetable oil products, comprising a concentrated form of d-alpha-tocopherol. It may contain an edible vegetable oil added to adjust the required amount of total tocopherols, and the content of d-alpha-tocopherol may be adjusted by suitable physical and chemical means*".

However, the Panel noted that according to European Commission specifications (Commission Regulation (EU) No 231/2012), E 306 must contain not less than 34 % w/w of total tocopherols. The accompanying matrix can be assumed to contain tocotrienols, triglycerides, free fatty acids and other low-volatile substances present in the original edible vegetable oil product. No clear information on the composition of the accompanying matrix was provided to the Panel.

2.1.2. α-Tocopherol (E 307)

According to Commission Regulation (EU) No 231/2012, α-tocopherol (E 307) (synonym: dl-α-tocopherol) is defined by the chemical names DL-5,7,8-trimethyltocol and DL-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol. Its chemical formula is $C_{29}H_{50}O_2$ and its molecular weight is 430.7 g/mol. The European Inventory of Existing Commercial Chemical Substances (EINECS) number (EC number) is 233-466-0; this corresponds to the CAS Registry Number 10191-41-0. The CAS database provides the following name: 2*H*-1-benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-.

According to general definitions in the literature, *all-rac*-α-tocopherol is a totally synthetic α-tocopherol and is a mixture (not necessarily equimolar) of all the four possible pairs of enantiomers (i.e. four racemates) (Hoffmann-Ostenhof, 1974).

Several synonyms are found in the literature, among others: *all-rac*-α-tocopherol, DL-α-tocopherol and dl-α-tocopherol.

dl-α-Tocopherol is practically insoluble in water, freely soluble in acetone, anhydrous ethanol, methylene chloride and fatty oils. dl-α-Tocopherol is described as a clear, odourless, or yellowish-brown, viscous oily liquid (PhEur 8.4 (European Pharmacopoeia, 2015)). The calculated value for the pK_a (predicted) is 11.40 ± 0.40 (SciFinder).

[11] 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. 1–295.

2.1.3. γ-Tocopherol (E 308)

According to Commission Regulation (EU) No 231/2012, γ-tocopherol (E 308) (synonym: dl-γ-tocopherol) is defined by the chemical name 2,7,8-trimethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol. It has the molecular formula $C_{28}H_{48}O_2$ and a molecular weight of 416.7 g/mol. The EINECS number is 231-523-4, that corresponds to the CAS Registry Number 7616-22-0. The CAS database provides the following name: 2*H*-1-benzopyran-6-ol, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-.

Several synonyms are found in the literature, among others, *all-rac*-**γ**-tocopherol and dl-**γ**-tocopherol.

γ-Tocopherol is insoluble in water, freely soluble in ethanol and miscible with ether. It is described as a clear, viscous, pale yellowish oil which oxidises and darkens on exposure to air or light (Commission Regulation (EU) No 231/2012).

2.1.4. δ-Tocopherol (E 309)

According to Commission Regulation (EU) No 231/2012, δ-Tocopherol (E 309) is defined by the chemical name 2,8-dimethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol. It has the molecular formula $C_{27}H_{46}O_2$ and a molecular weight of 402.7 g/mol. The EINECS number is 204-299-0, that corresponds to the CAS Registry Number 119-13-1. The Panel noted that this CAS Registry Number corresponds to (2*R*,4′*R*,8′*R*)-δ-tocopherol, which is the natural δ-tocopherol. The CAS database provides the following name: 2*H*-1-benzopyran-6-ol, 3,4-dihydro-2,8-dimethyl-2-[(4*R*,8*R*)–4,8,12-trimethyltridecyl].

Synonyms used for δ-tocopherol (E 309) are (+)-δ-tocopherol, (*R*,*R*,*R*)-δ-tocopherol, D-δ-tocopherol and d-δ-tocopherol.

δ-Tocopherol is insoluble in water, but is very soluble in ethanol, ether, acetone and chloroform. It is described as a clear, viscous, pale yellowish or orange oil which oxidises and darkens on exposure to air or light (Commission Regulation (EU) No 231/2012).

2.2. Specifications

Specifications for tocopherols have been defined in Commission Regulation (EU) No 231/2012 and by JECFA (JECFA, 2006a,b, 2007).

2.2.1. Tocopherol-rich extract (E 306), "Tocopherol concentrate, mixed (INS 307b)" and "d-α-tocopherol, concentrate (INS 307a)"

The specifications for tocopherol-rich extract (E 306), as defined in Commission Regulation (EU) No 231/2012, and for "Tocopherol concentrate, mixed (INS No 307b)", as defined by JECFA (JECFA, 2006a), and "d-α-tocopherol, concentrate (INS 307a)", as defined by JECFA (JECFA, 2007), are presented in Table 2.

Table 2: Specifications for tocopherol-rich extract (E 306) according to Commission Regulation (EU) No 231/2012, and for "Tocopherol concentrate, mixed (INS 307b)" and "d-α-tocopherol, concentrate (INS No 307a)" according to JECFA

	Commission Regulation (EU) No 231/2012	JECFA (2006a)	JECFA (2007)
Assay	Content not less than 34 % of total tocopherols	Not less than 34 % of total tocopherols	Not less than 40 % of total tocopherols, of which not less than 95 % consists of d-α-tocopherol

	Commission Regulation (EU) No 231/2012	JECFA (2006a)	JECFA (2007)
Description	Brownish-red to red, clear, viscous oil having a mild, characteristic odour and taste. May show a slight separation of wax-like constituents in microcrystalline form	Brownish-red to red, clear, viscous oil having a mild, characteristic odour; may show a slight separation of wax-like constituents in microcrystalline form. It oxidises and darkens slowly in air and on exposure to light, particularly when in alkaline media	Brownish-red to light yellow, nearly odourless, clear viscous oil, which oxidises and darkens slowly in air and on exposure to light

	Commission Regulation (EU) No 231/2012	JECFA (2006a)	JECFA (2007)
Identification			
By suitable gas liquid chromatographic method		The retention time of the third major peak (i.e. the peak occurring just before that of the internal standard) in the chromatogram of the assay preparation is the same as that of the standard procedure, both relative to the internal standard, as obtained in the assay	The retention time of the major peak in the chromatogram of the sample solution is the same as that of the standard solution, both relative to the internal standard, as obtained in the assay
Specific rotation	$[\alpha]_D^{20}$ not less than +20 °	[alpha] 25, D: not less than +20 °	alpha (25, D): not less than +24 °
Solubility tests	Insoluble in water; soluble in ethanol; miscible in ether	Insoluble in water; soluble in ethanol; miscible in ether	Insoluble in water; soluble in ethanol; miscible with ether
Colour reaction		Dissolve approximately 0.05 g of the sample in 10 mL of absolute ethanol. Add, with swirling, 2 mL of nitric acid and heat at approximately 75 °C for 15 minutes. A bright red to orange colour develops	Dissolve about 0.05 g of the sample in 10 mL of absolute ethanol. Add, with swirling, 2 mL of nitric acid and heat at about 75 °C for 15 min. A bright red to orange colour develops
Purity			
Sulphated ash	Not more than 0.1 %	Not more than 0.1 %	
Arsenic	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		
Acidity		Dissolve 1 g of the substance in 25 mL of a mixture of equal volumes of ethanol and ether that has been neutralised to phenolphthalein TS with 0.1 N sodium hydroxide, add 0.5 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds. Not more than 1.0 mL of 0.1 N sodium hydroxide is required	Dissolve 1 g of the sample in 25 mL of a mixture of equal volumes of ethanol and ether that has been neutralised to phenolphthalein TS with 0.1 N sodium hydroxide, add 0.5 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds. Not more than 1.0 mL of 0.1 N sodium hydroxide is required

2.2.2. α-Tocopherol (E 307)

The specifications for α-tocopherol (E 307), according to Commission Regulation (EU) No 231/2012, and dl-α-tocopherol, concentrate (INS (International Numbering System) 307c), according to JECFA (JECFA, 2006b), are presented in Table 3.

Table 3: Specifications for α-tocopherol (E 307) according to Commission Regulation (EU) No 231/2012 and dl-α-tocopherol (INS 307c) according to JECFA

	Commission Regulation (EU) No 231/2012 [(a)]	**JECFA (2006b)** [(a)]
Assay	Content not less than 96 %	Not less than 96 % and not more than 102 %
Description	Slightly yellow to amber, nearly odourless, clear, viscous oil which oxidises and darkens on exposure to air or light	Slightly yellow to amber, nearly odourless, clear, viscous oil; it oxidises and darkens in air and on exposure to light
Identification		
Solubility tests	Insoluble in water, freely soluble in ethanol, miscible in ether	Insoluble in water, freely soluble in ethanol, miscible with ether
Spectrophotometry	In absolute ethanol, the maximum absorption is at about 292 nm	In absolute ethanol the maximum absorption is about 292 nm
Specific rotation	$[\alpha]_D^{25}$ 0 ± 0.05 ° (1 in 10 solution in chloroform)	$[\alpha]_D^{20}$ 0 ± 0.05 ° (1 in 10 solution in chloroform)
Colour reaction		Dissolve about 0.01 g of the sample in 10 mL of absolute ethanol. Add, with swirling, 2 mL of nitric acid and heat at about 75 °C for 15 minutes. A bright red to orange colour develops
Purity		
Refractive index	$[n]_D^{20}$ 1.503–1.507	n (20, D) 1.503–1.507
Specific absorption in ethanol	$E^{1\%}_{1cm}$ (292 nm) 72–76 (0.01 g in 200 mL of absolute ethanol)	$E^{1\%}_{1cm}$ (292 nm) 71–76 (0.01 g in 200 mL of absolute ethanol)
Sulphated ash	Not more than 0.1 %	Not more than 0.1 %
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Acidity		Dissolve 1 g of the sample in 25 mL of a mixture of equal volumes of ethanol and ether that has been neutralised to phenolphthalein TS with 0.1 N sodium hydroxide, add 0.5 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds. Not more than 1.0 mL of 0.1 N sodium hydroxide is required.

(a): According to Commission Regulation (EU) No 231/2012 and JECFA, the specific absorption is measured by preparing a sample of 0.01 g in 200 mL (which would be ≈ 0.05 %); however, in the specific absorption it is indicated as 1 % ($E^{1\%}_{1cm}$).

The Panel noted that in the monograph (PhEur 8.4) on *all-rac*-α-tocopherol in the European Pharmacopoeia, limitations for further impurities, which may occur as by-products of the manufacturing process, are indicated (Bracher et al., 2014; European Pharmacopoeia, 2015). The maximum levels should not exceed 0.5 % for *all-rac-trans*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol, 1.5 % for *all-rac-cis*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol and 1.0 % for the sum of 4-methoxy-2,3,6-trimethyl-5-[(all-*RS*,*E*)-3,7,11,15-tetramethylhexadec-2-enyl]phenol and (all-*RS*,all-*E*)-2,6,10,14,19,23,27,31-octamethyldotriaconta-12,14,18-triene.

2.2.3. γ-Tocopherol (E 308)

The specifications for γ-tocopherol (E 308) according to Commission Regulation (EU) No 231/2012, are presented in Table 4.

Table 4: Specifications for γ-tocopherol (E 308) according to Commission Regulation (EU) No 231/2012

	Commission Regulation (EU) No 231/2012
Assay	Content not less than 97 %
Description	Clear, viscous, pale yellow oil which oxidises and darkens on exposure to air or light
Identification	
Spectrometry	Maximum absorptions in absolute ethanol at approximately 298 nm and 257 nm
Purity	
Specific absorption in ethanol	$E^{1\%}_{1cm}$ (298 nm) between 91 and 97 $E^{1\%}_{1cm}$ (257 nm) between 5.0 and 8.0
Refractive index	$[n]_D^{20}$ 1.503–1.507
Sulphated ash	Not more than 0.1 %
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

2.2.4. δ-Tocopherol (E 309)

The specifications for δ-tocopherol (E 309) according to Commission Regulation (EU) No 231/2012 are presented in Table 5.

Table 5: Specifications for δ-tocopherol (E 309) according to Commission Regulation (EU) No 231/2012

	Commission Regulation (EU) No 231/2012
Assay	Content not less than 97 %
Description	Clear, viscous, pale yellowish or orange oil which oxidises and darkens on exposure to air or light
Identification	
Spectrometry	Maximum absorptions in absolute ethanol at approximately 298 nm and 257 nm
Purity	
Specific absorption $E^{1\%}_{1cm}$ in ethanol	$E^{1\%}_{1cm}$ (298 nm) between 89 and 95 $E^{1\%}_{1cm}$ (257 nm) between 3.0 and 6.0
Refractive index	$[n]_D^{20}$ 1.500–1.504
Sulphated ash	Not more than 0.1 %
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg

The Panel noted that, according to the specifications, impurities of the toxic elements arsenic, lead and mercury are accepted up to a concentration of 3, 2 and 1 mg/kg, respectively, for tocopherol-rich extract (E 306), γ-tocopherol (E 308) and δ-tocopherol (E 309), while α-tocopherol (E 307) has a specification for lead only, which is accepted if not more than 2 mg/kg. Contamination at these levels could have a significant impact on the intake of these metals, for which the exposures are already close to the health-based guidance values established by EFSA (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009, 2010, 2012). The ANS Panel considered that the maximum limits for the impurities of toxic elements (arsenic, lead and mercury) in the EC specifications should be revised in order to ensure that tocopherols (E 306–E 309) as food additives will not be a significant source of exposure to these toxic elements in food.

2.3. Manufacturing process

Tocopherol-rich extract is manufactured by the vacuum steam distillation of edible vegetable oil products (JECFA, 2006a).

The most important commercial source of tocopherols comes from the processing of vegetable oils. The deodorising step in the oil processing involves distillation to remove free fatty acids, and the tocopherols are co-distilled with the fatty acids into the fatty acid distillate. A number of methods may then be used to extract the tocopherols from the distillate. These include esterification, saponification, distillation, chromatographic methods, liquid–liquid extraction, crystallisation, enzymatic methods and supercritical fluid extraction. These are used in various combinations, as alone, no method is sufficient. The first step is the removal of fatty components, which make up the major part of the distillate. This is usually achieved using esterification and saponification, followed by distillation. Non-saponifiable components can then be removed using chromatographic methods, crystallisation and molecular distillation. Individual components such as α-, γ- and δ-tocopherols can be isolated using chromatographic separation (Quek et al., 2007).

dl-α-Tocopherol (E 307) can be produced by the reaction of 2,3,5-trimethylhydroquinone and isophytol in the presence of tridecylamine and zinc chloride catalyst. The separated dl-α-tocopherol-containing phase is treated in an evaporator to remove traces of water under vacuum. The product is further purified by distillation.

2.4. Methods of analysis in food

Standard methods are available for the determination of individual tocopherols in edible fats and oils. The methods available have been reviewed by Cert et al. (2000). The most common methods utilise high performance liquid chromatography (HPLC) analysis with either ultraviolet (UV) or fluorescence detection and various standard methods are available, for example IUPAC method 2.432 (IUPAC, 1992), BVL (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) methods L 13.03/04-1 (BVL, 1987) and L 49.00-5 (BVL, 2006), and ISO (International Organization for Standardization) 9936:2006 (ISO, 2006). Analysis by HPLC, using normal-phase columns, allows good separation of α-, β-, γ- and δ-tocopherols, but analysis time is relatively long. Hewavitharana et al. (2004) employed a normal-phase silica column, with an initial pre-conditioning step to prevent irreversible binding. In the analysis of tocopherols from chicken meat, the lowest detectable levels were 0.73 ng (α-tocopherol) and 0.86 ng (γ-tocopherol). Reverse-phase columns have also been used and, although they have the advantage of shorter analysis times, they are not able to resolve β- and γ-tocopherol (Cert et al., 2000). Gliszczyńska-Swigło and Sikorska (2004) quoted detection limits for reverse-phase HPLC in edible plant oils of 8 ng/mL for γ-tocopherol, and of 28 ng/mL for α-tocopherol.

Analysis of tocopherols in fats and oils by capillary gas chromatography (GC) is also possible, but this normally involves warm saponification, thin layer chromatography (TLC) separation and derivitisation prior to analysis (Cert et al., 2000).

Several authors have described the use of a mass spectrometer as the detector following liquid chromatographic separation for the determination of tocopherols. Kalman et al. (2003) employed atmospheric pressure chemical ionisation mass spectroscopy in the analysis of α-tocopherol in infant foods, with a detection limit of 2.5 ng/mL. Lanina et al. (2007) used a similar approach in the analysis of the four tocopherols in sunflower oil and milk; the detection limits were 9 ng/mL for α-, 8 ng/mL for β- and 7.5 ng/mL for γ- and δ-tocopherols.

Supercritical fluid chromatography (SFC) is a more recently developed technique which has been used to separate the tocopherols from complex matrices for analysis. Choo et al. (2005) applied this method with a variable-wavelength UV detector to isolate minor components, including vitamin E forms, from crude palm oil and from the residual oil from palm-pressed fibre. Fratianni et al. (2002) compared supercritical fluid extraction using carbon dioxide with conventional extraction techniques for the

extraction of tocopherols from cereals, and found similar extraction yields and no significant selectivity between the different tocopherols.

2.5. Reaction and fate in food

Tocopherols act as antioxidants to inhibit the peroxidation of fats and lipids in food (EFSA, 2008). The tocopherols are relatively stable in foods; however, oxidation may occur when exposed to air, heat, acids, alkalis or metal ions (EFSA, 2008).

A number of authors have investigated the stability of tocopherols in foodstuffs over time. Rastrelli et al. (2002) investigated the degradation of α-tocopherol (and other components) in extra virgin olive oil under various storage conditions. Oil was stored in either dark or colourless bottles, which were completely filled or half-filled. The main changes found were in the half-filled bottles: α-tocopherol degraded by 20 % after 2 months and by 92 % after 12 months.

During storage, when peroxyl radicals are formed in oils or in the presence of unsaturated fatty acids, α-tocopherol reacts with these radicals, leading to the formation of tocopheroxyl radicals that further react with other peroxyl radicals to form non-radical products (Burton and Traber, 1990). The non-radical oxidation products of vitamin E have been identified as α-tocopheryl quinone, epoxy-alpha-tocopherylquinones and 8a-(lipid-dioxy)-alpha-tocopherones (Yamauchi et al., 2002).

The influence of drying and storage on the tocopherol content of rapeseed was investigated by Gawrysiak-Witulska et al. (2009). The levels of total tocopherol were determined after harvest and after drying. Drying at near-ambient temperatures resulted in a loss of 6–11 %, while drying with hot air led to a loss of 4–8 %. After storage for 12 months at 10 ± 2 °C, the concentration of tocopherols had further decreased by 23–30 %.

Capitani et al. (2011) studied the effect of temperature and storage time on the concentration of tocopherols in wheat germ oil. The level of total tocopherol decreased with time over 35 days, with no significant difference between the results at 27 °C and 45 °C. Both α- and γ-tocopherols showed the same pattern as total tocopherols, but for β-tocopherol the degradation rate increased with temperature.

Miquel et al. (2004) investigated the stability of tocopherols added to infant formula during storage. The α-, γ- and δ-tocopherols all decreased in concentration over time, with a loss of ≈50 % by the end of the 17-month storage period.

Steinhart and Rathjen (2003) investigated the effect of the method of preparation of hot meals on the stability of tocopherols. The tocopherols were added to the food through the margarines used. Although all preparation methods resulted in the loss of some tocopherols, in most cases this was less than 20 %. The roasting of meat resulted in a loss of nearly 70 % as a result of direct oxidation. A similar loss was seen with peas steamed in a metal container, but no losses were seen when this method was repeated in a glass container.

The decrease in the tocopherol content of foods is caused by oxidation or thermal degradation, depending on the processing procedures used, storage time, conditions and type of food. In sunflower oil heated to 180 °C, α-tocopherol reacts partly to produce oxidation and degradation products, such as α-tocopheryl quinone and α-tocopheryl fatty acids (Kreps et al., 2015). The changes in tocopherol values are summarised in Table 6 and expressed as the percentage of loss or the percentage of retention.

Table 6: Expected percentage of loss or retention of tocopherols during food processing or storage

Food group	Product	Treatment	Loss (%)	Retention (%)	References
Fats and oils	Corn oil	Deep fat frying		63.3	Simonne and Eitenmiller, 1998
	Soybean oil			11.8	
	Corn oil	Chemical refining	29.2		Ergönül and Köseoğlu, 2014
	Rapeseed oil		25		
	Sunflower oil	Microwave roasting		92	Yoshida and Kajimoto, 1989
	Olive oil	Storage (2 months)	20		Rastrelli et al., 2002
		Storage (12 months)	90		
Fruit and vegetables	Soybean seeds	Microwave processing	40		Yoshida and Kajimoto, 1989
	Beans	Cooking	13–28		Slupski and Lisiewska, 2012
		Storage (12 months)	13–53		
	Rapeseed	Storage (12 months)	23–30		Gawrysiak-Witulska et al., 2009
Food for infants	Infant milk	Storage (25 ºC, 30 ºC or 37 ºC)	40–50		García-Martínez et al., 2010
	Infant milk (powdered)	Storage (18 months, 40 ºC)	23–28		Chávez-Servín et al., 2008
	Infant formula	Storage (17 months)	50		Miquel et al., 2004
Other processed foods	Meat	Roasting	70		Steinhart and Rathjen, 2003
	Meat	Cooking	33–44		Bennink and Ono, 1982
	Rabbit meat	Boiling	39		Dal Bosco et al., 2001
		Frying	12		
		Roasting	14		

2.6. Case of need and proposed uses

Maximum Permitted Levels (MPLs) of tocopherols (E 306–E 309) have been defined in Annex II of Regulation (EC) No 1333/2008 on food additives for use in foods.

Tocopherols (E 306–E 309) are authorised antioxidants in the European Union at *quantum satis* (QS) levels in 68 food categories, at levels of 10–100 mg/kg in food for infants and young children (six food categories) and at a level of 200 mg/kg in fats and oils essentially free from water (only refined olive oils and only for E 307). Tocopherols are included in Group I of food additives.

Table 7 summarises foods that are permitted to contain tocopherols and the corresponding MPLs, as set by Annex II of Regulation (EC) No 1333/2008.

Table 7: MPLs of tocopherols (E 306–E 309) in foods and beverages according to Annex II of Regulation (EC) No 1333/2008

FCS category number	FCS food category	E number/ group	Restrictions/exceptions	Maximum level (mg/L or mg/kg as appropriate)
01.3	Unflavoured fermented milk products, heat-treated after fermentation	Group I		QS
01.4	Flavoured fermented milk products including heat-treated products	Group I		QS
01.6.3	Other creams	Group I		QS
01.7.1	Unripened cheese excluding products falling in category 16	Group I	Except mozzarella	QS
01.7.5	Processed cheese	Group I		QS
01.7.6	Cheese products (excluding products falling in category 16)	Group I		QS
01.8	Dairy analogues, including beverage whiteners	Group I		QS
02.1	Fats and oils essentially free from water (excluding anhydrous milkfat)	E 306–E 309	Except virgin oils and olive oils	QS
02.1	Fats and oils essentially free from water (excluding anhydrous milkfat)	E 307	Only refined olive oils, including olive pomace oil	200
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Group I		QS
02.3	Vegetable oil pan spray	Group I		QS
03	Edible ices	Group I		QS
04.2.1	Dried fruit and vegetables	Group I		QS
04.2.2	Fruit and vegetables in vinegar, oil, or brine	Group I		QS
04.2.4.1	Fruit and vegetable preparations excluding compote	Group I		QS
04.2.5.4	Nut butters and nut spreads	Group I		QS
04.2.6	Processed potato products	Group I		QS
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	Group I	Only energy-reduced or with no added sugar	QS
05.2	Other confectionery including breath-freshening microsweets	Group I		QS
05.3	Chewing gum	Group I		QS
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Group I		QS
06.2.2	Starches	Group I		QS
06.3	Breakfast cereals	Group I		QS
06.4.2	Dry pasta	Group I	Only gluten free and/or pasta intended for hypoproteic diets in accordance with Directive 2009/39/EC	QS
06.4.4	Potato gnocchi	Group I		QS
06.4.5	Fillings of stuffed pasta (ravioli and similar)	Group I		QS
06.5	Noodles	Group I		QS

FCS category number	FCS food category	E number/ group	Restrictions/exceptions	Maximum level (mg/L or mg/kg as appropriate)
06.6	Batters	Group I		QS
06.7	Pre-cooked or processed cereals	Group I		QS
07.1	Bread and rolls	Group I	Except products in 7.1.1 and 7.1.2	QS
07.2	Fine bakery wares	Group I		QS
08.3.1	Non-heat-treated meat products	Group I		QS
08.3.2	Heat-treated meat products	Group I	Except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*	QS
08.3.3	Casings and coatings and decorations for meat	Group I		QS
09.2	Processed fish and fishery products including molluscs and crustaceans	Group I		QS
09.3	Fish roe	Group I	Only processed fish roe	QS
10.2	Processed eggs and egg products	Group I		QS
11.2	Other sugars and syrups	Group I		QS
12.1.2	Salt substitutes	Group I		QS
12.2.2	Seasonings and condiments	Group I		QS
12.3	Vinegars	Group I		QS
12.4	Mustard	Group I		QS
12.5	Soups and broths	Group I		QS
12.6	Sauces	Group I		QS
12.7	Salads and savoury-based sandwich spreads	Group I		QS
12.8	Yeast and yeast products	Group I		QS
12.9	Protein products, excluding products covered in category 1.8	Group I		QS
13.1.1	Infant formulae as defined by Directive 2006/141/EC	E 306–E 309		10 [(a)]
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	E 306–E 309		10 [(a)]
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	E 306–E 309	Only fat-containing cereal-based foods including biscuits and rusks and baby foods	100 [(b)]
13.1.4	Other foods for young children	E 306–E 309		100 [(b)]
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	E 306–E 309		10 [(a)]
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	E 306–E 309		10 [(a)]
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	Group I		QS
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		QS

FCS category number	FCS food category	E number/ group	Restrictions/exceptions	Maximum level (mg/L or mg/kg as appropriate)
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	Group I	Including dry pasta	QS
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	Group I	Only vegetable juices	QS
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	Group I	Only vegetable nectars	QS
14.1.4	Flavoured drinks	Group I		QS
14.1.5.2	Other than coffee and coffee extracts	Group I	Excluding unflavoured leaf tea; including flavoured instant coffee	QS
14.2.3	Cider and perry	Group I		QS
14.2.4	Fruit wine and made wine	Group I		QS
14.2.5	Mead	Group I		QS
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Group I	Except whisky or whiskey	QS
14.2.7.1	Aromatised wines	Group I		QS
14.2.7.2	Aromatised wine-based drinks	Group I		QS
14.2.7.3	Aromatised wine-product cocktails	Group I		QS
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15 % alcohol	Group I		QS
15.1	Potato-, cereal-, flour- or starch-based snacks	Group I		QS
15.2	Processed nuts	Group I		QS
16	Desserts excluding products covered in categories 01, 03 and 04	Group I		QS
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	Group I		QS
17.2	Food supplements supplied in a liquid form	Group I		QS
17.3	Food supplements supplied in a syrup-type or chewable form	Group I		QS
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	Group I		QS

(a): E 306, E 307, E 308 and E 309 are authorised individually or in combination.
(b): E 304, E 306, E 307, E 308 and E 309 are authorised individually or in combination.
FCS, Food Categorisation System (food nomenclature) presented in Annex II of Regulation (EC) No 1333/2008.

In addition, tocopherols (E 306–E 309) are authorised, according to Annex III to Regulation (EC) No 1333/2008, for use as food additives in food enzyme preparations. Tocopherols are also authorised for use as food additives in nutrients at QS, except for nutrients intended to be used in foodstuffs for infants and young children, where tocopherols may be added in nutrient preparations under the condition that the maximum level in foods, mentioned in Annex II, Part E, point 13.1, is not exceeded (Table 7).

The Panel is aware that additional usages from the existing authorisation of tocopherols (E 306–E 309) as food additives in food enzyme preparations or as food additives in nutrients may add substantially to the overall exposure to tocopherols (E 306–E 309). The Panel noted that, from a methodological point of view, it was not feasible to differentiate between all contributions (i.e. uses as food additives in food, food enzyme preparations or nutrients) in the overall exposure to tocopherols (E 306–E 309). The Panel considered that the use of analytical data in the refined exposure assessment would be the most appropriate approach to capture all uses of tocopherols (E 306–E 309).

2.7. Reported use levels or data on analytical levels of tocopherols (E 306–E 309)

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. For those additives where no MPL is set and which are authorised at QS, information on actual use levels is required for performing an exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Regulation (EU) No 257/2010[12] regarding the re-evaluation of approved food additives, EFSA issued a public call[13] for scientific data on food additives, including present use and use patterns (i.e. which food categories and subcategories, proportion of food within categories/subcategories in which they are used, actual use levels (typical and maximum use levels), especially for those uses which are only limited by QS). Limited information had been provided by Mars (Mars Chocolate UK Ltd., 2010) and DSM Nutritional Products Ltd. (DSM, 2010).

In addition, a public call[14] for food additive usage levels and/or concentration data in food and beverages intended for human consumption was launched in March 2013, with a deadline in November 2013. Data on tocopherols (E 306–E 309), including present use and use patterns (i.e. which food categories and subcategories contain the additive, the proportion of foods within categories/subcategories in which it is used, and actual use levels (typical and maximum)), were requested from relevant stakeholders. European food manufacturers, national food authorities, research institutions, academics, food business operators and any other interested stakeholders were invited to submit usage and/or concentration data on tocopherols (E 306–E 309) in foods. The data submission to EFSA followed the requirements of the EFSA guidance on standard sample description for food and feed (EFSA, 2010a).

In response to this public call, updated information on the actual use levels of tocopherols (E 306–E 309) in food have been submitted by industry.

Analytical data were reported for α-tocopherol, γ-tocopherol and δ-tocopherol.

2.7.1. Summarised data on reported use levels in foods provided by industry

According to information provided in response to the EFSA call[13] for data launched in 2009, the level of use of dl-α-tocopherol in foods is variable depending on the properties and processing of the food. Typical use levels for fat-rich or highly processed products were reported to be between 100 and 2 000 mg/kg, or even higher (DSM, 2010). Typical and maximum levels of use of tocopherols (E 306–E 309) in chocolate and ice-cream were also provided (Mars Chocolate UK Ltd., 2010).

Following the call for food additive usage levels and/or concentration data launched in March 2013, updated information on the actual uses and use levels of tocopherols (E 306–E 309) was made available by the following interested parties: FoodDrinkEurope (FDE), Specialised Nutrition Europe

[12] Commission Regulation (EU) 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.

[13] Call for scientific data on food additives permitted in the EU and belonging to the functional classes of preservatives and antioxidants. Published 23 November 2009. http://www.efsa.europa.eu/en/dataclosed/call/ans091123a.htm

[14] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published 27 March 2013. http://www.efsa.europa.eu/en/dataclosed/call/130327.htm

(SNE), the International Chewing Gum Association (ICGA), Food Chemical Risk Analysis (FCRA) and the Association of the European Self-Medication Industry (AESGP).

Data (n = 114) on tocopherol-rich extract (E 306) were reported by FCRA (n = 70), FDE (n = 38), SNE (n = 5) and ICGA (n = 1). The data provided on tocopherol-rich extract (E 306) cover the majority of the food categories in which this food additive is authorised; most data were provided for soups and broths (Food Categorisation System (FCS) 12.5) and sauces (FCS 12.6). Data resulting from non-authorised uses (n = 3) were not considered in the exposure assessment. Values were reported on a whole-weight (50 %) or a fat-weight (50 %) basis; the latter were converted to values expressed on a whole-weight basis using data on fat content reported in the EFSA Comprehensive European Food Consumption Database.

Data (n = 179) on α-tocopherol (E 307) were reported by FDE (n = 96), FCRA (n = 70), SNE (n = 8), AESGP (n = 4) and ICGA (n = 1). The data provided on α-tocopherol (E 307) cover the majority of the food categories in which this food additive is authorised; most data were provided for edible ices (FCS 03), soups and broths (FCS 12.5) and sauces (FCS 12.6). Data resulting from non-authorised uses (n = 1) and from nutritional purpose uses (α-tocopherol not added for a technological purpose as a food additive) (n = 1) were not considered in the exposure assessment. In addition, one usage level with an insufficient description of the food product was also excluded. Values were reported on a whole-weight (64 %) or on a fat-weight (36 %) basis; the latter were converted to values expressed on a whole-weight basis using data on fat content reported in the EFSA Comprehensive European Food Consumption Database.

Limited usage data were reported for γ-tocopherol (E 308) (n = 3) and δ-tocopherol (E 309) (n = 3) for the following food categories: chewing gum (FCS 05.4), meat products (FCS 08.3) and flavoured drinks (FCS 14.1.4).

Appendices A and B provide data on the use levels of tocopherols (E 306–E 309) in foods, as reported by industry.

Overall, based on the information provided by industry, tocopherol-rich extract (E 306) and α-tocopherol (E 307) are the tocopherols most commonly used as food additives; their use is wide and covers several food categories. γ-Tocopherol (E 308) and δ-tocopherol (E 309) seem to have only limited uses.

2.7.2. Summarised data on concentration levels in foods submitted by Member States

Analytical results from Member States were collected through the EFSA call[14] for concentration data. The Panel noted that complete information on the methods of analysis was not made available to EFSA. However, all analytical results provided were from accredited laboratories and the majority of them were analysed by HPLC methods.

For α-tocopherol, a total number of 1 308 analytical results have been provided by two countries: Germany (n = 997) and Austria (n = 311). The data provided were mainly on food supplements (n = 420), followed by fats and oils essentially free from water (n = 266). Foods were sampled between 2004 and 2013. It should be noted that the sampling country was not always the same as the country of origin: in addition to data from European countries, the dataset also contained data originating from countries outside the EU (e.g. Sri Lanka, Thailand, Morocco, Algeria and the Russian Federation). Out of this dataset, α-tocopherol was not detected (< Limit of Detection (LOD)) in 123 samples and was not quantified (< Limit of Quantification (LOQ)) in nine samples. Data classified at insufficient level (n = 97) were not considered in the exposure assessment. In addition, 27 results were deemed as suspicious with regard to the quality of the analytical method used and were excluded from further analysis. Finally, 1 184 out of the 1 308 total analytical results reported for α-tocopherol in foods fulfilled the quality criteria and were included by the Panel in the exposure estimates.

For γ-tocopherol, a total number of 392 analytical results have been provided by one country only (Germany). However, these data originated from different countries, including countries outside Europe. The data provided were mainly on fats and oils and fine bakery wares. Foods were sampled between 2005 and 2013. Out of this dataset, γ-tocopherol was not detected (< LOD) in 20 samples and not quantified (< LOQ) in one sample. The dataset included two records classified at an insufficient level.

For δ-tocopherol, a total number of 336 analytical results have been provided by one country only (Germany). However, these data originated from different countries, including the countries outside Europe. The data provided were mainly on fats and oils and other confectionery products. Foods were sampled between 2005 and 2013. Out of this dataset, δ-tocopherol was not detected (< LOD) in 161 samples and not quantified (< LOQ) in 11 samples. The dataset included one record classified at an insufficient level.

Appendix C shows the analytical results in foods for α-tocopherol, γ-tocopherol and δ-tocopherol, as reported by Member States (the whole set of analytical data and the positive samples only are reported).

2.8. Information on existing authorisations and evaluations

An ADI of 0.15–2 mg/kg bw/day for α-tocopherol was allocated by JECFA in 1987 (JECFA, 1987). The SCF has not derived an ADI for vitamin E or any of the tocopherols, but established a UL of 300 mg/day for vitamin E in adults (SCF, 2003).

The safety of tocopherols used as food additives was initially evaluated by JECFA in 1961 and 1973 (JECFA, 1962, 1974). In 1961, JECFA provisionally estimated an ADI for humans of 0–2 mg/kg bw for α-tocopherol. In 1973, JECFA considered that "*though the toxicological studies are less than would normally be required for foreign substances used as food additives, it is considered that α-tocopherol is a nutrient*" and allocated an ADI of 0–2 mg/kg bw calculated as α-tocopherol, based on clinical experience in humans. The latest meeting of JECFA relevant to tocopherols took place in 1987 (JECFA, 1987). The Committee evaluated new data and amended the previously allocated ADI to 0.15–2 mg/kg bw/day, calculated as a group ADI for both dl-α-tocopherol and d-α-tocopherol, taking into account the fact that α-tocopherol is an essential nutrient (JECFA, 1987).

The SCF first evaluated tocopherols in 1989 (SCF, 1989), and concluded that the tocopherols can be regarded as toxicologically equivalent based on their chemical and biological similarities. The SCF opinion went on to state that "*the intake of tocopherols from natural sources will normally far exceed that from processed foods containing tocopherol as an antioxidant*" and that "*the use of tocopherol extract, α-, β-, γ- and δ-tocopherol as antioxidants in food was acceptable, but that it is not appropriate to establish an ADI*" (SCF, 1989). The SCF later reviewed vitamin E as a nutrient, but did not discuss ADIs (SCF, 1993). In the latest SCF evaluation (2003), effects on blood clotting and the study by Meydani et al. (1998), in which the No Observed Adverse Effect Level (NOAEL) was approximately 540 mg α-tocopherol equivalents (the highest dose tested in the study), were used as the basis for deriving an UL for vitamin E. Considering an uncertainty factor of two to cover for inter-individual differences in sensitivity, the SCF established an UL of 270 mg α-tocopherol equivalents for adults, which was rounded to 300 mg α-tocopherol equivalents (form not specified). This UL also applies to pregnant and lactating women. The UL was scaled for children in the age ranges 1–3, 4–6, 7–10, 11–14 and 15–17 years to give ULs of 100, 120, 160, 220 and 260 mg/day, respectively (SCF, 2003).

EFSA has not evaluated vitamin E or any of the tocopherols as food additives. For completeness, the most relevant of the opinions produced by other EFSA Panels are briefly summarised later in this section.

It is noted that the ANS Panel produced a scientific statement in response to the submission of eight scientific dossiers on vitamin E preparations, in which it concluded that "*it was not possible to assess*

the bioavailability of the tocopherols and tocotrienols from the various uncharacterised sources since no data on the bioavailability of the tocopherols and tocotrienols from these sources were provided. The Panel noted that it was not possible to assess the safety of the tocopherols and tocotrienols from the various uncharacterised sources since no data on the safety of these sources were provided" (EFSA, 2009).

The EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) produced an opinion on "mixed tocopherols, tocotrienol tocopherol and tocotrienols as sources for vitamin E added as a nutritional substance in food supplements" (EFSA, 2008). In this opinion, the AFC Panel concluded that mixed tocopherols (d-α-tocopherol, d-β-tocopherol, d-γ-tocopherol and d-δ-tocopherol) are not a safety concern at the proposed levels of use.

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) produced an opinion on the safety and efficacy of vitamin E in animal feed (EFSA FEEDAP Panel, 2010). Within this opinion, the FEEDAP Panel concluded that there is no concern regarding the safety of vitamin E for consumers of edible animal tissues or users of the animal feed. In 2012, the FEEDAP Panel adopted an opinion on the safety and efficacy of synthetic α-tocopherol for all animal species, and extended the conclusions drawn in its previous opinion on the safety of vitamin E (including dl-α-tocopheryl acetate) to dl-α-tocopherol. The FEEDAP Panel concluded that no concerns for user safety are expected from the use of dl-α-tocopherol in feed (EFSA FEEDAP Panel, 2012a). In addition, in 2012, the same Panel adopted an opinion on the safety and efficacy of tocopherol-rich extracts of natural origin, tocopherol-rich extracts of natural origin/delta rich, synthetic tocopherol for all animal species, concluding that no concern for user safety is expected from the use of tocopherol-rich extracts in feed (EFSA FEEDAP Panel, 2012b).

Two opinions from the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) were produced in 2005 and 2007 (EFSA, 2005, 2007a). These opinions discussed the allergenicity of tocopherol-rich extract, natural d-α tocopherol, natural d-α-tocopherol acetate and natural d-α tocopherol succinate derived specifically from soybean sources, as soy proteins can trigger allergic reactions. The Panel concluded that "*it is unlikely that natural mixed tocopherol/d-α tocopherols derived from soybean sources will trigger a severe allergic reaction in susceptible individuals*". In 2015, the NDA Panel adopted a scientific opinion on Dietary Reference Values for vitamin E as α-tocopherol (EFSA NDA Panel, 2015). Adequate Intakes (AIs), based on observed intakes in healthy populations with no apparent α-tocopherol deficiency, were defined, considering the range of average intakes of α-tocopherol and of α-tocopherol equivalents estimated from dietary surveys in children and adults in nine countries in the EU.

In a report published in 2002, TemaNord (TemaNord, 2002) concluded that it was unclear whether γ- and δ-tocopherols were commercially available, but that there was no need for an immediate re-evaluation of α-tocopherol and tocopherol-rich extract. It was also noted that the interaction of tocopherols with blood clotting required further investigation if exposure is significant ("significant" was not defined). The TemaNord report concluded that an exposure assessment was desirable, particularly as the current position of the SCF was that no ADI is required based on natural exposure to the tocopherols exceeding intake from food additives.

The UK's Expert Group on Vitamins and Minerals (EVM) established a NOAEL for humans (age not defined) of 540–970 mg d-α-tocopherol equivalents per day (EVM, 2003). An uncertainty factor to account for inter-individual differences was not considered necessary, as human study results (such as those of Meydani et al. (1998)) supported a NOAEL of 540 mg d-α-tocopherol equivalents per day; therefore, the safe upper limit was established as 540 mg d-α-tocopherol equivalents for supplemental vitamin E, which is equivalent to 9.0 mg/kg bw/day in a 60 kg adult (EVM, 2003).

The UL of any isomeric form of α-tocopherol is 1 000 mg/day, according to a review conducted by the USA's Institute of Medicine (IOM, 2000). This was based on a Lowest Observed Adverse Effect Level (LOAEL) of 500 mg/kg bw/day for dl-α-tocopherol (based on reduced blood clotting in the

study by Wheldon et al. (1983)), divided by an uncertainty factor of 36 (LOAEL to NOAEL = 2; subchronic to chronic intake = 2; intra-species variation = 3; inter-species variation = 3) and assuming a human body weight of 68.5 kg. The same UL for pregnant and lactating women was recommended. For infants (0–12 months), a UL was not determined, as it was considered that the only source of intake should be from food or formula. The recommended ULs for ages 1–3, 4–8, 9–13 and 14–18 years were 200, 300, 600 and 800 mg/day of any isomeric form of α-tocopherol, respectively (IOM, 2000).

Formulations of vitamin E (d-α-tocopherol, dl-α-tocopherol, d-α-tocopheryl acetate, dl-α-tocopheryl acetate and d-α-tocopheryl acid succinate) are also authorised for use in foods, under Regulation (EC) No 1925/2006[15] on the addition of vitamins and minerals and of certain other substances to foods, and in food supplements, according to Directive 2002/46/EC[16] relating to food supplements.

The Panel is aware that α-tocopherol has been evaluated by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers, which concluded that α-tocopherol in the form of α-tocopherol acetate does not pose a threat to the health of the consumer (SCCNFP, 2001).

2.9. Exposure assessment

2.9.1. Food consumption data used for exposure assessment

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database)[17] has been populated with data from national information 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 (EFSA, 2011a).

The food consumption data gathered by EFSA were collected using different methodologies and thus direct country-to-country comparison should be made with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced by subjects' possible under-reporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

For calculation of chronic exposure, intake statistics have been calculated based on individual average consumption over the total survey period, excluding surveys with only one day per subject. High-level consumption was only calculated for those foods and population groups where the sample size was sufficiently large to allow calculation of the 95th percentile (EFSA, 2011a). The Panel estimated chronic exposure for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Calculations were performed using individual body weights.

Thus, for the present assessment, food consumption data were available from 30 different dietary surveys carried out in 17 European countries, as mentioned in Table 8.

[15] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26.
[16] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51.
[17] Available online at http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Table 8: Population groups considered for the exposure estimates

Population	Age range	Countries with food consumption surveys covering more than one day
Infants [(a)]	From 4 up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers	From 12 up to and including 35 months of age	Belgium, Bulgaria, Finland, Germany, Netherlands, Italy, Spain
Children [(b)]	From 36 months up to and including 9 years of age	Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden
Adolescents	From 10 up to and including 17 years of age	Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Italy, Latvia, Spain, Sweden
Adults	From 18 up to and including 64 years of age	Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Spain, Sweden, UK
The elderly [(b)]	From 65 years of age and older	Belgium, Denmark, Finland, France, Germany, Hungary, Italy

(a): Only infants from 4 up to, and including, 11 months of age were considered for exposure assessment in relation to the ADI concept, which applies to only this range of age for infants (from 12 weeks onwards).
(b): The terms "children" and "the elderly" correspond, respectively, to "other children" and the merge of the "elderly" and the "very elderly" in the guidance of EFSA on the "Use of the EFSA Comprehensive European Food Consumption Database in exposure assessment" (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 FCS as presented in Annex II of Regulation (EC) No 1333/2008, Part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories and the exposure was calculated by multiplying maximum usage levels or values, reported in Appendix D and Appendix E for each food group, with the corresponding consumption amount per kg bw separately for each individual in the database. The exposure per food category was subsequently added to derive an individual total exposure per day. Finally, these exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. This was done for all individuals in the survey and per age group, resulting in distributions of individual average exposure per survey and population group (Table 8). Based on these distributions, the mean and 95th percentile exposures were calculated per survey for the total population and per population group.

2.9.1.1. α-Tocopherol selected for the exposure assessment of tocopherols (E 306–E 309)

The term tocopherols (E 306–E 309) has been used as the generic term for tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308) and δ-tocopherol (E 309). The Panel decided that only α-tocopherol would be considered for the exposure assessment performed in this opinion, as it is the predominant tocopherol used in the food industry, and in line with other authoritative bodies (IOM, 2000; Nordic Council of Ministers, 2014).

The Panel considered that the dataset on γ- and δ-tocopherols was too limited to be included in the safety assessment of tocopherols. Moreover, the Panel is aware that much lower concentration levels and fewer uses for γ- and δ-tocopherols are reported in food than for α-tocopherol.

2.9.1.2. Food categories selected for the exposure assessment of α-tocopherol (E 307)

The food categories in which the use of α-tocopherol (E 307) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system food codes), at a detailed level (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories and/or their relative restrictions/exceptions are not referenced in the EFSA Comprehensive Database and, therefore, could not be taken into account in the present estimate. This

results in an underestimation of the exposure. The food categories which were not taken into account are described below (in ascending order of the FCS codes):

- 01.6.3 Other creams;
- 01.7.6 Cheese products (excluding products falling in category 16);
- 02.2.2 Other fat and oil emulsions including spreads;
- 02.3 Vegetable oil pan spray;
- 05.4 Decorations, coatings and fillings, except fruit-based fillings covered by category 04.2.4;
- 06.4.2 Dry pasta, only gluten free and/or pasta intended for hypoproteic diet: gluten-free pasta and pasta intended for hypoproteic diets;
- 06.4.4 Potato gnocchi;
- 06.6 Batters;
- 06.7 Pre-cooked or processed cereals;
- 08.3.3 Casings and coatings and decorations for meat;
- 12.1.2 Salt substitutes;
- 13.1.5.1 Dietary foods for infants for special medical purposes and special formulae for infants;
- 13.1.5.2 Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC
- 14.1.3 Fruit nectars, only vegetable nectars;
- 14.1.5.2 Other than coffee and coffee extracts;
- 14.2.4 Fruit wine and made wine;
- 14.2.5 Mead;
- 14.2.7.2 Aromatised wine-based drinks;
- 14.2.7.3 Aromatised wine-product cocktails.

For the following food categories, the restrictions which apply to the use of α-tocopherol (E 307) could not be taken into account, and therefore the whole food category was considered for the exposure estimates; this results in an overestimation of the exposure:

- 02.1/02.1 Fats and oils essentially free from water, except virgin oils and olive oils, or only refined olive oils, including olive pomace oil: it was not possible within the FoodEx food classification to differentiate virgin and refined olive oils.

- 05.1 Cocoa and cocoa products, only energy-reduced or with no added sugar: energy-reduced or no added sugar cocoa and cocoa products are not referenced in the FoodEx classification nomenclature.

- 08.3.2 Heat-treated meat products, except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*: specific food products excluded from this food category are not referenced in the FoodEx classification nomenclature.

- 09.3 Fish roe, only processed fish roe: this exception could not be taken into account in the present exposure assessment, since no distinction is made in the FoodEx nomenclature between processed and non-processed fish roe. Therefore, the whole food category was taken into account.

- 13.1.3 Processed cereal-based foods and baby foods for infants and young children, only fat-containing cereal-based foods including biscuits and rusks and baby foods: fat-containing cereal-based foods for infants and young children are not referenced in the FoodEx classification nomenclature.

- 17.1/17.2/17.3 Food supplements: it was not possible to differentiate solid, liquid or syrup-type, or chewable forms of food supplements within the FoodEx codes.

Overall, 17 food categories were not taken into account in the exposure assessment because these are not referenced in the EFSA Comprehensive Database, and nine food categories were included in the exposure assessment without considering the restrictions as set in Annex II of Regulation (EC) No 1333/2008.

2.9.2. Exposure to α-tocopherol (E 307)

Dietary exposure to α-tocopherol (E 307) from its use as a food additive and to α-tocopherol from all food sources (food additive, enzyme preparations, nutrient as vitamin and from natural sources) was estimated using the approach adopted by the Panel at its 52nd plenary meeting[18]. This approach was followed to assess the exposure, as part of the safety assessment of food additives under re-evaluation, with the use of the food consumption data available within the EFSA Comprehensive Database, as presented in Table 8, and with the limitations described above.

The exposure assessment for food additives under re-evaluation was carried out by the ANS Panel based on (1) MPLs set down in EU legislation (defined as the "regulatory maximum level exposure assessment" scenario); and (2) the availability of adequate use levels or analytical data (defined as "refined exposure assessment" scenarios).

2.9.2.1. Maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs set in Annex II of Regulation (EC) No 1333/2008 and listed in Table 7. As α-tocopherol (E 307) is authorised according to QS in almost all food categories, a maximum level exposure assessment scenario was estimated based on the maximum reported use levels provided by industry, as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014).

The exposure estimates derived by following this scenario should be considered as the most conservative since it assumes that the consumer will be continuously (over a lifetime) exposed to α-tocopherol (E 307) present in the food at the maximum reported use levels.

[18] http://www.efsa.europa.eu/en/events/event/140701a-m.pdf

Appendix D summarises the concentration levels of α-tocopherol (E 307) used in the maximum level exposure assessment scenario for the exposure assessment of α-tocopherol (E 307) from its use as a food additive.

2.9.2.2. Refined exposure assessment scenarios

The refined exposure assessment scenarios are based on information on reported use levels provided by industry and/or analytical results submitted to EFSA by Member States. These exposure scenarios can only consider food categories where the above data were available to the Panel.

Based on the data made available to EFSA, reported use levels from industry and analytical data on α-tocopherol from Member States (see Section 2.7), the Panel performed different exposure scenarios.

Reported use levels from industry give information on the amount of the food additive added to food. The use of these data results in an exposure to α-tocopherol (E 307) at the moment that the food was produced. As described in Section 2.5, tocopherols are degraded during processing and storage. The loss of tocopherols in food is very likely to have an impact on the overall exposure estimates calculated using the reported use levels. Therefore, the Panel calculated additional exposure estimates for the additive itself, including potential loss factors, intended to reflect more closely the exposure to α-tocopherol (E 307) via foods as consumed.

On the other hand, the analytical levels provided by the Member States reflect the levels of α-tocopherol in foods, whatever its origin (food additive, enzyme preparations, nutrient as vitamin and from natural sources). Therefore, the exposure estimated using analytical data should reflect more closely what is ingested through the diet via all sources and, therefore, should represent the exposure coming from all sources (food additive, enzyme preparations, nutrient as vitamin and from natural sources). Analytical data from Member States were measured in different foods, i.e. not only the food categories in which α-tocopherol (E 307) is authorised as a food additive; however, not all food in which α-tocopherol occurs naturally (raw food commodities such as leafy vegetables) were analysed. When no analytical data were available for food categories in which α-tocopherol (E 307) is authorised, the usage levels were used, applying a correction factor to account for loss of α-tocopherol during processing and storage (as described in Section 2.5). In this way, the corrected usage level best represented the level of α-tocopherol in the consumed food (Appendix E).

Appendix D summarises the levels of α-tocopherol (E 307) used in the refined exposure assessment scenarios considering its use as a food additive.

Based on the available dataset, the Panel calculated two estimates based on different model populations:

(1) The brand-loyal consumer scenario, in which it was assumed that a consumer is exposed long term to the food additive present at the maximum reported use levels for one food category. This exposure estimate was calculated as follows:

   – by combining food consumption with the maximum of the maximum reported use levels for the main contributing food category at the individual level;

   – by using the mean of the typical reported use levels for the remaining food categories.

(2) The non-brand-loyal consumer scenario, in which it was assumed that the population is exposed long term to the food additive present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels for all food categories.

Appendix E summarises the concentration levels of α-tocopherol used in the refined exposure assessment scenarios considering all sources (food additive, enzyme preparations, nutrient as vitamin

and natural sources). Based on the available dataset, the Panel calculated one scenario using the mean analytical levels for all food categories.

In the refined exposure assessment scenarios, the concentrations considered by the Panel were extracted from the dataset received. To consider left-censored analytical data (i.e. analytical results that were < LOD or < LOQ), the substitution method, as recommended in the "Principles and Methods for the Risk Assessment of Chemicals in Food" (WHO, 2009) and the EFSA scientific report "Management of left-censored data in dietary exposure assessment of chemical substances" (EFSA, 2010b), was used. In the present opinion, analytical data below the LOD or LOQ were assigned a value of half of the LOD or LOQ, respectively (medium-bound (MB)). Subsequently, per food category, the mean or median, as appropriate, MB concentration was calculated. For the reported use levels, the mean typical reported use level per food category was calculated.

Food categories for which no or inadequate reported use/analytical levels of α-tocopherol were available were not considered in the refined exposure scenarios. This applies to the following food categories:

- In the exposure assessment of α-tocopherol (E 307) using reported use levels: fruit juices (FCS 14.1.2), cider and perry (FCS 14.2.3), and other alcoholic drinks (FCS 14.2.8).
- In the exposure assessment of α-tocopherol using analytical data: cider and perry (FCS 14.2.3) and other alcoholic drinks (FCS 14.2.8).

The Panel noted that if α-tocopherol (E 307) is nevertheless used in those food categories for which reported use/analytical levels were not available, the calculated refined exposure estimates might result in an underestimation of the exposure.

2.9.2.3. Anticipated exposure to α-tocopherol (E 307) from its use as a food additive

Table 9 summarises the estimated exposure to α-tocopherol (E 307) from its use as a food additive in six population groups using reported use levels provided by industry and for three exposure scenarios. For the refined exposure scenarios, estimates were calculated both with and without considering the losses of α-tocopherol (E 307) during processing and storage. The exposure results per population and survey are shown in Appendix F.

Table 9: Summary of anticipated exposure to α-tocopherol (E 307) from its use as a food additive using the maximum level exposure assessment scenario and refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw/day)

	Infants (4–11 months)	**Toddlers (12–35 months)**	**Children (3–9 years)**	**Adolescents (10–17 years)**	**Adults (18–64 years)**	**The elderly (≥ 65 years)**
Maximum level exposure assessment scenario						
Mean	1.2–4.8	2.7–6.5	2.2–5.7	0.9–3.2	1.0–2.2	0.8–1.7
High level (95th percentile)	3.4–9.7	7.1–11.9	6.0–11.4	2.1–7.7	2.2–5.4	2.0–3.6
Refined estimated exposure scenarios using reported use levels without loss factors						
Brand-loyal scenario						
Mean	1.1–4.2	2.1–4.5	1.6–4.1	0.7–2.5	0.8–1.9	0.7–1.4
High level (95th percentile)	3.0–8.6	5.6–9.7	5.1–9.5	1.7–6.6	1.8–5.0	1.7–3.3
Non-brand-loyal scenario						
Mean	0.4–1.5	1.5–3.1	1.1–2.9	0.5–1.8	0.6–1.3	0.5–1.0
High level (95th percentile)	1.4–4.5	4.1–7.2	3.6–6.5	1.2–4.5	1.3–3.4	1.3–2.3

	Infants (4–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Refined estimated exposure scenarios using reported use levels with loss factors						
Brand-loyal scenario						
Mean	0.7–4.0	1.9–3.8	1.4–3.5	0.6–2.0	0.7–1.5	0.6–1.1
High level (95th percentile)	2.2–8.4	4.7–8.1	3.9–7.2	1.3–5.2	1.5–3.8	1.4–2.5
Non-brand-loyal scenario						
Mean	0.3–1.2	1.3–2.7	0.9–2.4	0.4–1.4	0.5–1.0	0.4–0.7
High level (95th percentile)	1.1–3.5	3.5–5.9	2.8–5.2	0.9–3.4	1.0–2.6	1.0–1.7

From the use of α-tocopherol (E 307) as a food additive itself, the most realistic refined exposure (non-brand-loyal scenario with loss factors) ranges from 0.3 mg/kg bw/day in infants to 2.7 mg/kg bw/day in toddlers at the mean exposure level and from 0.9 mg/kg bw/day to 5.9 mg/kg bw/day in adolescents and toddlers, respectively, at the high exposure level.

The main food categories contributing to the total mean exposure to α-tocopherol (E 307) from its use as a food additive are presented in Appendix H.

It should be noted that meat products were the most important contributor to the total exposure of α-tocopherol (E 307) from its use as a food additive, an outcome that was mainly driven by the high usage levels reported by industry.

2.9.3. Exposure via other sources

2.9.3.1. Via regular diet

Tocopherols are naturally present in plant-derived foods, particularly fruit and vegetables, as components of vitamin E. The amount of vitamin E present is dependent on several factors including species, maturity, growing conditions, time and manner of harvesting and subsequent processing methods, storage time and storage conditions (Chun et al., 2006).

Chun et al. (2006) carried out a survey of the levels of tocopherols in raw and processed fruits (214 samples) and vegetables (329 samples) from the USA. α-Tocopherol was detectable in all products except coconut. The fruits with the highest α-tocopherol levels included green olives (3.81 mg/100 g edible weight), avocado (up to 2.66 mg/100 g), blackberries (1.43 mg/100 g), kiwi (1.31 mg/100 g) and cranberries (1.23 mg/100 g). The vegetables with the highest α-tocopherol levels included tomato products (0.52–4.66 mg/100 g) and spinach (1.96–4.00 mg/100 g). The level of γ-tocopherol was higher than that of α-tocopherol in some products, such as cantaloupes, coconut, figs, raspberries, cauliflower, maize products, cucumber, lettuce, mushrooms, mustard spread and green peas. The β- and δ-tocopherols were either not detectable or present in lower amounts: β-tocopherol was present at up to 0.08 mg/100 g in fruit (detected in 16 out of 47 types) and up to 0.03 mg/100 g in vegetables (detected in 18 out of 53 types); δ-tocopherol was present at up to 1.15 mg/100 g in fruit (detected in 11 out of 47 types) and up to 0.03 mg/100 g in vegetables (detected in 8 out of 53 types).

Two EFSA opinions (EFSA, 2007a, 2008) considered that plant oils were the main dietary sources of vitamin E (typical levels of 56–160 mg/100 g in soybean oil, 53–162 mg/100 g in corn oil and 5–15 mg/100 g in olive oil), with only relatively small contributions arising from meat (typical levels of 0.05–0.16 mg/100 g), poultry (typical levels of 0.16–0.4 mg/100 g) and dairy products (typical levels of 0.04–1.0 mg/100 g). The EFSA opinion published in 2008 gives a more detailed breakdown of the levels of α-, β-, γ- and δ-tocopherols in edible plant oils (EFSA, 2008).

In 2015, the EFSA NDA Panel issued an opinion on the dietary reference values for vitamin E (EFSA NDA Panel, 2015). This opinion reviewed vitamin E intakes among European populations for several age classes and by gender. Table 10 summarises those intakes (in mg/person per day) per population group. The intake estimates were based on consumption of foods, either fortified or not, but without taking dietary supplements into account.

Table 10: Intake ranges of α-tocopherol (mg/day) in different surveys based on Finnish and Swedish α-tocopherol composition data (EFSA NDA Panel, 2015)

	Infants (< 1 year)	Toddlers (1 to < 3 years)	Children (3 to < 10 years)	Adolescents (10 to < 18 years)	Adults (18 to < 65 years)	The elderly (≥ 65 years)
Lower end [(a)]	0.3–3.4	1.9–2.7	3.0–5.3	4.1–7.5	3.9–6.9	4.1–6.0
Mean range	2.9–5.4	4.0–5.7	5.4–10.9	8.2–14.3	8.8–16.0	7.8–12.7
Upper end [(a)]	6.4–8.9	6.6–9.6	9.7–19.6	14.1-.29.0	15.3–28.5	11.5–24.0

(a): Minimum - maximum of percentile (5th percentile for lower end and 95th percentile for upper end).

2.9.3.2. Via fortification/food supplements

The European food supplement producers (European Responsible Nutrition Alliance (ERNA)) indicated that, currently, soft drinks (such as sports drinks, multivitamin juices, "ACE-drinks"), cereals and dairy spreads are the most common types of foods fortified with vitamin E (ERNA, 2012). Typical vitamin E concentrations in ACE-drinks are in the range of 1–2.5 mg/100 mL. ERNA also commented that the addition of vitamin E to oils and foods rich in unsaturated fatty acids is, in most cases, to balance losses that occur during the refining or production processes, and is thus not considered to be fortification.

The Panel is aware that the intake of food supplements with vitamin E may add considerably to the total exposure to α-tocopherol (E 307) (Flynn et al., 2009).

There are huge differences in the surveys included in the EFSA Comprehensive Database with regard to collecting data on food supplements. Some surveys did not collect those data systematically, and for others, no harmonised approach was used. Therefore, the Panel noted that there are uncertainties as to which extend food supplement intake is adequately covered by the food survey data. According to literature, it can be concluded that users of supplements containing vitamin E will have a substantial intake from those products, in addition to the exposure due to the use of α- tocopherol as a food additive and from natural sources.

2.9.4. Exposure to α-tocopherol from all food sources based on analytical data

Table 11 summarises the estimated exposure to α-tocopherol from all food sources (food additives, enzyme preparations, nutrient as vitamin and from natural sources) in six population groups using reported analytical data from Member States. The exposure results per population and survey are shown in Appendix G.

Table 11: Summary of anticipated exposure to α-tocopherol from all food sources (food additives, enzyme preparations, nutrient as vitamin and from natural sources) based on analytical data using the refined exposure scenario (non-brand-loyal approach) in six population groups (minimum–maximum across the dietary surveys in mg/kg bw/day and in mg/day)

	Infants (4–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
mg/kg bw/day						
Mean	0.8–1.5	1.2–3.7	1.6–4.0	0.6–2.0	0.6–1.3	0.5–0.9
High level (95th percentile)	2.2–3.7	3.6–6.3	3.6–9.7 [(a)]	1.4–4.4	1.3–3.0	1.0–2.5
mg/day [(b)]						
Mean	6.7–14.2	12.9–51.0	35.0–107.3	31.3–91.4	46.4–98.3	33.8–67.4
High level (95th percentile)	19.4–35.5	36.7–87.8	80.0–243.2	61.6–209.0	99.2–228.5	74.0–188.9

(a): High levels observed at the upper end of the 95th percentile exposure in children may be a result of different methodologies used for reporting the amounts of consumed food supplements among dietary surveys (e.g. the amounts reported as diluted in water ready for consumption vs. the amounts reported as drops), or a result of not including the food supplements category in the dietary surveys. Due to lack of FoodEx linkage codes for different forms of food supplements (tablets, powder, drops, etc.), it was not possible to combine the occurrence and consumption data in an appropriate way (see Section 2.9.1.2).

(b): Default body weight values were used, based on body weights reported in the Comprehensive Database (EFSA, 2012).

The main food categories contributing to the total mean exposure to α-tocopherol from all sources are presented in Appendix I. For this scenario based on analytical data, meat products and fine bakery wares were the most important contributors to the total mean exposure to α-tocopherol. In adults and the elderly, food supplements were also important contributors.

Considering the exposure to α-tocopherol from its use as a food additive (E 307) (Section 2.9.2.3, Table 9), from natural sources (Section 2.9.3.1, Table 10) and from a combination of all possible food sources (Section 2.9.4, Table 11), the Panel decided to present a table summarising all possible sources of exposure to α-tocopherol. The results should be interpreted with caution, as different consumption surveys and food composition databases were used for the estimation of intakes of α-tocopherol from natural sources.

Table 12: Summary of anticipated exposure to α-tocopherol from its use as a food additive (with loss factor), from natural sources and from all sources, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw/day)

	Infants (4–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
From food additive use						
Refined estimated exposure scenario: non-brand-loyal scenario with loss factors						
Mean	0.3–1.2	1.3–2.7	0.9–2.4	0.4–1.4	0.5–1.0	0.4–0.7
High level	1.1–3.5	3.5–5.9	2.8–5.2	0.9–3.4	1.0–2.6	1.0–1.7
From natural sources [(a)]						
Mean	0.6–1.1	0.3–0.5	0.2–0.5	0.2–0.3	0.1–0.2	0.1–0.2
Upper end [(b)]	1.3–1.8	0.6–0.8	0.4–0.9	0.3–0.6	0.2–0.4	0.2–0.3
From all sources (food additive, enzyme preparations, nutrient as vitamin and natural sources)						
Mean	0.8–1.5	1.2–3.7	1.6–4.0	0.6–2.0	0.6–1.3	0.5–0.9
High level	2.2–3.7	3.6–6.3	3.6–9.7 [(c)]	1.4–4.4	1.3–3.0	1.0–2.5

(a): Data reported in Table 10 were used for this assessment. Default body weight values were used, based on body weights reported in the Comprehensive Database (EFSA, 2012).

(b): 95th percentile for upper end.
(c): High levels observed at the upper end of the 95th percentile exposure in children may be a result of different methodologies used for reporting the amounts of consumed food supplements among dietary surveys (e.g. the amounts reported as diluted in water ready for consumption vs. the amounts reported as drops), or a result of not including the food supplements category in the dietary surveys. Due to lack of FoodEx linkage codes for different forms of food supplements (tablets, powder, drops, etc.), it was not possible to combine the occurrence and consumption data in an appropriate way (see Section 2.9.1.2).

The Panel estimated that, when comparing all sources (from the additive itself, from natural sources and from all food sources), the contribution of α-tocopherol (E 307) from its use as a food additive may represent, in average, approximately 71 % (range 59–80 %) of the overall exposure to α-tocopherol, and around two to five times the intake from natural sources, with the exception of infants, whose intake from the use of α-tocopherol (E 307) as a food additive is likely to be 0.9-fold that of the intake from natural sources.

2.9.5. Uncertainty analysis

Uncertainties in the exposure assessment of α-tocopherol have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007b), the sources of uncertainties summarised in Table 13 have been considered.

Table 13: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction [(a)]
Consumption data: different methodologies/representativeness/under-reporting/misreporting/no portion size standard	+/–
Use of data from food consumption survey of a few days to estimate long-term (chronic) exposure for high percentiles (95th percentile)	+
Consumption data: different methodologies used to collect data on food supplements	+/–
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties on which precise types of food the levels refer to	+/–
Uncertainty in possible national differences in use levels of food categories, concentration data not fully representative of foods on the EU market	+/–
Food categories selected for the exposure assessment: exclusion of food categories due to missing FoodEx linkage (19/73 food categories)	–
Food categories selected for the exposure assessment: inclusion of food categories without considering the restrictions/exceptions in the legislation (9/73 food categories)	+
Use levels and concentration data on α-tocopherol only have been considered for exposure assessment	–
Use levels: applying conversion factors to convert concentrations expressed on a fat-weight basis to a whole-weight basis, and applying loss factors to account for losses during processing and storage	+/–
Use levels and analytical data: levels considered applicable for the entire food category	+/–
Use levels and analytical data: no data for some food categories (3/73 food categories)	–
Maximum level scenario: exposure calculations based on the maximum value (reported use from industries or analytical data from Member States)	+
Brand-loyal exposure model: exposure calculations based on the maximum reported use levels for one food category and mean reported use levels for the remaining food categories	+/–
Non-brand-loyal exposure model and exposure model based on analytical data: exposure calculations based on the mean reported use/analytical levels	+/–
Use levels and analytical data: levels on non-authorised food categories not considered	–

Sources of uncertainties	Direction [(a)]
Different dietary surveys used for exposure assessment of α-tocopherol from natural sources	–

(a): Uncertainties with potential to cause over-estimation of exposure are indicated by "+"; Uncertainties with potential to cause underestimation of exposure are indicated by "–".

The Panel considered that the uncertainties identified would tend to cause an overestimation of the actual exposure to α-tocopherol (E 307) as a food additive, particularly for the maximum level scenario, and to an underestimation of the actual exposure to α-tocopherol from all sources in European countries.

3. Biological and toxicological data

Some toxicological studies were submitted to EFSA following a public call for data for the evaluation of the tocopherols (α-, γ- and δ-tocopherols and tocopherol-rich extract). These are detailed in the following sections. In the available database, all toxicological testing was carried out with dl- or d-forms of the tocopherols of interest. No l-forms of tocopherols were used in the available toxicological studies.

It is assumed that α-tocopherol is representative of the other tocopherols and can be considered as a worst case, based on the fact that the body preferentially retains α-tocopherol, rather than any of the other tocopherol forms, and that α-tocopherol is the most biologically active.

The present opinion reports, in brief, key data discussed in previous major reviews by the SCF, JECFA, EFSA, the EVM and the IOM, but generally does not describe them in detail, as these data have already been extensively reviewed by these bodies, and their interpretation with regard to toxicology are comparable. Previously unavailable data, which were subsequently submitted to EFSA following a public call for data, have been described in detail and the results are discussed in relation to findings of the major reviews.

It should be noted that different forms of vitamin E are sometimes referred to in terms of international units (IU). The most biologically active antioxidant is d-α-tocopherol. Vitamin E activity is expressed as d-α-tocopherol equivalents. Where activity is given in IU, 1 IU of d-α-tocopherol is equivalent to 0.67 mg. If the vitamin E is present in the form of dl-α-tocopherol (E 307), then 1 IU is equivalent to 0.91 mg (EVM, 2003).

Absorption, distribution, metabolism and excretion (ADME) and toxicological studies with α-tocopherol derivatives have been considered for the safety assessment of α-tocopherol: d-α-tocopheryl acetate,[19] dl-α-tocopheryl acetate,[20] d-α-tocopheryl poly(ethylene glycol) 1000 succinate,[21] d-α-tocopheryl acid succinate[22] and *RRR*-α-tocopheryl phosphate.[23] The Panel considered that such esters would be hydrolysed following absorption and deliver α-tocopherol.

3.1. Absorption, distribution, metabolism and excretion

An EFSA public call for data did not indicate that any new relevant data are available on the toxicokinetics of tocopherol-rich extract, or α -, γ- or δ-tocopherols. The literature search revealed several sources relating to the toxicokinetics of tocopherols.

[19] d-α-Tocopheryl acetate: CAS Registry Number 58-95-7, EC number 200-405-4.
[20] dl-α-Tocopheryl acetate: CAS Registry Number 52225-20-4, EC number 257-757-7.
[21] d-α-Tocopheryl poly(ethylene glycol) 1000 succinate: CAS Registry Number 9002-96-4.
[22] d-α-Tocopheryl acid succinate: CAS Registry Number 55134-51-5.
[23] d-α-Tocopheryl phosphate: CAS Registry Number 71276-5-1.

3.1.1. Absorption

Absorption of the tocopherols from the gastrointestinal tract begins with emulsification with dietary lipids. Absorption of lipids together with the fat-soluble vitamins depends on biliary secretion of bile acids and salts, which aid the emulsification process, to form micelles with the hydrolysed fat. The micelles containing tocopherols are then absorbed by passive diffusion at the brush border enterocytes of the small intestine (Traber et al., 1986; IOM, 2000; SCF, 2003; EFSA, 2008).

The proportion of tocopherol intake that is absorbed from the small intestine appears to depend on the intake. Traber et al. (1986) measured the absorption of tocopherol during constant infusions of saline and soybean oils containing vitamin E, using rats (seven animals, sex and strain not stated) cannulated at the thoracic lymph duct for lymph collection. The amount of tocopherol infused was estimated to provide approximately 100 mg/kg bw/day. The absorption of α-tocopherol was approximately 64 %. The results of this study also showed that the percentage of α-tocopherol absorbed decreased with the administration of large oral doses of vitamin E in rats. Traber et al. (1986) also found that the proportion of γ-tocopherol absorbed was approximately 51 %, and was not decreased by administration of large doses of α-tocopherol, even when the amount of α-tocopherol exceeded γ-tocopherol by more than 50-fold. The authors of this study concluded that this finding indicates that gastrointestinal absorption of α- and γ-tocopherol are independent (Traber et al., 1986). The SCF opinion (SCF, 2003) stated that the average absorption of vitamin E is 40–60 %, but did not cite the sources for this conclusion.

Anwar et al. (2007) investigated vitamin E transport and absorption in male Sprague–Dawley rats and C57BL/6J mice using d-α-[H^3]tocopherol. In this study, it was confirmed that absorption of vitamin E is primarily by secretion by the enterocytes into the lymphatics in the form of chylomicrons. This pathway of absorption is dependent on an exogenous lipid supply, oleic acid and microsomal triglyceride transfer protein. In the case of lower lipid supply, vitamin E is secreted with larger lipoproteins without the need for chylomicrons. The size of the lipoprotein with which vitamin E is secreted is, in turn, dependent on the concentration of oleic acid. Higher concentrations of oleic acid are required for secretion with chylomicrons. The authors of this study noted that the non-chylomicron route of absorption might be useful in targeting therapeutic administration in individuals with fat malabsorption syndromes (Anwar et al., 2007). The EFSA opinion (EFSA, 2008; source documents not cited) stated that the chylomicrons contain the various forms of vitamin E, including α-, γ- and δ-tocopherols. All of the forms of vitamin E studied, including α- and γ-tocopherols, show similar apparent efficiencies of intestinal absorption and subsequent secretion in chylomicrons (IOM, 2000).

3.1.2. Distribution

Vitamin E (d-α-tocopheryl acetate) does not appear to have a specific carrier protein in the plasma, but is rapidly transferred from chylomicrons to plasma lipoproteins, to which it binds non-specifically (Bjorneboe et al., 1990). The half-life of chylomicrons *in vivo* is approximately 5–15 minutes, due to the action of lipoprotein lipase, which forms chylomicron remnants. These remnants are rapidly taken up via apolipoprotein E receptors on the surface of hepatocytes. Therefore, it is possible that α-tocopherol is cleared from the blood with the remnants of the chylomicrons. Vitamin E is then secreted from the hepatocytes in association with very-low-density lipoproteins (VLDLs). Once the vitamin E and VLDL complex is broken down by lipoprotein lipase, vitamin E is available for uptake into liver cells and peripheral cells (Bjorneboe et al., 1990). Brigelius-Floh and Traber (1999) noted that it is only after passage through the liver that α-tocopherol preferentially appears in the plasma. Most of the ingested β-, γ- and δ-tocopherol is secreted into bile, or not absorbed from the gastrointestinal tract and therefore excreted in faeces. The selectivity is due to hepatic α-tocopherol transport protein (α-TTP), which has a preference for 2*R*-stereoisomers of α-tocopherol (Brigelius-Floh and Traber, 1999). Tocopherols can be taken up unchanged by virtually all tissues and plasma. Liver, skeletal muscle and adipose tissue have the potential to accumulate α-tocopherol (Bjorneboe et al., 1990). Mobilisation from the adipose tissue is slow. The adrenal glands had the highest α-tocopherol concentration per gram of tissue. The authors speculated that this could be due to the specific binding of high density lipoprotein, and therefore α-tocopherol, by rat adrenal glands. The

lungs have been shown to have a relatively high concentration of α-tocopherol, which might be due to the need for protection by α-tocopherol against hyperoxia. Testes and cerebrum contain less α-tocopherol per gram of tissue than most organs (Bjorneboe et al., 1990).

Mourvaki et al. (2008) investigated the distribution of α-, γ- and δ-tocopherol in the seminal plasma, spermatozoa and seminal vesicles of New Zealand white rabbits. Semen samples (80 samples) from 20 rabbits were collected weekly for four weeks whilst rabbits were fed a diet containing 50 mg/kg α-tocopherol. It was found that the tocopherols were not homogeneously distributed in rabbit semen fractions. Overall, α-tocopherol was the most abundant tocopherol, but γ- and δ-tocopherols were more abundant in germ cells and seminal plasma, respectively. Mourvaki et al. (2008) concluded that the more polar tocopherols, such as δ-tocopherol, have a higher affinity for aqueous seminal plasma, while the less polar tocopherols have a higher affinity for the lipid-rich cell membrane and vesicles.

The report by TemaNord (2002) stated that the efficiency of absorption of tocopherols is dose-dependent in humans (96.6 % with a 10 mg oral dose, 81.5 % with a 100 mg dose and 55.2 % with a 2 000 mg dose); references were not provided.

Parker (1988) investigated the tocopherol composition of adipose tissue in human subjects not receiving tocopherol supplementation. Samples of adipose tissue were removed from the abdominal area of 19 healthy adult volunteers (stated to be of approximately equal number of each sex) of various ages who were undergoing minor corrective surgery. The predominant tocopherol in these tissue samples was α-tocopherol, constituting, on average, almost 81 % of the total tocopherol content and ranging in concentration from 61 to 811 µg/g adipose tissue. The content of γ- and β-tocopherols was, on average, approximately 25 % of the α-tocopherol content. δ-Tocopherol constituted only a small fraction of total tocopherol content. The relative concentrations of the tocopherols were less variable than their absolute concentrations. Overall, the α-tocopherol content of adipose tissue was highly correlated with the total tocopherol content of adipose tissue, because α-tocopherol was by far the predominant tocopherol present in this tissue.

Kitagawa and Mino (1989) examined the bioavailability of high doses of d-α-tocopherol in 19 healthy male college student volunteers, aged 24 or 25 years, using a single-blind method. The subjects were randomly assigned to the vitamin treatment group (14 subjects) or control/placebo group (five subjects). Each subject was asked to take a total of 600 mg (900 IU) of d-α-tocopherol daily in three equal doses, with meals, for three months. The control subjects were asked to take identical placebo capsules. No other aspects of the subjects' diets were controlled or measured. Fasting (overnight) blood samples were taken at the same time of day (8.00 a.m.) on day 0 (at the beginning of the study), and one, two and three months after the final supplementation. Blood samples were also taken 3, 7 and 28 days after supplementation had finished. α-Tocopherol concentrations in plasma, red blood cells, platelets, leucocytes and buccal mucosal cells were measured. α-Tocopherol rose to levels between 2.5 and 3 times the baseline levels in plasma, red blood cells and leucocytes approximately four weeks after supplementation was initiated, and then remained on a plateau. α-Tocopherol in platelets and buccal cells also reached approximately three-fold higher concentrations than the baseline, but this increase required 12 weeks. Levels of α-tocopherol in red blood cells returned to baseline within seven days after the end of the supplementation period, but were still elevated after one month in buccal cells. The authors of this study speculated that this difference might show a slower turn-over in tissue cells compared with the blood cells. γ-Tocopherol concentrations in plasma and red blood cells were measured, and found to decrease with increasing α-tocopherol concentrations (Kitagawa and Mino, 1989).

Eichhorn et al. (2004) studied the kinetics of α-tocopherol in human subjects (n = 38; no further details on subjects stated). Each subject was given a daily dose of 15, 100, 200 or 400 mg α-tocopherol acetate (form of supplement not specified, but assumed to be tablet form) for 21 days (each subject underwent all four treatments). Subjects donated blood and urine samples before supplementation started, to establish baseline α- and γ-tocopherol concentrations, and weekly, during supplementation and the three-week wash-out period. Urinary α- and γ-2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-

hydroxychroman (CEHC) and α-quinone lactone (QL) concentrations were also determined. The study showed that supplementation with α-tocopherol acetate increased plasma α-tocopherol and decreased γ-tocopherol concentrations. There was a statistically significant increase (in a dose-dependent manner) in urinary α-CEHC and α-QL concentrations ($p < 0.05$ for 15 mg, and $p < 0.0001$ for all other doses), but γ-CEHC concentrations did not change (with statistical significance) at any dose of α-tocopherol acetate. Within one week post-supplementation, all concentrations of tocopherols and their metabolites in the plasma and urine had returned to baseline. The authors of this study concluded that α-tocopherol appears to replace γ-tocopherol following high oral intakes of α-tocopherol. The decrease in γ-tocopherol did not lead to an increase in γ-CEHC excretion into urine, implying that there might be a different route of metabolism and excretion for γ-tocopherol. The plasma α-tocopherol and urinary α-CEHC were correlated, and the authors concluded that this might reflect the excess of α-tocopherol, which was surplus to the requirements of the body (Eichhorn et al., 2004).

Based on low fetal vitamin E stores observed at birth, it is assumed that transfer of vitamin E across the placenta is low in humans. Didenco et al. (2011) stated that transfer of vitamin E is "*limited and selective for the natural RRR stereoisomer*" and that "*limited maternal-fetal transfer to the fetus may be a combination of inefficient placental transfer of plasma lipids and the stereoselective transport of only the 2R-α-tocopherols*". The α-TTP has been isolated from human placental trophoblast cells, and it has been proposed that these stereoselective transporters are responsible for the selective transport of tocopherols across the placenta. Didenco et al. (2011) investigated the concentrations of α- and γ-CEHC in maternal and umbilical cord blood pairs and examined these concentrations in relation to circulating maternal α- and γ-tocopherol and maternal vitamin E intake. In conducting this study, Didenco et al. (2011) also investigated the possibility that the fetal liver actively metabolises vitamin E. Following a fasting period, together with the previous day's 24-hour diet history, blood samples were obtained during the pregnancies (at least one per subject in accordance with the prenatal appointments; specific gestation days not stated) of non-smoking women ($n = 19$). Umbilical cord blood was also collected at the birth of the infants. Dietary vitamin E (α- and γ-tocopherols), total fat, total cholesterol and energy intake were estimated from dietary information. Tocopherols and α- and γ-CEHCs were quantified in blood samples. Total lipids were also calculated. There were no apparent associations between birth weight or the type of delivery and cord plasma variables. Concentrations of α- and γ-tocopherol were significantly lower in cord blood compared with maternal blood ($p < 0.001$). α-Tocopherol:total lipids and γ-tocopherol:total lipids ratios were statistically significantly lower in cord blood ($p < 0.001$ and $p < 0.005$, respectively). Although the absolute α- and γ-CEHC concentrations in maternal and cord blood did not differ significantly, there was a trend towards the cord blood concentrations of these metabolites being lower. Also, α-CEHC:α-tocopherol and γ-CEHC:γ-tocopherol ratios were statistically significantly higher in the cord blood ($p < 0.01$ and 0.001, respectively). Maternal and umbilical cord plasma α-tocopherol concentrations were associated after adjustment for total lipids; this association was not found for γ-tocopherol. There was also a strong correlation between maternal and cord blood α-CEHC and γ-CEHC concentrations ($r = 0.7$, $p = 0.002$ and $r = 0.7$, $p = 0.002$, respectively). With regard to the dietary intake of vitamin E, maternal α-tocopherol and α-CEHC concentrations were statistically significantly correlated with dietary vitamin E (including that from supplements) ($r = 0.5$, $p = 0.04$ and $r = 0.62$, $p = 0.02$, respectively). However, this correlation was not found for α-tocopherol in cord blood. Cord blood α-CEHC concentrations were, however, correlated with maternal dietary vitamin E ($r = 0.69$, $p = 0.003$). The author of the study speculated that, based on these results, a higher intake of vitamin E during pregnancy results in elevated metabolite concentrations in the fetal blood, without increasing the fetal blood vitamin E. However, the source of the metabolite was not determined, and could have been maternal liver, fetal liver or placenta. Therefore, if vitamin E supplements are taken during pregnancy to increase fetal stores, in reality there might be an increase in metabolites, rather than increasing circulating tocopherol (Didenco et al., 2011).

In an epidemiology study of 1 231 pregnant women, Scholl et al. (2006) (see Section 3.2.6.1 for more details on this study) confirmed that supplements that contain α-tocopherol reduce maternal circulating concentrations of γ-tocopherol. Instead, circulating γ-tocopherol was related to dietary fat intake.

Yoshikawa et al. (2005) noted that after absorption, γ-tocopherol accumulates in some human tissues and that it is metabolised to γ-CEHC. The authors of this study also confirmed the reduction in plasma γ-tocopherol and increase in plasma γ-CEHC following ingestion of α-tocopherol supplements, and noted that this is considered to be due to accelerated γ-tocopherol metabolism. Yoshikawa et al. (2005) went on to investigate the effects of γ-tocopherol administration on α- and γ-tocopherol concentrations and metabolism in healthy volunteers. Healthy male volunteers (n = 13) with a mean age of approximately 28 years were enrolled into the study. None of the subjects was taking vitamin supplements. The volunteers were randomly divided into a group of seven volunteers who were given tocopherol supplement capsules containing mainly d-γ-tocopherol (the tocopherol content in each capsule was 2.5 mg d-α-, 1.4 mg d-β-, 93.2 mg d-γ- and 2.3 mg d-δ-tocopherol), and a control group of six volunteers who were given α-tocopherol (5 mg d-α-tocopherol). Supplements were taken for 28 consecutive days, and blood samples were taken from each volunteer on days 0 (before the first supplement was taken), 14, 28, 35, 42 and 56, after an overnight fast. A 24-hour urine sample was also collected from each volunteer on the same day that the blood samples were taken. Dietary information was also obtained. There was a statistically significant increase in plasma γ-tocopherol concentration ($p < 0.01$) during administration of γ-tocopherol, whereas there was a statistically significant decrease in plasma α-tocopherol levels ($p < 0.01$). Plasma concentrations of the metabolites α-CEHC and γ-CEHC showed the same pattern of change as their corresponding parent tocopherols. These changes in parent and metabolite concentrations returned to baseline within one week after the end of the supplementation period. Urinary γ-CEHC and α-CEHC increased in the γ-tocopherol supplement group. The authors of this study explained that, in the liver, α-TTP selects α-tocopherol (the highest affinity is for d-α-tocopherol) more readily than the other forms of tocopherol for incorporation into VLDLs and transfer to the plasma. Therefore, under normal conditions, plasma concentrations of γ-tocopherol would be lower than those of α-tocopherol. Under the conditions of this study by Yoshikawa et al. (2005), excess γ-tocopherol was taken up by the liver and, consequently, α-TTP combined with it more than usual. The increase in γ-tocopherol binding leads to a higher transport of γ-tocopherol, and a lower transport of α-tocopherol, into the blood.

3.1.3. Metabolism

The primary hepatic oxidation product of α-tocopherol is α-tocopherylquinone, through a semi-stable intermediate, α-tocopheroxyl radical. The first stage in this reaction is reversible, whereas the conversion of the intermediate to the quinone is not. The quinone molecule, which has no vitamin E activity, can be changed by another reversible reaction to the hydroquinone. This hydroquinone can be conjugated with glucuronic acid, and the product secreted in the bile or eliminated in the faeces (Bjorneboe et al., 1990; Brigelius-Floh and Traber, 1999).

Another metabolite of α-tocopherol is α-CEHC. Brigelius-Floh and Traber (1999) noted that α-CEHC excretion increased when concentrations of d-α-tocopherol in the plasma reached a particular threshold (threshold not stated), and that the intact chromanol structure of α-CEHC indicates that it is derived from unreacted α-tocopherol, i.e. it has not reacted as an antioxidant. Overall, therefore, excretion of α-CEHC in the urine could indicate adequate or excess α-tocopherol. However, γ- and δ-tocopherols are almost completely metabolised to their corresponding CEHCs and excreted in urine.

3.1.4. Excretion

One of the main routes of elimination of absorbed oral α-, γ- and δ-tocopherols from the body is via biliary recycling and faecal excretion. Faecal excretion also includes non-absorbed tocopherols, as well as tocopherols not used in their antioxidant capacity (Brigelius-Floh and Traber, 1999; IOM, 2000; EFSA, 2008). The EVM report (2003, source reference not cited) stated that 30–70 % of vitamin E is excreted in the faeces via the bile, whereas less than 1 % is excreted in the urine.

Clifford et al. (2006) conducted a cross-over design study in which a 36-year old healthy male subject was given a single oral dose of 0.001821 μmol (0.09 mg) [5-$^{14}CH_3$]d-α-tocopherol acetate. Samples of blood were collected for 63 days, faeces for six days and urine for eight days after dosing. After three months, the same subject was given an oral dose of 0.001667 μmol of [5-$^{14}CH_3$]dl-α-tocopherol

acetate, and similar samples collected. Meals were strictly controlled on the days that the tocopherols were administered. The two tocopherols were absorbed equally (approximately 78 %), and approximately 90 % of the absorbed dose was excreted in urine as α-CEHC. dl-α-Tocopherol was preferentially metabolised and eliminated in the urine.

3.1.5. Summary of the absorption, distribution, metabolism and excretion data

The key toxicokinetics data can be summarised as follows: absorption of the tocopherols varies with dose, and the efficiency of absorption decreases with increasing intake (Traber et al., 1986; Kitagawa and Mino, 1989). Absorption across the gastrointestinal tract occurs along with dietary lipids and is dependent on biliary secretion of bile acids and salts, which aid the emulsification process, forming micelles with the hydrolysed fat. The micelles containing the vitamin E are then absorbed by passive diffusion at the brush border enterocytes of the small intestine (Anwar et al., 2007). Once absorbed, the tocopherols enter the blood and lymph in chylomicrons, and are transported to the tissues. The liver appears to select α-tocopherol using α-TTP. Most γ- and δ-tocopherols ingested are eliminated by the liver into the bile and excreted in the faeces (Bjorneboe et al., 1990; Brigelius-Floh and Traber, 1999). The liver, skeletal muscle, adrenals, adipose and lung tissues all have comparatively higher concentrations of α-tocopherol, but tocopherols can be taken up into most tissues and plasma (Bjorneboe et al., 1990). The dynamics of tocopherol concentrations in the plasma change depending on the intake of various forms of tocopherol. For example, an increase in the dose of α-tocopherol leads to a decrease in the plasma concentration of γ-tocopherol (Eichhorn et al., 2004). The main route of excretion (30–70 %) of unabsorbed tocopherols and tocopherols excreted into bile is via the faeces (EVM, 2003). Although urinary excretion of tocopherols as the metabolite CEHC is a minor route of excretion for α-tocopherol, it has been extensively studied in humans; however, is still not very well understood. The levels of plasma α-tocopherol correlate with the levels of urinary α-CEHC, with the presence of α-CEHC in the urine appearing to indicate a surplus of α-tocopherol (Brigelius-Floh and Traber, 1999). It is also noteworthy that, following ingestion of α-tocopherol, there is a reduction in plasma γ-tocopherol and an increase in plasma γ-CEHC. This is probably linked to the selectivity in the body towards α-tocopherol, which replaces γ-tocopherol whenever the levels of α-tocopherol are sufficient to do so (Eichhorn et al., 2004). Human studies suggest that the maternal intake of vitamin E increases the concentration of fetal CEHC, rather than increasing the level of fetal vitamin E (Didenco et al., 2011).

The Panel considered that the data for α- and γ-tocopherol are relevant to the tocopherol-rich extract which is a mixture of tocopherols. There are not many data on δ-tocopherol; however, since the liver, and consequently the whole body, preferentially retains α-tocopherol, it would follow that the kinetics of δ-tocopherol might be similar to those of γ-tocopherol, i.e. it would normally be absorbed unchanged in chylomicrons and mainly eliminated into the bile by the liver, and it might be replaced by α-tocopherol when internal levels of α-tocopherol are sufficient.

3.2. Toxicological data

3.2.1. Acute toxicity

A literature search did not identify any new relevant data in the published literature on the acute toxicity of tocopherol-rich extract or α-, γ- or δ-tocopherol. Three acute toxicity studies have been made available via an EFSA public call for data.

dl-α-Tocopherol (technical grade) was tested in an acute oral limit test (Winter, 1988; unpublished report). In this test, which was conducted in accordance with OECD Test Guideline (TG) 401 (OECD, 1981) and Good Laboratory Practice (GLP), Fü-albino rats (five animals/sex/group) were given, by gavage, a single dose of 2 000 mg/kg bw α-tocopherol in rapeseed oil. There were no deaths, adverse clinical signs, effects on body weight or adverse findings at necropsy. Therefore, the LD_{50} was concluded by the study author to be greater than 2 000 mg/kg bw.

Gelbke and Freisberg (1978; unpublished report) conducted a study, which was pre-GLP, but appears to have been conducted using a protocol similar to that specified by OECD TG 401 (OECD, 1981). In that study, 10 male and 10 female Sprague–Dawley rats were given, by gavage, a single dose of 10 000 mg/kg bw dl-α-tocopherol in olive oil, followed by a 14-day observation period and macroscopic examinations. Body weights were not measured. There were no deaths, no toxicologically significant adverse clinical effects or adverse necropsy findings. Therefore, the LD_{50} was concluded by the study author to be greater than 10 000 mg/kg bw.

In a study by Pool et al. (1972; unpublished report), which was not conducted in accordance with an OECD test guideline or with GLP, 10 neonatal Wistar rats (sex not specified) were administered 4 000 mg/kg bw dl-α-tocopherol, by gavage, in 5 % gum acacia solution and observed for five days. Four of the rats died, and cyanosis and respiratory depression were noted (no further information available). The study author concluded that the LD_{50} in neonatal Wistar rats was greater than 4 000 mg/kg bw.

The very low acute toxicity of α-tocopherol observed in these studies is in agreement with the overall conclusions of authoritative reviews by EFSA (2008), the EVM (2003) and the SCF (2003). These opinions commonly cite an acute toxicity study conducted by Krasavage and Terhaar (1977). In this study, mature CD rats (10 animals/sex/group) were fasted for 16 hours before being given either d-α-tocopheryl poly(ethylene glycol) 1 000 succinate, polyethylene glycol 1 000 or d-α-tocopheryl acid succinate at 7 000 mg/kg bw. All animals were observed for clinical signs of toxicity for 14 days, after which, gross necropsies were conducted. Six of the 60 animals died within 48 hours of treatment; all deaths were attributed to dosing errors. After an initial transient 24-hour period of listlessness and diarrhoea, no further adverse effects were observed. The LD_{50} values for all three test substances were greater than 7 000 mg/kg bw.

Overall, the acute oral toxicity of α-tocopherol is consistently very low, with LD_{50} values reported to be greater than 2 000 mg/kg bw for rats (Gelbke and Freisberg, 1978; Pool et al., 1972; Winter, 1988, all unpublished reports). Krasavage and Terhaar (1977) also noted the low acute toxicity in rats, mice and rabbits.

3.2.2. Short-term and subchronic toxicity

The effects of tocopherols (primarily α-tocopherol) following repeated exposures in short-term and subchronic studies have been previously reviewed (IOM, 2000; EVM, 2003; SCF, 2003). The key studies (Krasavage and Terhaar, 1977; Abdo et al., 1986) cited in these reviews are summarised in the following paragraphs.

In a 90-day dietary study conducted by Krasavage and Terhaar (1977), CD weanling rats were randomly assigned to four groups (30 animals/sex/group) and were fed diets containing 0, 0.002, 0.2 or 2 % d-α-tocopheryl poly(ethylene glycol) 1 000 succinate (calculated by the study authors to be 0, 0.5, 50 or 500 mg/kg bw/day vitamin E, respectively). The rats were observed for clinical signs of toxicity, and body weights were recorded prior to treatment, twice during the first week of treatment, and weekly thereafter. Food consumption was recorded at the same time as the body weights. Haematology and clinical chemistry parameters were measured on days 42 and 84 (15 rats/sex from the control and highest dose group). These rats were then killed on day 91 and histopathological examinations were conducted. The remaining rats were used for the reproductive toxicity study (see Section 3.2.5). There were no adverse findings in this study. Blood clotting parameters, such as prothrombin time, were not measured; however, there were no reports of excessive bleeding or haemorrhages (Krasavage and Terhaar, 1977). The Panel concluded that the NOAEL for this study is ≥ 500 mg/kg bw/day d-α-tocopheryl poly(ethylene glycol) 1 000 succinate.

A 13-week oral gavage study conducted by Abdo et al. (1986) was also included in the SCF opinion (SCF, 2003). In this study, which appears to have been conducted in accordance with a protocol that is comparable with OECD TG 408 (OECD, 1998a), weanling Fischer 344 rats (10 animals/sex/group)

were dosed with 0, 125, 500 or 2 000 mg/kg bw/day d-α-tocopherol acetate in corn oil. The untreated controls were dosed with corn oil only. Body weights and food consumption were recorded on a weekly basis. In addition, the rats were observed for clinical signs of toxicity throughout the study. Blood samples for haematology and blood chemistry determination were taken from 10 rats from each group on days 5, 45 and 90 of treatment. A complete necropsy was performed on all rats after scheduled sacrifice on day 90. Deaths occurred in male rats that had received the highest dose only (7 out of 10 male rats in this group died or were killed in a moribund state); these deaths were attributed to internal haemorrhage. Signs of toxicity observed in the male rats that had received the highest dose were diarrhoea, tachypnoea, nose bleeds, dark faeces and red crusts around the eyes. There were no adverse effects on body weight or food consumption. Statistically significant increase of the liver-to-body-weight ratios of females in the 500 and 2 000 mg/kg bw/day groups ($p < 0.05$) was observed. There was a significant dose-related trend ($p < 0.02$) for increased thromboplastin time, activated partial thromboplastin time, fibrinogen, and reticulocyte, white blood cell, lymphocyte and segmented neutrophil counts (statistically significant at 90 days, $p < 0.05$) in males. There was also a decrease in haematocrit, red blood cell count and haemoglobin concentrations after 90 days (statistically significant at 90 days, $p < 0.05$) in males. Activated partial thromboplastin time was also increased in the 500 mg/kg bw/day group at 90 days ($p < 0.05$). In females, statistically significantly increased reticulocyte counts, decreased red blood cell counts and haemoglobin concentrations (p-values not given) were observed on days 5 to 45, but there was no dose-dependent trend. There was, however, a dose-dependent increase in activated partial thromboplastin time in females at 90 days. There were statistically significant increases in serum chloride and γ-glutamyl transpeptide concentrations in males of the highest dose group, but the change was not dose-dependent (p-value not stated). Thyroid stimulating hormone was statistically significantly increased in all treated male and female rats at 90 days ($p < 0.05$). Haemorrhagic diathesis (haemorrhage or haemorrhagic inflammation in the nose, oesophagus, salivary gland, trachea, mediastinum, epididymis or meninges of the brain) occurred in 7 out of 10 males and in 2 out of 10 females in the 2 000 mg/kg bw/day group. Increased extramedullary erythropoiesis of the spleen was observed in highest dose males (4/10 rats). Adenomatous hyperplasia and chronic interstitial inflammation of the lung were observed in all vitamin E-treated rats; the incidence and severity increased in a dose-dependent manner (Abdo et al., 1986). In the SCF opinion (SCF, 2003), the NOAEL derived for this study was 125 mg/kg bw/day, based on the serum chemistry and the effects on the liver that indicated hepatotoxicity.

3.2.2.1. New studies

A literature search retrieved only one relevant study (Gianello et al., 2007) that had not previously been evaluated. Nine previously unevaluated repeated-dose oral toxicity studies have been made available via a call for data. These studies comprised three 28-day rat studies, one 28-day hamster study, three 90-day rat studies, one 90-day hamster study and one 90-day minipig study. These studies used α-tocopherol or its derivatives, or γ-tocopherol.

Rats

In a GLP study conducted by Gelbke et al. (1983; unpublished report), Sprague–Dawley rats (20 rats/sex/dose) were administered dl-α-tocopherol acetate at concentrations of 2 500, 5 000, 10 000 or 20 000 mg/kg diet (corresponding to 300, 600, 1 200 and 2 400 mg/kg bw/day) for four weeks, followed by a two-week recovery period (10 animals/sex/dose). There were no deaths or clinical signs of toxicity, and no effects on body weight and food consumption. The only finding was a reversible dose-dependent increase in liver weight (p-value not stated) in all female groups, with fat changes in peripheral hepatocytes in the highest dose group. The Panel derived a NOAEL of ≥ 20 000 mg/kg dl-α-tocopherol acetate in the diet (equivalent to a dose of 2 400 mg/kg bw/day), assuming that the effect on liver weight is an adaptive, non-toxicological effect.

In a 28-day study (Pfister et al., 1999a; unpublished report) conducted in accordance with OECD TG 407 (OECD, 2008), but not with GLP, dl-α-tocopherol acetate was administered, by gavage, to Wistar rats (10 rats/sex/group) at a dose of 500 mg/kg bw/day, either as a 12.5 % w/v (dose volume of 4.0 mL/kg bw/day) or 50 % w/v (dose volume of 1.0 mL/kg bw/day) solution (using soybean oil as a

vehicle). The statistically significant findings were reduced total lipids, total cholesterol, triglycerides, phospholipids and uric acid in treated females (both solutions) compared with the untreated control females ($p < 0.01$ or $p < 0.05$). These findings were not considered adverse, and the study authors concluded the NOAEL to be 500 mg/kg bw/day. The Panel concluded that the NOAEL of this study would be less than 500 mg/kg bw/day, based on reduced total lipids, total cholesterol, triglycerides and phospholipids in females.

In a 28-day study conducted on dl-α-tocopherol acetate (Pfister et al., 1999b; unpublished report) in accordance with an EU test guideline (No. L 270/32, 91/507/EEC,[24] September 26, 1991) and with GLP, Wistar rats (10 animals/sex/group) were given the test substance in soybean oil, by gavage, at 180, 600 or 2 000 mg/kg bw/day for 28 consecutive days. Examinations were comparable with those recommended in OECD TG 407 (OECD, 2008). The only statistically significant finding was a reduction in total cholesterol ($p < 0.05$) and phospholipids ($p < 0.01$) in females, and a reduction in absolute and relative spleen weights in males given 2 000 mg/kg bw/day ($p < 0.01$). These findings were not considered toxicologically relevant, and the study authors derived a NOAEL of 2 000 mg/kg bw/day. The Panel noted that effects on total cholesterol and phospholipids are commonly observed in studies on tocopherols, and to allow comparison of NOAELs across studies, concluded that the NOAEL of this study would be 600 mg/kg bw/day, based on reduced total cholesterol and phospholipids in females.

Pfister et al. (1999c; unublished report) conducted a 13-week feeding study in Wistar rats. This study was conducted in accordance with the US Food and Drug Administration (FDA) test guideline for 'Subchronic toxicity tests with Rodents and Non-rodents' (FDA, 2000) and in accordance with GLP. In this study, rats (20 animals/sex/group) were fed a diet providing the equivalent of 360, 1 200 or 4 000 mg/kg bw/day of d-α-tocopherol acetate. There were no deaths, no effect on food consumption or body weight, and no adverse findings in the ophthalmoscopic examination or functional observation battery. Males had significantly prolonged prothrombin times and activated partial thromboplastin times after 5, 9 and 14 weeks on the test diet at 4 000 mg/kg bw/day. Females in the 1 200 and 4 000 mg/kg bw/day groups had significantly prolonged activated partial thromboplastin times during week 9 only ($p < 0.01$). These effects are understood to be due to the ability of tocopherols to inhibit or reduce the intestinal uptake of vitamin K. Other haematological, clinical chemistry and urinalysis findings were not considered to be of toxicological significance due to their minor and/or transient nature lacking histopathological changes, or because they were considered to be physiological adaptive responses. Therefore, based on the prolongation of prothrombin time and activated partial thromboplastin time in males at 4 000 mg/kg bw/day, the authors of the study concluded that the NOAEL was 1 200 mg/kg bw/day for d-α-tocopherol acetate. The Panel agreed with this conclusion.

Pfister et al. (1999d; unpublished report) conducted a 13-week gavage GLP study in rats. This study was stated to be conducted using a protocol based on OECD TG 408 (OECD, 1998a). However, there are several limitations to the study compared with this guideline, including the use of fewer animals, fewer dose levels and only a single sex tested at one of the dose levels (1 600 mg/kg bw/day). d-α-Tocopherol acetate and dl-γ-tocopherol in soybean oil were administered by gavage to Wistar rats for 13 weeks. One control group (6 animals/sex/group) remained untreated, and a second control group (6 animals/sex/group) received soybean oil. d-α-Tocopherol acetate was administered at a dose of 800 mg/kg bw/day to six rats per sex. dl-γ-Tocopherol was administered at doses of 800 and 1 600 mg/kg bw/day (6 animals/sex/group, except males were not tested in the 1 600 mg/kg bw/day group). Blood and urine were collected for clinical chemistry, haematology and urinalysis. All animals were sacrificed, and necropsy and microscopic examination performed. For the histopathology, the small intestine (duodenum, jejunum and ileum), mesenteric lymph nodes and all gross lesions were examined. This histopathological examination is, therefore, not as extensive as the OECD test guideline recommends. There were no deaths nor clinical signs of toxicity, and body weights and food

[24] Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. OJ L 270, 26.9.1991, p. 32.

consumption of treated rats were comparable to those of control rats for all groups. Male rats treated with d-α-tocopherol acetate had statistically significantly increased alkaline phosphatase activity and bilirubin compared with untreated controls ($p < 0.05$). Females had statistically significantly reduced total lipids, total cholesterol and phospholipids ($p < 0.01$ or $p < 0.05$). Females also had increased absolute and relative (to body weight) liver ($p < 0.05$) and spleen ($p < 0.01$) weights. No changes in organ weights were found in male rats. Two male and three female rats had macrophage aggregates (some resembling early granulomas), often with fine cytoplasmic vacuoles in mesenteric lymph nodes. Moderate sinus histiocytosis was associated with this change in one female rat. In rats administered dl-γ-tocopherol, females in both dose groups had statistically significantly dose-dependent reduced platelet counts ($p < 0.05$ or $p < 0.01$). These female rats also had statistically significantly reduced total lipids, total cholesterol and phospholipids ($p < 0.01$ or $P < 0.05$), and statistically significantly increased creatine kinase activity ($p < 0.05$). In the 1 600 mg/kg bw/day female group, bilirubin levels, alanine aminotransferase activity ($p < 0.05$), and absolute and relative (to body and brain weight) liver and spleen weights were statistically significantly increased ($p < 0.05$, except spleen to body weight which was $p < 0.01$). Males at 800 mg/kg bw/day (only dose tested) had statistically significantly increased creatine kinase and alanine aminotransferase activity ($p < 0.01$ or $p < 0.05$, respectively). Macrophage aggregates (some resembling early granulomas), often with fine cytoplasmic vacuoles, were observed in the mesenteric lymph nodes of males ($n = 5$) and females ($n = 5$) treated with 800 mg/kg bw/day dl-γ-tocopherol, and all rats (females only tested) at 1 600 mg/kg bw/day. In two rats from the 1 600 mg/kg bw/day group the latter changes were associated with moderate sinus histiocytosis. As noted in Pfister et al. (1999c), the findings in the lymph nodes represent a physiological response to sequester or remove excess combined test substance or its metabolites. Also, liver weight changes are considered to be an adaptive response. The authors of this study did not reach a conclusion regarding the NOAEL.

In a 13-week gavage study conducted in accordance with Commission Directive No 96/54/EC[25] (B.26. "Subchronic Oral Toxicity", 30 September 1996) and comparable with OECD TG 408 (OECD, 1998a), Wistar rats (10 rats/sex/group) were given vitamin E acetate at doses of 180, 600 and 2 000 mg/kg bw/day, or d-α-tocopheryl acetate at doses of 180 or 2 000 mg/kg bw/day in soybean oil (Wolz et al., 2000; unpublished report). The vehicle control group received soybean oil only. At the end of the treatment period, five rats per low- and high-dose group formed the recovery groups. The recovery period was four weeks. There were no deaths, clinical signs of toxicity or effects on body weight or food consumption with either test substance. Activated partial thromboplastin time was statistically significantly prolonged in males at all doses of both test substances ($p < 0.01$, except for the low-dose d-α-tocopheryl acetate group, for which $p < 0.05$). Prothrombin time was statistically significantly prolonged in males of the highest dose groups of both test substances ($p < 0.01$). Conversely, prothrombin time was statistically significantly shortened in females given vitamin E acetate at 2 000 mg/kg bw/day, and both doses of d-α-tocopheryl acetate ($p < 0.01$). In addition, females in the highest dose vitamin E acetate group had statistically significantly decreased total lipids ($p < 0.05$), total cholesterol ($p < 0.05$), triglycerides ($p < 0.01$) and phospholipids ($p < 0.05$). γ-Glutamyltransferase values were slightly increased ($p < 0.01$) in males of the high-dose d-α-tocopheryl acetate group, and absolute and relative liver weights were increased at both doses ($p < 0.05$). At the end of the recovery period, all values were comparable with those of the controls for all groups. There were no necropsy or histopathology findings related to treatment at 13 weeks or at the end of the recovery period. The authors of the study concluded that the NOAEL for this study was 2 000 mg/kg bw/day. They considered that the effects on coagulation parameters were due to suboptimal supplementation with vitamin K and are not toxicologically relevant (Wolz et al., 2000; unpublished report). The Panel noted that effects on coagulation are commonly observed in studies on tocopherols, and to allow comparison of NOAELs across studies, concluded that the NOAEL for this study was 600 mg/kg bw/day, based on reduced total lipids, total cholesterol, triglycerides and phospholipids in females, and prolonged prothrombin time in males.

[25] Commission Directive No 96/54/EC of 30 July 1996 adapting to technical progress for the twenty-second time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ L 248, 30.9.1996, p. 1.

In addition to the studies obtained through the public call for data, a study by Gianello et al. (2007), described below, was also identified from the literature search.

In this 90-day dietary study (Gianello et al., 2007), conducted in accordance with OECD TG 408 (OECD, 1998a) and GLP, Sprague–Dawley rats aged between six and eight weeks were allocated to four treatment groups (10 animals/sex/group). The test substance was mixed tocopheryl phosphates, which is a mixture of d-α-tocopheryl phosphate and d-α-di-tocopheryl phosphate (together constituting 72 % of the mixture) and d-α-tocopherol (13 % of the mixture), plus water and phosphonic acid. Rats were fed diets containing 0, 1, 3 or 5 % (calculated by study authors to be approximately 0, 600, 1900 and 3 200 mg/kg bw/day, respectively) mixed tocopheryl phosphates for 90 days. The authors noted that the major metabolite of mixed tocopheryl phosphates is α-tocopherol; therefore, the Panel considered the findings of this study to be relevant to this re-evaluation. There were some statistically significant changes in haematology and clinical chemistry parameters. However, they were not dose-dependent, occurred in one sex or group and/or remained within the historical control range for this strain of rat. Blood clotting parameters, such as prothrombin times, were not determined in this study. Histopathological examinations revealed changes in the mesenteric lymph nodes and small intestines of treated male and female rats. There was a dose-related appearance of macrophages containing crystal-like foreign material in both tissues. The authors noted that "*In the lymph nodes, sinus histiocytosis increased with dose, but the severity was similar between the control and low dose groups. Foreign-body granulomatous inflammation, associated with Maltese-cross birefringence of the crystals was seen in the mid- and high-dose rats, but not in the low-dose rats. Similarly, the small intestine showed increasing amounts of foreign material and inflammation in the mid- and high-dose*". Therefore, the authors of this study concluded that the NOAEL was a 1 % concentration (approximately 600 mg/kg bw/day) of mixed tocopheryl phosphates (Gianello et al., 2007). However, they noted that the crystals in the lymph nodes and small intestine were likely to be tocopheryl phosphate, probably in the polymerised state. Therefore, the Panel concluded that these findings are not relevant to the tocopherols covered by the re-evaluation. Because of the availability of other good quality studies on the tocopherols, and the fact that studies on the mixed tocopheryl phosphates give toxicological findings that are not relevant to this re-evaluation, additional studies on mixed tocopheryl phosphates are not included herein.

Hamsters

In a non-GLP study (Pfister et al., 1999e; unpublished report) reported to be based on OECD TG 407 (OECD, 2008), d-α-tocopheryl acetate and dl-γ-tocopherol (in soybean oil) were administered, for at least 28 days, by oral gavage to SPF-bred Syrian golden hamsters (10 animals/sex/group). In the treated groups, each hamster was given 2 000 mg/kg bw/day tocopherol. There were also two control groups; one group was given the vehicle only, and the other group remained untreated. Concentrations of the tested tocopherols in plasma and liver were also measured at the end of the exposure period. There were no test substance-related deaths, clinical signs of toxicity, or effects on food consumption or body weights in any group. d-α-tocopheryl acetate and dl-γ-tocopherol caused a statistically significantly prolonged prothrombin time and activated partial thromboplastin time in males and females after 28 days treatment ($p < 0.05$ ad $p < 0.01$, respectively) when compared with hamsters that were untreated. Male and female hamsters treated with d-α-tocopheryl acetate had statistically significantly lower levels of total lipids, total cholesterol and phospholipids ($p < 0.05$ or $p < 0.01$) compared to the untreated controls. Total bilirubin (males and females) and creatinine (males only) were statistically significantly increased ($p < 0.01$) compared with untreated hamsters. Alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and γ-glutamyltransferase activities were all statistically significantly higher (p-values not stated) in treated females than in untreated females. Female hamsters given dl-γ-tocopherol had statistically significantly decreased ($p < 0.05$ or $p < 0.01$) total lipids, total cholesterol and phospholipids compared with untreated females. Creatinine levels were significantly raised (p value not stated) in males when compared with untreated males. The authors of this study noted that the effects on prothrombin times and activated partial thromboplastin times, and the decreases in lipid, total cholesterol and phospholipids are well known effects of tocopherols. The authors questioned the toxicological relevance of the effect on creatinine. Plasma and

liver concentrations of α-tocopherol were increased after d-α-tocopheryl acetate administration, and decreased after dl-γ-tocopherol administration, compared with controls. Following administration of dl-γ-tocopherol, plasma and liver concentrations of γ-tocopherol were higher (Pfister et al., 1999e).

Pfister et al. (1999d; unpublished report) conducted a 13-week gavage study in hamsters. This study was stated to be conducted in accordance with GLP using a protocol based on OECD TG 408 (OECD, 1998a). However, there are several limitations to the study compared with this guideline, including the use of fewer animals, fewer dose levels and only a single sex. dl-γ-Tocopherol (800 mg/kg bw/day) was administered orally, by gavage, in soybean oil to 10 female Syrian golden hamsters for 13 weeks. One control group (10 female hamsters) remained untreated and a second control group (10 female hamsters) received soybean oil. All animals were sacrificed, and necropsy and microscopic examination performed. Blood samples were collected for haematology and clinical chemistry evaluation. For the histopathology, the small intestine (duodenum, jejunum and ileum), mesenteric lymph nodes and all gross lesions were examined. The examinations were therefore not as extensive as the OECD test guideline recommends. There were no deaths or clinical signs of toxicity. Body weights and food consumption of treated hamsters were comparable with control hamsters. Female Syrian hamsters showed statistically significantly prolonged activated partial thromboplastin time and prothrombin time ($p < 0.01$). Functional changes such as statistically significantly increased bilirubin (< 0.01), alkaline phosphatase ($p < 0.01$) and γ-glutamyltransferase ($P < 0.01$) were observed. There were no treatment-related changes to organ weights. Macrophage aggregates in the mesenteric lymph nodes were also identified in hamsters (Pfister et al., 1999c; unpublished report). The Panel concluded that, based on the occurrence of prolonged clotting parameters and functional changes, the NOAEL for dl-γ-tocopherol in hamsters was less than 800 mg/kg bw/day under the conditions of this study.

Minipigs

Pfannkuch et al. (2000; unpublished report) conducted a 13-week oral study, reported to be conducted in accordance with OECD TG 409 (OECD, 1998b) and GLP. Two different preparations of d-α-tocopherol acetate (test and reference; it is not clear from the study report how these preparations differ, except that they have different purities (91.4 and 79.3 %, respectively)) were administered orally (180, 600 or 2 000 mg/kg bw/day and 180 and 2 000 mg/kg bw/day, respectively), by gavage, in soybean oil to Göttingen minipigs (two animals/sex/group) for a period of 13 weeks. Control animals received 5 mL/kg soybean oil. Animals from the two highest dose groups for each preparation were then observed for the duration of a four-week recovery period. One animal from each of the test preparation groups and one animal from the highest reference preparation group died or were killed because of their poor condition during the treatment period. In the minipigs that survived, there were no adverse clinical findings, no effect on food consumption and no effects on the eyes or organ weights, which were comparable with those of the controls. Treated animals gained less weight than controls, which was related to the intake of calories from the soybean vehicle. Slightly longer, dose-dependent activated partial thromboplastin times were seen for both preparations ($p < 0.01$). This effect was no longer apparent at the end of the four-week recovery period, and was considered to be due to inadequate vitamin K supplementation. There were effects on the lungs that were due to dosing errors. The authors of the study concluded that the No Observed Effect Level (NOEL) was 2 000 mg/kg bw/day for both preparations. The Panel identified a NOAEL value of 600 mg/kg bw/day for d-α-tocopherol acetate based on the dose-dependent increase in coagulation times, which only reached statistical significance at a dose of 2 000 mg/kg bw/day.

3.2.3. Genotoxicity

The SCF (2003) could not identify any studies designed to investigate the genotoxic potential of vitamin E. In addition, a literature search did not indicate that any new relevant published data are available on the genotoxicity of tocopherol-rich extract, α-, γ- or δ-tocopherol. Three Ames tests, an *in vitro* chromosomal aberration test and an *in vivo* mutagenicity study, that have not been previously evaluated, were submitted to EFSA following the public call for data, and are reviewed below.

In a standard *in vitro* bacterial mutagenicity test (Ames test) (Gocke, 1999; unpublished report), conducted in accordance with OECD TG 471 (OECD, 1997a) and GLP, dl-α-tocopherol was evaluated at concentrations of 5–5 000 µg/plate. Five *Salmonella typhimurium* tester strains (TA 97, TA 98, TA 100, TA 102 and TA 1535) were employed, with and without a metabolic activation system (S9). The activity of the S9 and the responsiveness of the tester strains were verified by including appropriate controls. Cytotoxic effects were generally not observed, with the exception of a weak reduction of background growth in strain TA 98, without S9. No increase in the number of revertant colonies was apparent for any of the tester strains after treatment, and positive controls gave appropriate results. Therefore, the authors concluded that the test substance was devoid of mutagenic activity in this test. The Panel agreed with this conclusion.

In an Ames test conducted by Gocke (1998; unpublished report), d-α-tocopheryl acetate was evaluated for mutagenic activity. In this test, which was conducted in accordance with OECD TG 471 (OECD, 1997a) and GLP, d-α-tocopheryl acetate was evaluated using concentrations of 5–5 000 µg/plate. Five *S. typhimurium* tester strains (TA 97, TA 98, TA 100, TA 102 and TA 1535) were employed, with and without a metabolic activation system (S9). The activity of the S9 and the responsiveness of the tester strains were verified by including appropriate controls. No increase in the number of revertant colonies was apparent for any of the tester strains after treatment, and the positive controls gave appropriate results. Therefore, the study authors concluded that the test substance did not induce an increase in the number of revertant colonies/plate in any of the tester strains, and was devoid of mutagenic activity in this test. The Panel agreed with this conclusion.

Engelhardt (1989; unpublished report) also conducted a bacterial gene mutation assay in accordance with OECD TG 471 (OECD, 1984). No tests in *S. typhimurium* TA 102 strain or in an *Escherichia coli* strain were included, as these strains were not recommended at the time the study was performed. This assay was not performed in accordance with GLP. Vitamin E acetate (no further information) was tested at concentrations in the range of 20–5 000 µg/plate in *S. typhimurium* tester strains TA 98, TA 100, TA 1535 and TA 1537, with and without metabolic activation (S9), in two independent assays using standard incorporation and preincubation assay. No cytotoxicity was evident in any of the tester strains with vitamin E acetate. There was no increase in the number of revertant colonies for any of the tester strains after treatment with vitamin E acetate. Positive controls gave appropriate results. Therefore, as with other reported Ames tests, vitamin E did not show any evidence of mutagenic activity.

Chételat (1999; unpublished report) conducted an *in vitro* chromosomal aberration test with human peripheral blood lymphocytes in accordance with OECD TG 473 (OECD, 1997b) and GLP. dl-α-Tocopheryl acetate was used at concentrations in the range of 75–1800 µg/mL (limited by solubility). Treatment in the absence of metabolic activation was continuous for either 24 hours or 3 hours, followed by a recovery period of 21 hours. In the presence of metabolic activation (S9), treatment with the dl-α-tocopheryl acetate was for 3 and 5 hours, followed by recovery periods of 21 or 19 hours, respectively. A second harvest time 48 hours after the beginning of treatment was included in one experiment. Bleomycin and cyclophosphamide were used as positive controls. Both of these substances significantly increased the rate of structural chromosomal aberrations. dl-α-Tocopheryl acetate did not increase the frequency of cells with structural or numerical chromosome aberrations to a biologically relevant extent. Therefore, the Panel concluded that dl-α-tocopheryl acetate is not clastogenic or aneuploidogenic under the conditions of this test.

Umegaki et al. (1997) published the findings of two *in vivo* methods that investigated the influence of dietary vitamin E (in the form of dl-α-tocopheryl acetate) on chromosomal damage (peripheral blood micronucleus test) and DNA damage (sister chromatid exchanges (SCEs)) in bone marrow in mice. Male ICR mice were fed a low (no vitamin E added to diet), basal (30 mg vitamin E/kg diet added) or high (1 000 mg vitamin E/kg diet added) vitamin E diet for 50 weeks. During the experimental period, a micronucleus assay was conducted periodically (after 6, 8, 17, 24, 28, 34, 37, 46 and 50 weeks) on peripheral blood. At the end of the experimental period, the remaining mice were killed, and DNA damage was directly assessed in bone marrow cells by examining SCEs. Results for SCEs were

compared with results for the positive control cyclophosphamide. At 50 weeks, DNA damage, assessed using SCEs, did not vary with the concentration of vitamin E in the diets. The micronucleus assay showed that the incidence of reticulocytes containing micronuclei was not affected by vitamin E in the diet.

In the absence of published studies on the genotoxicity of tocopherols, previous reviews by the SCF (2003) and the EVM (2003) mainly focused on the antioxidant properties of tocopherols, which appear to support antimutagenic and anticlastogenic activity. For example, in an *in vitro* investigation into the anticlastogenic activity of vitamin E (tocopherol form not specified) in human peripheral blood lymphocytes from healthy blood donors, vitamin E decreased the chromosome-damaging action of the alkylating agent trenimon, both with and without S9. The potential anti-SCE activity of vitamin E on trenimon- and cyclophosphamide-induced DNA damage was also investigated, but vitamin E treatment was found to have no effect on SCE formation (Gebhart et al., 1985). Gebhart et al. (1985) shortly reported the antimutagenic activity of vitamin E on chemical mutagens/carcinogens observed in bacterial tests. The potential for vitamin E to protect against some mutagenic and clastogenic activity is outside the remit of this opinion, and the data are therefore not reviewed further.

All the available tests have been conducted on the α-tocopherol and its acetate derivative; there are no genotoxicity tests on tocopherol-rich extract, or γ- or δ-tocopherol.

Overall, the Panel considered that there is no evidence to suggest that α-tocopherol is genotoxic (Engelhardt, 1989; Gocke, 1998, 1999; Chételat, 1999, all unpublished reports; Umegaki et al., 1997). Moreover, there are *in vitro* studies that support the antioxidant properties of vitamin E being protective against genetic damage (Gebhart et al., 1985). The Panel concluded that the available results from *in vitro* and *in vivo* genotoxicity studies performed with α-tocopherol do not raise any concern, and considered that this also applies to γ-tocopherol, δ-tocopherol and tocopherol-rich extracts.

3.2.4. Chronic toxicity and carcinogenicity

A literature search and an EFSA public call for data did not indicate that any new relevant data are available on the chronic toxicity and carcinogenicity of tocopherol-rich extract, or α-, γ- or δ-tocopherol. There is one rat chronic toxicity study and one rat carcinogenicity study available, which have previously been reviewed (TemaNord, 2002; EVM, 2003; SCF, 2003; EFSA, 2008); these are summarised below.

Groups of weanling female Wistar rats were fed diets containing 0, 25, 250, 2 500, 10 000 or 25 000 IU vitamin E (as dl-α-tocopheryl acetate)/kg diet, equivalent to approximately 0, 1.25, 12.5, 125, 500 and 1 250 mg/kg bw/day, respectively, for 8 and 16 months (Yang and Desai, 1977). The initial number of animals is not clear. At 8 months, 4 animals from each dose group were sacrificed and examined. The remaining animals continued with treatment until their sacrifice at 16 months. There appear to have been four, nine, six, seven and five rats in the 25, 250, 2 500, 10 000 and 25 000 IU of vitamin E groups, respectively, at 16 months. Body weight gain was depressed at doses of 10 000 IU/kg diet and above, and relative heart and spleen weights were increased in this dose group at 8 and 16 months, respectively. In the same dose groups, there was an increase in plasma alkaline phosphatase and a decrease in the bone ash content after 16 months. Prothrombin time was reduced ($p < 0.02$) at 12 months, but not at 9 or 16 months. Urinary excretion of creatine and creatinine was normal at 11 months. No histological examinations were reported. No adverse effects were associated with vitamin E at levels of 2 500 IU/kg diet (Yang and Desai, 1977). The NOAEL can be estimated to be approximately 125 mg/kg bw/day.

Groups of CD rats (60 animals/sex/group) were fed vitamin E (dl-α-tocopherol acetate) in the diet at doses calculated to provide 500, 1 000 or 2 000 mg vitamin E/kg bw/day for 104 weeks (Wheldon et al., 1983). A further 10 rats per group were killed after 12 months of treatment. The control diet contained 39 mg per kg vitamin E (equivalent to approximately 2 mg/kg bw/day). At all dose levels,

between 15 and 18 weeks, the male animals developed spontaneous haemorrhages in the gut, urinary tract, meninges and orbit. This led to some mortality, but in survivors the condition was corrected by administration of 10 mg vitamin K/kg bw/day from week 24 onwards, first in drinking water and then in diet (both in controls and treated rats). Blood samples from 10 rats per sex from the control and highest dose groups were taken after 4, 8, 13, 26, 52 and 95 weeks of treatment to examine haematological parameters. Similarly, serum chemistry was examined in half of the animals, and urine samples from 10 rats per sex of the control and highest dose groups were collected, all at approximately the same time intervals. After 52 weeks of treatment, 10 animals/sex/group were killed for histopathological examinations. After 104 weeks of treatment, all surviving rats were also killed and examined. Organ weights and organ-to-body weight ratios were determined for adrenals, brain, heart, liver, lungs, testes, ovaries, pituitary, spleen, thyroids, prostate and uterus in all rats. Histopathological examinations of selected tissues were conducted for controls and highest dose group rats. The liver was examined in all animals. Effects on prothrombin times were not observed after initiation of vitamin K supplementation. Absolute liver weights were slightly increased ($p < 0.05$) in the highest dose females only at the interim 12-month sacrifice. At 104 weeks, no effects on liver weights were found. The only other treatment-related effect of significance was the presence of vacuolated lipid staining macrophages in the liver in all vitamin E-treated groups, with females showing the highest incidence (17 % of treated males and 77 % of treated females across the groups). While this finding did not show dose dependency, it was not observed in the control group. There was a trend towards fewer mammary tumours in the females (the same effect was suggested in males but was not statistically significant). Otherwise, the tumour profile was not altered by treatment (Wheldon et al., 1983). The Panel concluded that a NOAEL for general systemic toxicity could not be established in this study due to the effects on blood clotting and liver tissue. No carcinogenic effect was observed up to a level of 2 000 mg/kg bw/day.

Overall, it is concluded by the Panel that although the data available are limited, there is no evidence to suggest that α-tocopherol is carcinogenic.

In summary, the chronic toxicity/carcinogenicity studies available were conducted on dl-α-tocopherol acetate; there are no studies on tocopherol-rich extract, or γ- or δ-tocopherol (Yang and Desai, 1977; Wheldon et al., 1983).

With regard to non-carcinogenic effects following chronic exposure, the critical adverse effect observed in the subchronic toxicity studies was reduced blood clotting. This effect was confirmed in the carcinogenicity study in rats by Wheldon et al. (1983), in which a NOAEL could not be determined. The LOAEL for this study was 500 mg/kg bw/day. In the chronic toxicity study by Yang and Desai (1977), a NOAEL of 125 mg/kg bw/day was determined, based on effects that included reduced body weight gain and increased heart and spleen relative weights.

3.2.5. Reproductive and developmental toxicity

A literature search revealed several studies that had not previously been evaluated and these are described in this section and Section 3.2.6.1 on human studies. An EFSA public call for data did not indicate that any new relevant data are available on the reproductive and developmental toxicity of tocopherol-rich extract, or α-, γ- or δ-tocopherol. There are three main studies (Hook et al., 1974; Krasavage and Terhaar, 1977; Martin and Hurley, 1977) available, which have previously been reviewed (EVM, 2003; SCF, 2003; TemaNord, 2002); these are discussed below.

The beneficial vitamin activities of the tocopherols are outside the remit of this opinion and are not discussed further, but are considered when discussing the importance of data gaps for the reproductive and developmental toxicity endpoint. In addition, there are only studies on α-tocopherol, and none on γ- or δ-tocopherol, or on tocopherol-rich extract.

A previously not evaluated study, conducted by Betti et al. (2011), investigated the effects of α-tocopherol supplementation on the developing rat brain. Sprague–Dawley rats (10 females) were fed a

diet supplemented with 1 000 mg d-α-tocopherol/kg bw/day. The control group (10 females) was fed a standard diet. The diets were administered for two weeks before mating and then throughout pregnancy and lactation. Once weaned, the offspring were fed a standard diet. Offspring were sacrificed at postnatal days 0 (day of birth), 7, 14, 21 (weaning) and 60–90 (adulthood). There were no adverse effects on survival, weight of pups, litter size, and no apparent teratogenic effects or effects on the timing of developmental milestones, such as eye opening and hair coat development. The offspring from the group supplemented with d-α-tocopherol had double the concentration of α-tocopherol in the hippocampus on postnatal days 0 and 21 compared with controls. On these same days, the liver α-tocopherol was eight-fold higher in treated group offspring than in controls. The authors of the study concluded that "*Although processes of neuronal maturation, synapse formation and targeting appeared unaffected, offspring of supplemented mothers displayed a marked reduction of long-term synaptic plasticity in juvenile hippocampus. Interestingly, this impairment persisted to adulthood, when a deficit in hippocampus-dependent, long-lasting spatial memory was also revealed*" (Betti et al., 2011).

The potential effects of high doses of vitamin E on pregnant rats and their offspring have been investigated in a comprehensive pre-GLP study (Martin and Hurley, 1977). This is an informative study that was not reported in detail in previous reviews. Owing to the lack of more recent data, this study is reported in more detail in this opinion. Pregnant Sprague–Dawley rats (the number of rats used in this study is unclear, but appears to be in the range of 3–12, depending on the group and experiment) were supplemented orally with large amounts of vitamin E (as dl-α-tocopheryl acetate dissolved in corn oil) during gestation, or during gestation and lactation. There were six experiments organised as follows:

- In experiment I, rats were administered 22.5, 45, 90, 450 and 900 mg/kg bw/day of dl-α-tocopheryl acetate during gestation only. Only pregnant animals were supplemented. Suckling pups were prevented from eating the supplement at all times.

- In experiments II and III, rats were given 0, 450, 900 and 2 252 mg/kg bw/day of dl-α-tocopheryl acetate during gestation and lactation. dl-α-Tocopheryl acetate and lipids were measured in the plasma and livers of the rats given 0 and 2 252 mg/kg bw/day. Suckling pups were prevented from eating the supplement at all times.

- In experiment IV, rats were given 0 and 2 252 mg/kg bw/day dl-α-tocopheryl acetate during gestation, and fetuses were examined at term by caesarean section. Plasma and liver dl-α-tocopheryl acetate and lipids were measured.

- In experiment V, the offspring from experiment I were allowed to mate, and the survival and health of their offspring were studied. Only pregnant animals were supplemented. Suckling pups were prevented from eating the supplement at all times.

- In experiment VI, the offspring from experiment III were allowed to mate, and survival and the health of their offspring were studied. Only pregnant animals were supplemented. Suckling pups were prevented from eating the supplement at all times.

In experiments I–III, lactating females and two pups from each litter were anesthetised on the 21st day of lactation, and blood and liver samples were taken for lipid analysis. Dams and their offspring were examined for teratogenicity, survival, body weight changes, vitamin E content of the liver and plasma, and liver and plasma neutral lipids. Body weight gains of dams and the number of pups per litter were not affected, except at doses of 450 and 900 mg/kg bw/day dl-α-tocopheryl acetate during gestation. In these groups there was a statistically significant ($p < 0.05$) gain in weight during lactation compared with controls (corn oil only). Birth weights and postnatal growth were not affected by treatment in any experiment. Postnatal survival of the offspring was unaffected, except for the offspring of females that were administered 90 mg/kg bw/day dl-α-tocopheryl acetate during gestation only. These offspring had a lower survival rate throughout the lactation period compared with controls. However, the Panel

noted that the lack of dose–response relationship for this effect means that it can be discounted as a toxicologically significant effect. Postnatal survival of the second generation rats was unaffected, except for the offspring of females that were administered 900 mg/kg bw/day dl-α-tocopheryl acetate during gestation. These offspring had a lower survival rate throughout the lactation period compared with the controls. The maternal liver weights of rats given 90 or 900 mg/kg bw/day dl-α-tocopheryl acetate during gestation (experiment I) were statistically significantly greater ($p < 0.02$ and $p < 0.001$, respectively) than controls. When expressed relative to body weights, liver weights were statistically significantly greater ($p < 0.02$ up to 450 mg/kg bw/day and $p < 0.001$ for 900 mg/kg bw/day) in all but the lowest dose group. Effects on liver weight were not observed in experiments II and III, except when 900 mg/kg bw/day dl-α-tocopheryl acetate was administered. Conversely, the liver weights of rats given 2 252 mg/kg bw/day dl-α-tocopheryl acetate were statistically significantly lower ($p < 0.01$) than that of the controls. The total lipids in the plasma of rats that were given 2 252 mg/kg bw/day dl-α-tocopheryl acetate were significantly higher ($p < 0.05$) than those of the control rats at term (experiment IV) and at the end of lactation (experiment III). However, there was no statistically significant increase in any of the individual lipids. In rats administered 2 252 mg/kg bw/day, dl-α-tocopheryl acetate in maternal plasma was higher than in controls at term (experiment IV), but not at the end of lactation (experiment III). Maternal liver dl-α-tocopheryl acetate content was statistically significantly higher than controls at term (experiment IV), and also at the end of lactation (experiment IV), although to a lesser extent ($p < 0.02$ compared with $p < 0.05$, respectively). In newborn rats, plasma dl-α-tocopheryl acetate was statistically significantly higher ($p < 0.01$) in the offspring of the treated group than in controls (experiment III). dl-α-Tocopheryl acetate in the liver was also statistically significantly higher ($p < 0.02$) in the offspring of the group supplemented with 2 252 mg/kg bw/day during gestation and lactation, but no dl-α-tocopheryl acetate was found in the livers of full-term fetuses. This indicates that dl-α-tocopheryl acetate is effectively transferred through the mammary gland, but not the placenta. It was noted that several of the newborns in the 450 mg/kg dose group (first and second generations) showed delayed opening of the eyelids, but this was not statistically significant. There were no fetal abnormalities in any of the experimental groups. The NOAEL for reproductive and developmental toxicity is $\geq$ 2 252 mg/kg bw/day, based on the observation that there are no significant, dose-dependent adverse effects on reproductive or developmental parameters investigated, at any dose.

Krasavage and Terhaar (1977) conducted a series of studies to investigate the toxicity of d-α-tocopheryl poly(ethylene glycol) 1 000 succinate. Following a 90-day dietary study in which rats were fed a diet containing 0.002, 0.2 or 2 % d-α-tocopheryl poly(ethylene glycol) 1 000 succinate (calculated by the study authors to be 0.5, 50 or 500 mg/kg bw/day vitamin E, respectively), half of the rats (15 animals/sex/dose) from each group were designated the parent generation (F_0) and subsequently mated to produce two first generation litters (F_{1a} and F_{1b}). F_0 rats had been ingesting their allocated diets for 112 days and 175 days when mated to produce the F_{1a} and F_{1b} generations, respectively. Different male to female pairs were used in producing the two litters. All pups were weaned at 21 days of age, and killed five weeks after weaning. Histopathological examinations were conducted on four pups (two per sex where possible) from each litter. All other pups were examined for gross pathology. Mean gestation period, litter size, sex ratio, mortality of pups and parents, and the mean postnatal body weights per litter at four days, weaning, one and two weeks after weaning, and at necropsy, were recorded. Insemination, fertility, gestation, viability and lactation indices were calculated. With regard to the F_0 rats, organ weights, haematology and clinical chemistry parameters were also recorded for the control and highest dose group. There were no adverse findings for any of the parameters or indices. All findings were comparable with those in the control group (Krasavage and Terhaar, 1977). The Panel concluded that the NOAEL for reproductive toxicity in this study was $\geq$ 500 mg/kg bw/day vitamin E.

In a teratology study conducted by Krasavage and Terhaar (1977), 50 male and 100 female CD rats were mated to obtain 75 pregnant rats. The inseminated females were randomly assigned to five groups: one negative control group, one positive control group and three treatment groups. The positive control group received a diet containing technical grade opholate (concentration not stated). The treatment groups received a diet containing 0.002, 0.2 and 2 % d-α-tocopheryl poly(ethylene

glycol) 1 000 succinate (calculated by the study authors to be 0.5, 50 and 500 mg/kg bw/day vitamin E, based on reported food consumption data, respectively) on gestation days 6 to 16. Maternal body weights were recorded daily and food consumption was recorded for gestation days 0–6, 6–16 and 16–20. On gestation day 20, the rats were killed. Subsequently, implantation sites were categorised as live fetuses, dead fetuses or resorptions. The fetuses were sexed and examined for gross abnormalities. Half of each litter was then examined for internal soft tissue anomalies, and the other half for skeletal abnormalities. There were no adverse effects on body weight or food consumption of rats in the d-α-tocopheryl poly(ethylene glycol) 1 000 succinate groups. However, there was a reduction in food consumption and body weight during weeks 6–16 in rats of the positive control group. There were no treatment-related abnormalities in fetal development in the d-α-tocopheryl poly(ethylene glycol) 1 000 succinate-treated groups. The positive control group had increased numbers of resorptions and abnormal fetuses, and decreased viable fetuses and fetal body weights (Krasavage and Terhaar, 1977). Therefore, the Panel concluded that d-α-tocopheryl poly(ethylene glycol) 1 000 succinate does not have adverse effects on organogenesis in rats up to doses of 500 mg/kg bw/day.

According to the SCF guideline (SCF, 2001), there are insufficient studies to address the reproduction and developmental endpoints, as there are no multigeneration studies conducted in accordance with appropriate test guidelines. However, the results of the study conducted by Martin and Hurley (1977), in which two of the test groups were extended into a second generation, are useful in addressing the reproductive toxicity and developmental endpoints. There are only developmental studies in rats; a second species has not been tested.

3.2.6. Other studies

3.2.6.1. Human studies

The EFSA call for data did not reveal any human studies. Human studies have been discussed previously in the SCF opinion (SCF, 2003), the TemaNord review (TemaNord, 2002), the EVM review (EVM, 2003) and the IOM review (IOM, 2000). The EFSA opinions (EFSA, 2008; EFSA FEEDAP Panel, 2010) did not add any new human studies, but instead primarily summarised findings from the SCF (2003) and EVM (2003). An extensive number of published papers have been reviewed, particularly in the EVM review; not all are included in this opinion, rather key papers that impart the key, current areas of research and discussion are summarised. New relevant publications, published since 2003 and retrieved through the literature search, are also included in this section.

Cardiovascular system and haematology

In the study upon which the current UL derived in the SCF opinion (2003) is based, Meydani et al. (1998) conducted a double-blind placebo-controlled study to assess the effects of dl-α-tocopherol on general health, nutrient status, liver enzyme function, thyroid hormone concentrations, creatinine concentrations, serum autoantibodies, cytotoxic ability of neutrophils against *Candida albicans*, and bleeding time, in 88 healthy male and female subjects aged 65 years and older. Subjects were randomly assigned to four groups that were given capsules containing 60, 200 or 800 IU (55, 182 or 727 mg, respectively) vitamin E per day (n = 19, 18 and 19, respectively). The vitamin E in these capsules contained 30, 100, or 400 IU (27, 91 or 364 mg, respectively) dl-α-tocopherol in soybean oil. There was also a placebo group (n = 17); this placebo group was given capsules that contained only soybean oil and were identical in taste and appearance to the vitamin E capsules. Plasma vitamins, trace elements, antioxidant status, haematological status, hepatic and renal function, intermediary metabolism, bleeding time, serum autoantibodies, and the ability of neutrophils to kill *C. albicans* were assessed before and after four months of supplementation. It was concluded that supplementation did not affect the plasma concentrations of other antioxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase or total cysteine. There was no statistically significant effect of vitamin E on serum non-specific immunoglobulin concentrations, or anti-DNA and anti-thyroglobulin antibodies. The cytotoxic ability of neutrophils against *C. albicans* was not compromised. Vitamin E had no effect on body weight, plasma total proteins, albumin, glucose, plasma lipids, or the lipoprotein profile, total bilirubin, serum liver enzymes, blood count, platelet number, haemoglobin, haematocrit,

urinary or serum creatinine levels. A treatment-related adverse effect on bleeding time was not observed (method of determination not stated) when compared with placebo subjects. Therefore, as has been previously concluded by the SCF (2003) and the EVM (2003), the NOAEL for this study was 800 IU vitamin E per day (or 537 mg d-α-tocopherol equivalents/day). The Panel agreed with this conclusion.

The EVM report (EVM, 2003) also discusses a study conducted by Stephens et al. (1996), which was a double-blind, placebo-controlled study aimed at investigating the hypothesis that treatment with a high dose of α-tocopherol would reduce the subsequent risk of myocardial infarction and cardiovascular death in patients with established ischaemic heart disease. In this study, 2 002 male and female patients with proven coronary atherosclerosis were enrolled. Of these, 546 patients received 800 IU vitamin E per day (537 mg as d-α-tocopherol/day), 489 received 400 IU vitamin E per day (268 mg as d-α-tocopherol/day) and 967 received identical placebo capsules. The median follow-up period was 1.5 years. Treatment with α-tocopherol significantly reduced the risk of composite cardiovascular death and non-fatal myocardial infarction by 47 % ($p < 0.005$). The reduction in this risk was mainly accounted for by the significantly reduced risk of non-fatal myocardial infarction by 77 % ($p < 0.005$), which was apparent after approximately 200 days of treatment with α-tocopherol. There was also an apparent, non-statistically significant, excess of cardiovascular deaths in the treatment group ($p < 0.61$), but the study authors noted that these events tended to occur early on in the study, perhaps before the treatment had had any effect. They also speculated that these might be chance findings or reflect a difference in biological events leading to the deaths, compared with those leading to non-fatal myocardial infarction. The EVM report (EVM, 2003) concluded that this result and the one from the Meydani et al. (1998) study, confirm the NOAEL of 537 mg d-α-tocopherol equivalents per day.

Diplock (1995) concluded that there is evidence to suggest that vitamin E can exacerbate the blood coagulation defect of vitamin K deficiency caused by malabsorption or anticoagulant therapy, and suggested that high vitamin E intake is contraindicated in these subjects. An example of this was exhibited in a study conducted by Corrigan and Ulfers (1981), in which 12 adult cardiology patients (eight male and four female) that were being prescribed warfarin on a long-term basis (mean of 6.2 years of treatment) consented to take supplemental vitamin E orally. Patients took either 100 or 400 IU (equivalent to 67 or 268 mg) of α-tocopherol per day for four weeks. Blood samples were collected monthly for five months before the vitamin E supplementation commenced, and then weekly during the supplementation period. Fifty adult patients, without known liver disease or vitamin K deficiency, served as controls. It was shown that the effect of warfarin was intensified when administered along with vitamin E; for example, prothrombin time was statistically significantly increased in the vitamin E-treated patients compared with controls (Corrigan and Ulfers, 1981).

However, the SCF report (SCF, 2003) included studies on healthy humans, which showed that there was no adverse effect on platelet aggregation or adhesion when supplements of up to 800 mg α-tocopherol equivalents (1 200 IU) were taken (Farrell and Bieri, 1975; Tsai et al., 1978). Also, in the study by Kitagawa and Mino (1989; further details in Section 3.1.2), 19 healthy male students did not show any signs of toxicity or effects on thyroid, liver or kidney function, coagulation activity or immunoglobulin levels while taking 600 mg (900 IU) d-α-tocopherol per day for three months.

Studies, such as those by Boaz et al. (2000), Lippman et al. (2009) and Leppala et al. (2000a), provide evidence for vitamin E having no adverse or beneficial effects on cardiovascular disease. Boaz et al. (2000) specifically investigated the effect of high doses of vitamin E on cardiovascular disease outcomes in haemodialysis patients ($n = 196$; 40–75 years old, male and female) with pre-existing cardiovascular disease. Patients were given supplements containing either 800 IU vitamin E per day or the placebo for two months, and followed up for a median of 519 days. Primary outcomes, myocardial infarction (fatal and non-fatal), ischaemic stroke, peripheral vascular disease and unstable angina, as well as secondary outcomes, such as total mortality and mortality related to cardiovascular disease, were monitored for associations with vitamin E supplementation. It was found that a total of 15 (16 %) of the 97 patients assigned to the vitamin E group, and 33 (33 %) of the 99 patients assigned to the

placebo group had a primary endpoint (acute myocardial infarction (fatal and non-fatal); ischaemic stroke; peripheral vascular disease (excluding the arterio-venous fistula) in a limb not previously affected; unstable angina) (relative risk 0.46; 95 % confidence interval (CI) 0.27–0.78; p = 0.014). Five (5.1 %) patients assigned to the vitamin E group and 17 (17.2 %) patients assigned to the placebo group had a myocardial infarction (relative risk 0.3; 95 % CI 0.11–0.78; p = 0.016). No statistically significant differences in other secondary endpoints (fatal and non-fatal myocardial infarction, cardiovascular-disease mortality (fatal myocardial infarction, ischaemic stroke or sudden death), total mortality, ischaemic stroke, peripheral vascular disease, and unstable angina), cardiovascular disease, or total mortality were detected. The study authors concluded that vitamin E supplementation (800 IU/day) in haemodialysis patients with cardiovascular disease reduces composite cardiovascular disease outcomes and myocardial infarction.

Leppala et al. (2000a, b) conducted a population-based, randomised, double-blind, placebo-controlled trial, in which 29 133 male smokers aged 50 to 69 years were recruited and randomised into treatment groups to investigate whether vitamin E could prevent stroke in men at high risk of haemorrhagic or ischaemic events. Vitamin E (as dl-α-tocopherol) at 50 mg/day or placebo were taken by the subjects, who were followed up for a median length of six years. The authors of the study concluded that, while the risk of cerebral infarction in hypertensive men was reduced (relative risk, 0.7; 95 % CI 0.55–0.89), there was no effect in men with normal blood pressure. The risk of subarachnoid haemorrhage was increased (relative risk 2.45; 95 % CI 1.08–5.55) in hypertensive men only. However, vitamin E decreased (relative risk 0.33; 95 % CI 0.14–0.78) the risk of cerebral infarction, without increasing the risk of subarachnoid haemorrhage among hypertensive men with diabetes. Therefore, it appears that vitamin E has the potential to prevent ischaemic stroke in high-risk hypertensive patients (Leppala et al., 2000a).

Importantly, the Lippman et al. (2009) study, which primarily investigated prostate cancer prevention, also found that there was no effect on the number of non-fatal strokes or other cardiovascular events in healthy men. Eidelman et al. (2004) concluded that, based on available large-scale trials, there is a lack of support for any beneficial effects of vitamin E on cardiovascular disease. Miller et al. (2005) analysed a number of randomised controlled trials, and concluded that there was an increased risk of all-cause mortality for high doses of vitamin E (at least 400 IU). However, the authors noted that this analysis was limited by the fact that high-dose trials were often small and involved patients with chronic diseases, and that the applicability of this finding to healthy individuals was uncertain.

It is of interest that Liu et al. (2003) discussed the conflicting results with regard to beneficial effects of α-tocopherol on cardiovascular events, and, using human subjects, showed that mixed tocopherols (rich in γ-tocopherol) are more potent than α-tocopherol alone in preventing platelet aggregation. Hence, studies that test only α-tocopherol are less likely to detect a beneficial effect on cardiovascular events than those that test mixed tocopherols, particularly γ-tocopherol. The Panel noted that this finding might have implications for the assumption that α-tocopherol is the most biologically active form. The findings with regard to beneficial effects suggest that α-tocopherol might be less potent than γ-tocopherol in protecting against cardiovascular events. Booth et al. (2004) conducted a study in order to investigate the vitamin K status in healthy men (16 men in each of the age ranges 18–35 years and 65–80 years) recruited from the general population. Vitamin E (1 000 IU, equivalent to 671 mg d-α-tocopherol/day in soybean oil) or vehicle control were administered daily for 12 weeks. Proteins induced by vitamin K absence, factor II (PIVKA-II), a functional measure of biological activity of hepatic vitamin K, and the percentage of undercarboxylated osteocalcin (ucOC), a marker of vitamin K status in extrahepatic tissues, were measured in blood samples before and after the 12-week treatment period. PIVKA-II significantly increased ($p < 0.001$) during the vitamin E treatment compared with the control group. This was indicative of a poor vitamin K status in the treated subjects. In contrast, ucOC did not change significantly. However, the study also showed that vitamin K absorption was not affected, as there was no change in ucOC levels, and the authors therefore speculated that the effect on vitamin K occurs in the tissues.

In summary, the principal adverse effects of the tocopherols is on prothrombin times and factors relating to blood clotting, via an interaction with vitamin K or vitamin K-dependent proteins, that is as yet not understood (Booth et al., 2004). However, it does appear that in humans this effect is only observed at high doses, which are not relevant to the use of tocopherols as food additives (IOM, 2000). Susceptible subgroups appear to be individuals with already compromised blood clotting capacity, and those with low vitamin K status (Corrigan and Ulfers, 1981; Diplock, 1995). While not all studies are consistent, it also appears that while cardiovascular disease is not affected by vitamin E in healthy individuals (Lippman et al., 2009), it has the potential to reduce primary cardiovascular outcomes, such as stroke, in patients with existing cardiovascular disease (Boaz et al., 2000; Stephens et al., 1996).

Cancer

Antioxidant nutrients, such as vitamin E, protect cell constituents from the damaging effects of free radicals that might contribute to cancer development (US ARS, 2011). Several studies have examined whether vitamin E intake and/or supplemental vitamin E affects the risk of developing prostate cancer. A prospective cohort study of > 29 000 men found no association between dietary or supplemental vitamin E intake and prostate cancer risk (Kirsh et al., 2006). A large randomised clinical trial (the so-called SELECT trial) started in 2001 to determine whether 7–12 years of daily supplementation with synthetic vitamin E (400 IU, as dl-α-tocopherol acetate), with or without selenium (200 µg as L-selenomethionine), reduced the number of new prostate cancers in > 35 000 healthy men aged 50 and older. The trial was discontinued in 2008, when the supplements, taken alone or together for about 5.5 years, did not prevent prostate cancer (NCI, 2008).

The evidence to date is insufficient to support taking vitamin E to prevent cancer. In fact, daily use of large doses of vitamin E supplements (270 mg) may increase, rather than diminish, the risk of prostate cancer (NIH, 2013).

Reproductive toxicity

Boskovic et al. (2004) investigated prospectively the safety of high doses of vitamin E supplementation during the first trimester of pregnancy in 82 pregnant women exposed to 400–1 200 IU/day vitamin E. Pregnancy outcomes were compared with a control group of women (n = 130) who were counselled on non-teratogenic exposure. The women were then followed up until 2–6 months after their expected dates of delivery. For one out of the 82 women in the vitamin E group, versus none of the 130 women in the control group, a major malformation was reported (details not stated). The mean birth weight of the vitamin E group was statistically significantly lower than the control group (3 173 ± 467 g versus 3 417 ± 565 g; $p < 0.0015$). There were no statistically significant differences in live birth rates, premature births, miscarriages or stillbirths (Boskovic et al., 2004; no further details).

Scholl et al. (2006) used a cohort of 1 231 pregnant women (from a population susceptible to poor diet) to examine the relationship between maternal plasma concentrations of α- and γ-tocopherols and fetal growth. Samples of blood were taken from the women at 16 and 28 weeks of pregnancy and concentrations of the tocopherols were determined after adjustment for total cholesterol. In this study, the concentrations of both tocopherols increased significantly ($p < 0.0001$) between 16 and 28 weeks of pregnancy: α-tocopherol by 20.5 % (11.37 compared with 13.70 µg/mL) and γ-tocopherol by 9.9 % (1.92 compared with 2.11 µg/mL). After adjustment for confounding variables, such as age and smoking status, α-tocopherol showed a positive linear relationship with birth weight, but there was no such relationship with γ-tocopherol. The relationship with fetal growth was also observed in a study conducted by Masters et al. (2007), which showed that maternal vitamin E is essential for normal growth and development of the human fetus. In this study, babies born to mothers with low plasma concentrations of α-tocopherol (<500 µg/dL) weighed less and had a smaller head circumference. The beneficial activities of the tocopherols are outside the remit of this opinion and are not discussed further, but are considered in discussing the importance of data gaps for the reproductive and developmental toxicity endpoint.

Intra-cytoplasmic sperm injection (ICSI), an *in vitro* fertilisation procedure, involves injection of a single sperm into an egg in order to fertilise it. Poor implantation and pregnancy rates have been reported when the sperm have elevated DNA fragmentation (Greco et al., 2005). Therefore, Greco et al. (2005) conducted a study in order to investigate the potential benefit of antioxidant treatment prior to collection of spermatozoa. Following one failed attempt at ICSI, 38 men with elevated (at least 15 %) DNA-fragmented spermatozoa were treated with antioxidants (1 g each of vitamin C and E) for two months. Treatment led to a decrease in DNA-fragmented spermatozoa in 76 % of men. In a second attempt at ICSI, fertilisation was not affected by treatment, but the pregnancy rates increased from 6.9 % to 48.2 %, and implantation increased from 2.2 % to 19.6 % in the treated group, compared with the pre-treated rates. It is not clear from these results which of the vitamins, or if both, had the beneficial effect. The Panel noted that this study may point to a protective role for vitamin E in male fertility.

Although the study conducted by Boskovic et al. (2004) indicated that vitamin E supplements lead to reduced birth weights in humans, this result was not representative of the data as a whole. Overall, the data from human studies do not suggest that the tocopherols have an adverse effect on reproduction and development; on the contrary, it appears that they are essential for normal fetal growth and male fertility.

4. Discussion

The present opinion deals with the re-evaluation of the safety of tocopherol-rich extract of natural origin (E 306), synthetic α-tocopherol (*all-rac*-α-tocopherol; dl-α-tocopherol) (E 307), synthetic γ-tocopherol (dl-γ-tocopherol) (E 308) and synthetic δ-tocopherol (E 309), used in foods to inhibit the peroxidation of fats and lipids.

The present re-evaluation is based primarily upon previous evaluations by the SCF (2003), JECFA (1987) and EFSA (2008), studies submitted following an EFSA public call for data and a literature search that was limited to publications from 2003 onwards.

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that has become available since then and the data provided following a public call for data. The Panel noted that not all of the original studies on which the previous evaluations were based were available for re-evaluation by the Panel.

Tocopherols belong to the group of substances named vitamin E. Vitamin E is the collective term for a family of structurally related substances, namely tocopherol- and tocotrienol-derivatives, that exhibit, qualitatively, the biological activity of the naturally occurring d-α-tocopherol. Vitamin E is an essential vitamin and is naturally present in plant-derived foods, particularly fruit and vegetables.

All tocopherols evaluated in this opinion are used as antioxidants in food, either individually or in combination, and are authorised under Annex II of Regulation (EU) No 1333/2008 on food additives. Specifications for tocopherol-rich extract of natural origin (E 306) and synthetic α-tocopherol (E 307) have been defined in Commission Regulation (EU) No 231/2012 and by JECFA (JECFA, 2006b, 2007). Specifications for synthetic γ-tocopherol (E 308) and synthetic δ-tocopherol (E 309) have been defined in only Commission Regulation (EU) No 231/2012.

The Panel considered that the maximum limits for the impurities of toxic elements (arsenic, lead and mercury) in the EC specifications for tocopherols should be revised in order to ensure that tocopherols (E 306–E 309) as food additives will not be a significant source of exposure to these toxic elements in food.

The SCF has not set an ADI for tocopherols, but considered the use of tocopherols as antioxidants in food acceptable. The SCF, in its evaluation of vitamins and minerals, established an UL of 300 mg/day for vitamin E (SCF, 2003). Effects on blood clotting were used as the basis for deriving the UL of 300 mg d-α-tocopherol/day for vitamin E (the NOAEL of the study performed by Meydani

et al., 1998 was 800 IU vitamin E per day, equivalent to 537 mg d-α-tocopherol/day). This UL also applies to pregnant and lactating women. The UL was scaled for children in the age ranges 1–3, 4–6, 7–10, 11–14 and 15–17 years to give ULs of 100, 120, 160, 220 and 260 mg/day, respectively (SCF, 2003).

The current ADI allocated by JECFA for α-tocopherol is 0.15–2 mg/kg bw/day (JECFA, 1987). The JECFA ADI of 0.15–2 mg/kg bw/day for dl-α-tocopherol is based on clinical studies in humans (JECFA, 1987) and takes into account the fact that α-tocopherol is an essential nutrient.

Tocopherols are relatively stable in foods, but oxidation may occur when exposed to air, heat, acids, alkalis or metal ions. During storage, when peroxyl radicals are formed in oils or in the presence of unsaturated fatty acids, α-tocopherol reacts with these radicals, leading to the formation of tocopheroxyl radicals that further react with other peroxyl radicals to form non-radical products (Burton and Traber, 1990). The non-radical oxidation products of vitamin E have been identified as α-tocopheryl quinone, epoxy-alpha-tocopherylquinones and 8a-(lipid-dioxy)-alpha-tocopherones (Yamauchi et al., 2002). The decrease in tocopherol content that occurs during food processing is caused by oxidation or thermal degradation depending on the processing procedures, storage time, conditions and type of food. In sunflower oil heated to 180 °C, α-tocopherol reacts partly to produce oxidation and degradation products, such as α-tocopheryl quinone and α-tocopheryl fatty acids (Kreps et al., 2015).

Based on toxicokinetics data for α-, γ- and δ-tocopherols and tocopherol-rich extract, α-tocopherol is the most biologically active and is, therefore, the form that is most often used in toxicity testing. For the purpose of this opinion, it was assumed that α-tocopherol is representative of the other tocopherols as a worst case, based on the fact that this form of vitamin E is the only form that the liver can re-secrete into the plasma, hence maintaining plasma concentrations and prolonging time in the plasma before elimination (Brigelius-Floh and Traber, 1999). In testing α-tocopherol, it is likely that the most conservative NOAEL is determined. Therefore, results from toxicity studies on α-tocopherol are assumed to also apply to γ-tocopherol, δ-tocopherol and tocopherol-rich extract.

Absorption of the tocopherols varies with dose, and the efficiency of absorption decreases with increasing intake (Traber et al., 1986; Kitagawa and Mino, 1989). Absorption across the gastrointestinal tract occurs along with dietary lipids and is dependent on biliary secretion of bile acids and salts, which aid the emulsification process, to form micelles with the hydrolysed fat. These micelles containing the vitamin E are then absorbed by passive diffusion at the brush border enterocytes of the small intestine (Anwar et al., 2007). Once absorbed, the tocopherols enter the blood and lymphatics in chylomicrons, and are transported to the tissues. The liver appears to select α-tocopherol using α-TTP, whereas most ingested γ- and δ-tocopherols are eliminated by the liver into the bile and excreted in the faeces (Bjorneboe et al., 1990; Brigelius-Floh and Traber, 1999). The liver, skeletal muscle, adrenals, adipose and lung tissues all have comparatively high concentrations of α-tocopherol (Bjorneboe et al., 1990). The dynamics of tocopherol concentrations in the plasma change depending on the intake of the various forms of tocopherol. The main route of elimination (30–70 %) of tocopherols is via the faeces (EVM, 2003). Urinary excretion of tocopherols in the form of their metabolite CEHC is a minor route of excretion of α-tocopherol. The levels of plasma α-tocopherol correlate with the levels of urinary α-CEHC, with the presence of α-CEHC in the urine appearing to indicate a surplus of α-tocopherol (Brigelius-Floh and Traber, 1999). It is also noteworthy that following ingestion of α-tocopherol, there is a reduction in plasma γ-tocopherol and an increase in plasma γ-CEHC. This is probably linked to the selectivity in the body for α-tocopherol, which replaces γ-tocopherol by the α-form whenever the levels of α-tocopherol are sufficient to do so (Eichhorn et al., 2004). Human studies suggest that maternal intake of vitamin E increases the concentration of fetal CEHC rather than increasing the level of fetal vitamin E (Didenco et al., 2011).

The acute oral toxicity of tocopherols is very low, with LD_{50} values for α-tocopherol reported to be greater than 2 000 mg/kg bw for rats (Pool et al., 1972; Gelbke and Freisberg, 1978; Winter, 1989; all

unpublished reports). Krasavage and Terhaar (1977) noted the low acute toxicity in rats, mice and rabbits.

The critical effects observed in a subchronic study on haematology (blood clotting) and clinical chemistry (total cholesterol, total lipids and phospholipids) are not expected to vary qualitatively among the various forms of tocopherols, i.e. prolonged coagulation times are common to all tocopherols and are thought to be due to reduced absorption of vitamin K from the gastrointestinal tract, as supplementation with vitamin K prevents the effects of the tocopherols on blood clotting (Abdo et al., 1986; Pfister et al., 1999c, unpublished report; Wolz et al., 2000, unpublished report). The effects on blood clotting are assumed to be toxicologically relevant; however, the doses of tocopherol administered to experimental animals were high and internal exposures were likely to be affected by the dose vehicle. A study conducted by Abdo et al. (1986) provides the most convincing data for this effect in experimental animal studies. The Panel noted that the vehicle must also be taken into account when interpreting the results of experimental animal studies. The absorption of tocopherols is known to be dependent upon dietary lipids (Anwar et al., 2007). Therefore, absorption is likely to be greater in studies that dose by gavage in oil (usually soybean oil). In the experimental animal studies, the oral doses at which the reversible effects occurred on blood and clinical chemistry parameters, most importantly blood coagulation, were high (hundreds or thousands of mg/kg bw/day) and are therefore unlikely to be reached through natural and food additive sources (Pfister et al., 1999a, b, c, d, e; Wolz et al., 2000; all unpublished reports; and Abdo et al., 1986).

There is no evidence to suggest that tocopherol-rich extract or α-, γ- or δ-tocopherol are genotoxic. Well-conducted genotoxicity studies (three Ames tests, an *in vitro* chromosomal aberration test and an *in vivo* mutagenicity study) available from the public call for data were all negative (Chételat, 1999; Engelhardt, 1989; Gocke, 1998, 1999; all unpublished reports; Umegaki et al., 1997).

There is one limited carcinogenicity study, carried out in rats (Wheldon et al., 1983). A NOAEL for general systemic toxicity could not be established in this study due to the effects on blood clotting and liver tissue. The NOAEL for carcinogenicity was > 2 000 mg/kg bw/day. The chronic study in rats by Yang and Desai (1977) is not adequate to address the carcinogenicity endpoint, as the duration of this study (16 months only) was too short for a carcinogenicity study. In this study, a NOAEL of 125 mg/kg bw/day was determined based on reduced body weight and increased relative weights of heart and spleen. The Panel concluded that there is no concern that α-tocopherol is carcinogenic.

Overall, there are insufficient studies to address the reproduction and developmental endpoints and no multigeneration studies conducted according to appropriate test guidelines. Therefore, the Panel considered the overall toxicity database insufficient to establish an ADI for tocopherol-rich extract and α-, γ- and δ-tocopherols.

There are studies in humans that investigate the potential effects of vitamin E and tocopherols on fertility and fetal development. No adverse effects were seen in the study by Boskovic et al. (2004). Other studies, such as those by Scholl et al. (2006), Masters et al. (2007) and Greco et al. (2005), have shown that tocopherols have a positive effect on fetal growth and male fertility.

Studies in humans give conflicting results with respect to the potential of vitamin E to affect the incidence of cardiovascular disease and subsequent mortality (Boaz et al., 2000; Lippman et al., 2009; Leppala et al., 2000a). It appears that, as was observed in animal studies, the principal adverse effect of the tocopherols is on prothrombin times and factors related to blood clotting, via an interaction with vitamin K or vitamin K-dependent proteins (Booth et al., 2004). However, it does appear that in humans this effect is only observed at high doses (NIH, 2013), which are not relevant compared to the exposure to tocopherols used as food additives. Susceptible subgroups appear to be individuals with already compromised blood clotting capacity, and those with low vitamin K status (Corrigan and Ulfers, 1981; Diplock, 1995). Although not all studies are consistent, it appears that while vitamin E does not affect cardiovascular disease in healthy individuals (Lippman et al., 2009), it has the potential

to reduce primary cardiovascular outcomes, such as stroke, in patients with existing cardiovascular disease (Boaz et al., 2000; Stephens et al., 1996).

The term tocopherols (E 306–E 309) has been used as a generic term for tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308) and δ-tocopherol (E 309). Therefore, the Panel decided that only α-tocopherol would be considered for the exposure assessment performed in this opinion, as it is the predominant tocopherol used in the food industry, and in line with other authoritative bodies (IOM, 2000; Nordic Council of Ministers, 2014).

The exposure assessment for food additives under re-evaluation is carried out by the Panel based on MPLs set down in EU legislation, and reported usage levels or analytical data. For tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308) and δ-tocopherol (E 309), it was not possible to carry out an exposure assessment scenario based on MPLs since, for most of the food categories, these food additives are authorised according to QS. Therefore, maximum levels of the available usage data reported by industry were used instead to provide a conservative exposure estimate scenario (noted as maximum level exposure assessment scenario).

Based on the available dataset, and in addition to the "maximum level exposure assessment scenario", the Panel calculated, for the compound α-tocopherol, refined exposure scenarios on the basis of different assumptions: a "brand-loyal consumer scenario", where it is assumed that the population is exposed long term to the food additive present at the maximum reported use levels for one food category and at the mean levels for the remaining food categories; and a "non-brand-loyal scenario", where it is assumed that the population is exposed long term to the food additive present at the mean reported use levels in all foods.

The Panel considered that the refined exposure assessment approach is a more realistic scenario, since it is based on the extensive range of data submitted to EFSA, assuming that the processed foods and beverages contain the additive at the mean concentration level for all products ("non-brand-loyal consumer scenario") and one product contains the food additive at the maximum concentration level ("brand-loyal consumer scenario"). The Panel noted that the refined exposure estimates will not cover future changes in the level of use of the food additive.

Reported use levels from industry give information on the amount of the food additive added to food. The use of these data results in an exposure to α-tocopherol (E 307) at the moment that the food was produced. As described in Section 2.5, tocopherols are degraded during processing and storage. The loss of tocopherols in food is very likely to have an impact on the overall exposure estimates calculated based on the reported use levels. Therefore, the Panel calculated additional exposure estimates for the additive itself, including potential loss factors, so that these estimates reflect more closely the exposure to α-tocopherol (E 307) via foods as consumed.

Based on the data made available to EFSA on α-tocopherol (E 307) (use levels reported by industry and analytical data from Member States) and the assumptions mentioned above, the Panel then performed different exposure scenarios to characterise the most realistic exposure estimates from the food additive itself, from natural sources (EFSA NDA Panel, 2015) and from all food sources (food additive, enzyme preparations, nutrient as vitamin and natural sources).

The total exposure to α-tocopherol from all food sources (food additive, enzyme preparations, nutrient as vitamin and from natural sources) would reach up to 6.3 mg/kg bw/day in toddlers at the high level (with the exception of children in one survey from one country, achieving up to 9.7 mg/kg bw/day). From the use of α-tocopherol (E 307) as a food additive itself, the exposure (non-brand loyal scenario, considering loss factors) would range from 0.3 mg/kg bw/day in infants to 2.7 mg/kg bw/day in toddlers at the mean, and from 0.9 mg/kg bw/day in adolescents to 5.9 mg/kg bw/day in toddlers at the high level.

The Panel estimated that, when comparing all sources (from the additive itself, from natural sources and from all food sources), the contribution of α-tocopherol (E 307) from its use as a food additive may represent, on average, approximately 71 % (range 59–80 %) of the overall exposure to α-tocopherol, and around a two- to five-fold higher intake than from natural sources, with the exception of infants whose intake from the use of α-tocopherol (E 307) as a food additive is likely to be 0.9-fold that of the intake from natural sources.

The Panel considered that the uncertainties identified would tend to overestimate the actual exposure to α-tocopherol (E 307) as a food additive, particularly for the maximum level scenario, and to an underestimation of the actual exposure to α-tocopherol from all sources in European countries.

Taking into account that:

- vitamin E is widely consumed via human food;
- it is an essential nutrient;
- there is no indication of genotoxic and carcinogenic potential;
- animal and human studies available have not shown adverse effects, except effects on blood clotting at high levels;
- that the exposure to α-tocopherol resulting from all food sources does not exceed the ULs for vitamin E (SCF, 2003) in any population group, except in children in one survey from only one country,

the Panel considered that α-tocopherol (E 307) at the reported uses and use levels as a food additive is not of safety concern.

The Panel noted that the exceedance of the UL observed in children in one survey from one country may be a result of the different methodologies used among dietary surveys for reporting the amounts of food supplements consumed.

The Panel considered that the database on γ- and δ-tocopherols was too limited to be included in the safety assessment of tocopherols. However, the Panel is aware that much lower concentration levels and fewer uses for γ- and δ-tocopherols are reported in food than for α-tocopherol. The Panel considered that data on α-tocopherol can be read-across to the other tocopherols, based on the similarities in the chemical structure, and the fact that α-tocopherol represents a worst case, as it is the form which the body selectively retains. The Panel noted that it would be prudent to re-assess the appropriateness of this read-across as new data on γ- and δ-tocopherols become available. Therefore, the Panel considered that, overall, the use of tocopherols (E 306–E 309) as food additives would not be of safety concern at the levels used in food.

The Panel noted that in Annex II of Regulation (EC) No 1333/2008, use levels of tocopherols (E 306–E 309) in food for infants under the age of 12 weeks are included in categories 13.1.1, 13.1.5.1 and 13.1.5.2. The Panel considered that these uses would require a specific risk assessment in line with the recommendations given by JECFA (1978) and the SCF (1998) and endorsed by the Panel. Therefore, the current re-evaluation of tocopherols (E 306–E 309) as food additives is not considered to be applicable to infants under the age of 12 weeks.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

Although the overall toxicity database was considered insufficient to establish an ADI for tocopherols (E 306–E 309), based on the arguments described above, the Panel concluded that the use of tocopherols (E 306–E 309) as food additives would not be of safety concern at the reported uses and use levels.

The Panel concluded that the current re-evaluation of tocopherols (E 306–E 309) as food additives is not applicable to infants under the age of 12 weeks.

RECOMMENDATIONS

The Panel recommended that the maximum limits for the impurities of toxic elements (arsenic, lead and mercury) in the EC specifications for tocopherols should be revised in order to ensure that tocopherols (E 306–E 309) as food additives will not be a significant source of exposure to these toxic elements in food.

The Panel recommended re-assessing the appropriateness of the read-across from α-tocopherol to the other tocopherols as new data on γ- and δ-tocopherols become available.

DOCUMENTATION PROVIDED TO EFSA

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APPENDICES

Appendix A. Summary of reported use levels (mg/kg) of tocopherols (E 306–E 309) provided by industry

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
Tocopherol-rich extract (E 306)								
01.3	Unflavoured fermented milk products	QS		1	300 [(a)]	500 [(a)]	FCRA	
01.4	Flavoured fermented milk products including heat-treated products	QS		1	300 [(a)]	500 [(a)]	FCRA	
01.6.3	Other creams	QS		1	200 [(a)]	400 [(a)]	FCRA	No FoodEx linkage
01.7.1	Unripened cheese	QS	Except mozzarella	1	200 [(a)]	500 [(a)]	FCRA	
01.7.5	Processed cheese	QS		1	200 [(a)]	500 [(a)]	FCRA	
01.7.6	Cheese products	QS		1	200 [(a)]	500 [(a)]	FCRA	
01.8	Dairy analogues, including beverage whiteners	QS		1	200 [(a)]	400 [(a)]	FCRA	
02.1	Fats and oils essentially free from water	QS/200	Except virgin oils and olive oils/only refined olive oils, including olive pomace oil	1	500 [(a)]	1 000 [(a)]	FRCA	
02.2.2	Other fat and oil emulsions	QS		1	500 [(a)]	1 000 [(a)]	FRCA	No FoodEx linkage
02.2.2	Other fat and oil emulsions	QS		3	149	595	FDE	No FoodEx linkage
02.3	Vegetable oil pan spray	QS		1	500 [(a)]	1 000 [(a)]	FRCA	No FoodEx linkage
03	Edible ices	QS		1	300 [(a)]	500 [(a)]	FRCA	
04.2.1	Dried fruit and vegetables	QS		2	300 [(a)]	500 [(a)]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
04.2.2	Fruit and vegetables in vinegar, oil or brine	QS		2	300 [(a)]	500 [(a)]	FRCA	
04.2.4.1	Fruit and vegetable preparations excluding compote	QS		2	300 [(a)]	500 [(a)]	FRCA	
04.2.5.4	Nut butters and nut spreads	QS		1	150 [(a)]	300 [(a)]	FRCA	
04.2.6	Processed potato products	QS		1	300 [(a)]	500 [(a)]	FRCA	
05.1	Cocoa and chocolate products			1	300 [(a)]	500 [(a)]	FRCA	
05.1	Cocoa and chocolate products			1	7	10	MARS	Data from call for scientific data on food additives (2009)
05.2	Other confectionery including breath freshening microsweets	QS		1	300[(a)]	500[(a)]	FRCA	
05.3	Chewing gum	QS		1	–	245	ICGA	
05.3	Chewing gum	QS		1	300 [(a)]	500 [(a)]	FRCA	
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	QS		1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
06.2.2	Starches	QS		1	–	250 [(a)]	FRCA	
06.3	Breakfast cereals	QS		1	–	250 [(a)]	FRCA	
06.4.2	Dry pasta	QS	Only gluten free and/or pasta intended for hypoproteic diets in accordance with directive 2009/39/EC	1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
06.4.4	Potato gnocchi	QS		1	–	250 [(a)]	FRCA	No FoodEx linkage

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
06.4.5	Fillings of stuffed pasta (ravioli and similar)	QS		1	–	500 [a]	FRCA	
06.5	Noodles	QS		1	300 [a]	500 [a]	FRCA	
06.7	Pre-cooked or processed cereals	QS		1	–	500 [a]	FRCA	No FoodEx linkage
07.1	Bread and rolls	QS	Except products in 7.1.1 and 7.1.2	1	300 [a]	500 [a]	FRCA	
07.2	Fine bakery wares	QS		1	218	218	FDE	
07.2	Fine bakery wares	QS		1	–	400 [a]	FRCA	
08.3	Meat products	QS		1	1500	1 500	FDE	
08.3.1	Non-heat-treated meat products	QS		1	–	300 [a]	FRCA	
08.3.2	Heat-treated meat products	QS	Except *foie gras, foie gras entier, blocs de foie gras, libamaj, libamaj egeszben, libamaj tömbben*	1	–	300 [a]	FRCA	
08.3.3	Casings and coatings and decorations for meat	QS		1	–	300 [a]	FRCA	No FoodEx linkage
09.2	Processed fish and fishery products	QS		1	200 [a]	500 [a]	FRCA	
09.3	Fish roe	QS	Only processed fish roe	1	200 [a]	500 [a]	FRCA	
10.2	Processed eggs and egg products	QS		1	400 [a]	800 [a]	FRCA	
11.2	Other sugars and syrups	QS		1	300 [a]	500 [a]	FRCA	
12.1.2	Salt substitutes	QS		1	300 [a]	500 [a]	FRCA	No FoodEx linkage
12.2.2	Seasonings and condiments	QS		1	300 [a]	500 [a]	FRCA	
12.2.2	Seasonings and condiments	QS		5	36.2	200	FDE	
12.3	Vinegars	QS		1	300 [a]	500 [a]	FRCA	
12.4	Mustard	QS		1	200 [a]	400 [a]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
12.4	Mustard	QS		1	0.9	0.9	FDE	
12.5	Soups and broths	QS		8	10.8	30.5	FDE	
12.5	Soups and broths	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.6	Sauces	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.6	Sauces	QS		7	40.9	177.8	FDE	
12.7	Salads and savoury-based sandwich spreads	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.8	Yeast and yeast products	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.9	Protein products, excluding products covered in category 1.8	QS		1	200 [(a)]	400 [(a)]	FRCA	
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10		2	–	10	FRCA	
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10		3	1.7	10	FRCA, SNE	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	Only fat-containing cereal-based foods including biscuits and rusks and baby foods	2	20	100	SNE, FRCA	
13.1.4	Other foods for young children	100		1	–	100	FRCA	
13.2	Dietary foods for special medical purposes	QS		1	–	800 [(a)]	FRCA	
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual	QS		1	17.5	17.5	FDE	
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	QS	Including dry pasta	1	–	800 [(a)]	FRCA	No FoodEx linkage
14.1.4	Flavoured drinks	QS		5	5.1	10	FDE	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
14.1.5.2	Other than coffee and coffee extracts	QS	Excluding unflavoured leaf tea; including flavoured instant coffee	6	9.9	17.7	FDE	No FoodEx linkage
14.2.3	Cider and perry	QS		1	300 [a]	500 [a]	FRCA	
14.2.4	Fruit wine and made wine	QS		1	300 [a]	500 [a]	FRCA	No FoodEx linkage
14.2.5	Mead	QS		1	300 [a]	500 [a]	FRCA	No FoodEx linkage
14.2.6	Spirit drinks	QS		1	300 [a]	500 [a]	FRCA	
14.2.7.1/ 14.2.7.2	Aromatized wines/ Aromatized wine-product cocktails	QS		1	300 [a]	500 [a]	FRCA	No FoodEx linkage
14.2.8	Other alcoholic drinks including spirits with less than 15 % of alcohol and mixtures of alcoholic drinks with non-alcoholic drinks	QS	Except whisky or whiskey	1	300 [a]	500 [a]	FRCA	
15.1	Potato-, cereal-, flour- or starch-based snacks	QS		1	100 [a]	200 [a]	FRCA	
15.2	Processed nuts	QS		1	200 [a]	400 [a]	FRCA	
16	Desserts	QS		1	100 [a]	200 [a]	FRCA	
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	QS		1	–	1 000 [a]	FRCA	
17.2	Food supplements supplied in a liquid form	QS		1	–	1 000 [a]	FRCA	
17.3	Food supplements supplied in a syrup-type or chewable form	QS		1	–	1 000 [a]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	QS		1	–	1 000 [(a)]	FRCA	
			α-Tocopherol (E 307)					
01.3	Unflavoured fermented milk products	QS		1	300 [(a)]	500 [(a)]	FCRA	
01.4	Flavoured fermented milk products including heat-treated products	QS		1	300 [(a)]	500 [(a)]	FCRA	
01.6.3	Other creams	QS		1	200 [(a)]	400 [(a)]	FCRA	No FoodEx linkage
01.6.3	Other creams	QS		3	3.8	53.8	FDE	No FoodEx linkage
01.7.1	Unripened cheese	QS	Except mozzarella	1	200 [(a)]	500 [(a)]	FCRA	
01.7.5	Processed cheese	QS		1	200 [(a)]	500 [(a)]	FCRA	
01.7.6	Cheese products	QS		1	200 [(a)]	500 [(a)]	FCRA	
01.8	Dairy analogues, including beverage whiteners	QS		1	200 [(a)]	400 [(a)]	FCRA	
02.1	Fats and oils essentially free from water	QS/200	Except virgin oils and olive oils/only refined olive oils, including olive pomace oil	2	475 [(a)]	750 [(a)]	FRCA, FDE	
02.1	Fats and oils essentially free from water	QS/200	Except virgin oils and olive oils/only refined olive oils, including olive pomace oil	1	2.9	2.9	FDE	
02.2.2	Other fat and oil emulsions	QS		1	200 [(a)]	400 [(a)]	FRCA	No FoodEx linkage

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
02.2.2	Other fat and oil emulsions	QS		6	0.4	1.9	FDE	No FoodEx linkage
02.3	Vegetable oil pan spray	QS		1	200 [(a)]	400 [(a)]	FRCA	No FoodEx linkage
03	Edible ices	QS		1	300 [(a)]	500 [(a)]	FRCA	
03	Edible ices	QS		24	7.5	48.7	48.7	
03	Edible ices	QS		1	2	40	MARS	Data from call for scientific data on food additives (2009)
04.2.1	Dried fruit and vegetables	QS		2	300 [(a)]	500 [(a)]	FRCA	
04.2.2	Fruit and vegetables in vinegar, oil or brine	QS		2	300 [(a)]	500 [(a)]	FRCA	
04.2.4.1	Fruit and vegetable preparations excluding compote	QS		2	300 [(a)]	500 [(a)]	FRCA	
04.5.2.4	Nut butters and nut spreads	QS		1	150 [(a)]	300 [(a)]	FRCA	
04.2.6	Processed potato products	QS		1	300 [(a)]	500 [(a)]	FRCA	
04.2.6	Processed potato products	QS		1	1.3	1.3	1.3	
05.1	Cocoa and chocolate products	QS		1	300 [(a)]	500 [(a)]	FRCA	
05.1	Cocoa and chocolate products			1	2	7	MARS	Data from call for scientific data on food additives (2009)

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
05.2	Other confectionery including breath freshening microsweets	QS		1	300 [(a)]	500 [(a)]	FRCA	
05.3	Chewing gum	QS		1	1	670		
05.3	Chewing gum	QS		1	300 [(a)]	500 [(a)]	FRCA	
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	QS		1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
06.2.2	Starches	QS		1	–	250 [(a)]	FRCA	
06.3	Breakfast cereals	QS		1	–	250 [(a)]	FRCA	
06.3	Breakfast cereals	QS		3	0.04	0.08	FDE	
06.4.2	Dry pasta	QS	Only gluten free and/or pasta intended for hypoproteic diets in accordance with directive 2009/39/EC	1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
06.4.4	Potato gnocchi	QS		1	–	250 [(a)]	FRCA	No FoodEx linkage
06.4.5	Fillings of stuffed pasta (ravioli and similar)	QS		1	–	500[(a)]	FRCA	
06.5	Noodles	QS		1	300[(a)]	500[(a)]	FRCA	
06.7	Pre-cooked or processed cereals	QS		1	–	500 [(a)]	FRCA	No FoodEx linkage
07.1	Bread and rolls	QS	Except products in 7.1.1 and 7.1.2	1	300 [(a)]	500 [(a)]	FRCA	
07.2	Fine bakery wares	QS		1	6.2	6.2	FDE	
07.2	Fine bakery wares	QS		1	–	400 [(a)]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
08.3	Meat products	QS		1	1 500	1 500	FDE	Value reported to be valid for 08.3.1. and 08.3.2
08.3.1	Non-heat-treated meat products	QS		1	–	300 [a]	FRCA	
08.3.2	Heat-treated meat products	QS	Except *foie gras, foie gras entier, blocs de foie gras, libamaj, libamaj egeszben, libamaj tömbben*	1	0.001	0.001	FDE	
08.3.2	Heat-treated meat products	QS	Except *foie gras, foie gras entier, blocs de foie gras, libamaj, libamaj egeszben, libamaj tömbben*	1	–	300 [a]	FRCA	
08.3.3	Casings and coatings and decorations for meat	QS		1	–	300 [a]	FRCA	No FoodEx linkage
09.2	Processed fish and fishery products	QS		1	200 [a]	500 [a]	FRCA	
09.3	Fish roe	QS	Only processed fish roe	1	200 [a]	500 [a]	FRCA	
10.2	Processed eggs and egg products	QS		1	400 [a]	800 [a]	FRCA	
11.2	Other sugars and syrups	QS		1	300 [a]	500 [a]	FRCA	
12.1.2	Salt substitutes	QS		1	300 [a]	500 [a]	FRCA	No FoodEx linkage
12.2.2	Seasonings and condiments	QS		1	300 [a]	500 [a]	FRCA	
12.2.2	Seasonings and condiments	QS		3	1.6	4.6	FDE	
12.3	Vinegars	QS		1	300 [a]	500 [a]	FRCA	
12.4	Mustard	QS		1	200 [a]	400 [a]	FRCA	
12.5	Soups and broths	QS		1	200 [a]	400 [a]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
12.5	Soups and broths	QS		19	12.4	28.8	FDE	
12.6	Sauces	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.6	Sauces	QS		9	39.4	326.9	FDE	
12.7	Salads and savoury-based sandwich spreads	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.8	Yeast and yeast products	QS		1	200 [(a)]	400 [(a)]	FRCA	
12.9	Protein products, excluding products covered in category 1.8	QS		1	200 [(a)]	400 [(a)]	FRCA	
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10		4	7.5	10	FRCA, SNE	
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10		4	6.5	10	FRCA, SNE	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	Only fat-containing cereal-based foods including biscuits and rusks and baby foods	2	3	100	FRCA, SNE	
13.1.4	Other foods for young children	100		2	10	100	FRCA, SNE	
13.2	Dietary foods for special medical purposes	QS		1	–	800 [(a)]	FRCA	
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual	QS		1	0.3	0.7	FDE	
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual	QS		1	–	800 [(a)]	FRCA	
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	QS	Including dry pasta	1	–	800 [(a)]	FRCA	No FoodEx linkage

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
14.1.4	Flavoured drinks	QS		6	13.8	62.5	FDE	
14.1.5.2	Other than coffee and coffee extracts	QS	Excluding unflavoured leaf tea; including flavoured instant coffee	8	9.5	19.3	FDE	No FoodEx linkage
14.2.3	Cider and perry	QS		1	300 [(a)]	500 [(a)]	FRCA	
14.2.4	Fruit wine and made wine	QS		1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
14.2.5	Mead	QS		1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
14.2.6	Spirit drinks	QS		1	300 [(a)]	500 [(a)]	FRCA	
14.2.7.1/14.2.7.2	Aromatized wines/aromatized wine-product cocktails	QS		1	300 [(a)]	500 [(a)]	FRCA	No FoodEx linkage
14.2.8	Other alcoholic drinks including spirits with less than 15 % of alcohol and mixtures of alcoholic drinks with non-alcoholic drinks	QS	Except whisky or whiskey	1	300 [(a)]	500 [(a)]	FRCA	
15.1	Potato-, cereal-, flour- or starch-based snacks	QS		1	100 [(a)]	200 [(a)]	FRCA	
15.2	Processed nuts	QS		1	200 [(a)]	400 [(a)]	FRCA	
16	Desserts	QS		1	100 [(a)]	200 [(a)]	FRCA	
16	Desserts	QS		7	2.3	12	FDE	
17	Food supplements	QS		4	2 506	5 500	AESGP	
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	QS		1	–	1 000 [(a)]	FRCA	
17.2	Food supplements supplied in a liquid form	QS		1	–	1 000 [(a)]	FRCA	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels as provided by industry (mg/kg or mg/L)		Information provided by	Comments
					Typical mean	Highest maximum level		
17.3	Food supplements supplied in a syrup-type or chewable form	QS		1	–	1 000 [(a)]	FRCA	
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	QS		1	–	1 000 [(a)]	FRCA	
			γ-Tocopherol (E 308)					
05.3	Chewing gum	QS		1	50	80	ICGA	
08.3	Meat products	QS		1	1 500	1 500	FDE	
14.1.4	Flavoured drinks	QS		1	270	270	FDE	
			δ-Tocopherol (E 309)					
05.3	Chewing gum	QS		1	50	80	ICGA	
08.3	Meat products	QS		1	1 500	1 500	FDE	
14.1.4	Flavoured drinks	QS		1	107	107	FDE	

(a): Expressed on fat weight.

Appendix B. Summary of reported use levels (mg/kg) of α-tocopherol (E 307) provided by industry, expressed on a whole-weight basis, as considered for exposure assessment

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels expressed on a whole-weight basis		Information provided by	Comments
					Typical mean	Highest maximum level		
01.3	Unflavoured fermented milk products	QS		1	99.6	159	FCRA	
01.4	Flavoured fermented milk products including heat-treated products	QS		1	99.6	159	FCRA	
01.6.3	Other creams	QS		4	18.8	127	FCRA, FDE	No FoodEx linkage
01.7.1	Unripened cheese	QS	Except mozzarella	1	48.4	121	FCRA	
01.7.5	Processed cheese	QS		1	48.4	121	FCRA	
01.7.6	Cheese products	QS		1	48.4	121	FCRA	No FoodEx linkage
01.8	Dairy analogues, including beverage whiteners	QS		1	53.6	107	FCRA	
02.1	Fats and oils essentially free from water	QS/200	Except virgin oils and olive oils/only refined olive oils, including olive pomace oil	3	308	726	FRCA, FDE	
02.2.2	Other fat and oil emulsions	QS		7	21.2	292	FRCA, FDE	No FoodEx linkage
02.3	Vegetable oil pan spray	QS		1	200	400	FRCA	No FoodEx linkage
03	Edible ices	QS		26	7.36	48.7	FRCA, FDE, MARS	
04.2.1	Dried fruit and vegetables	QS		2	1.05	2.50	FRCA	
04.2.2	Fruit and vegetables in vinegar, oil or brine	QS		2	0.39	3.0	FRCA	
04.2.4.1	Fruit and vegetable preparations excluding compote	QS		2	0.39	3.0	FRCA	
04.2.5.4	Nut butters and nut spreads	QS		1	80.1	160	FRCA	
04.2.6	Processed potato products	QS		2	5.87	17.3	FRCA, FDE	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels expressed on a whole-weight basis		Information provided by	Comments
					Typical mean	Highest maximum level		
05.1	Cocoa and chocolate products			2	40.0	130	FRCA, MARS	
05.2	Other confectionery including breath freshening microsweets	QS		1	18.0	30.0	FRCA	
05.3	Chewing gum	QS		2	9.5	670	ICGA, FRCA	
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	QS		1	18.0	30.0	FRCA	No FoodEx linkage
06.2.2	Starches	QS		1	–	0.35	FRCA	
06.3	Breakfast cereals	QS		4	0.04	10.0	FRCA, FDE	
06.4.2	Dry pasta	QS	Only gluten free and/or pasta intended for hypoproteic diets in accordance with directive 2009/39/EC	1	3.2	5.3	FRCA	No FoodEx linkage
06.4.4	Potato gnocchi	QS		1	–	10.0	FRCA	No FoodEx linkage
06.4.5	Fillings of stuffed pasta (ravioli and similar)	QS		1	–	20.0	FRCA	
06.5	Noodles	QS		1	3.2	5.3	FRCA	
06.7	Pre-cooked or processed cereals	QS		1	–	7.0	FRCA	No FoodEx linkage
07.1	Bread and rolls	QS	Except products in 7.1.1 and 7.1.2	1	9.0	15.0	FRCA	
07.2	Fine bakery wares	QS		2	6.2	68.8	FRCA, FDE	
08.3.1	Non-heat-treated meat products	QS		2	1500	1500	FRCA, FDE	
08.3.2	Heat-treated meat products	QS	Except *foie gras, foie gras entier, blocs de foie gras, libamaj, libamaj egeszben, libamaj tömbben*	3	750	1500	FRCA, FDE	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels expressed on a whole-weight basis		Information provided by	Comments
					Typical mean	Highest maximum level		
08.3.1/08.3.2	Non-heat-treated meat products and heat-treated meat products	QS		5	1000	1500	FRCA, FDE	Considered as one food category for exposure assessment
08.3.3	Casings and coatings and decorations for meat	QS		1	–	47.7	FRCA	No FoodEx linkage
09.2	Processed fish and fishery products	QS		1	21.0	52.5	FRCA	
09.3	Fish roe	QS	Only processed fish roe	1	19.8	49.5	FRCA	
10.2	Processed eggs and egg products	QS		1	76.0	152	FRCA	
11.2	Other sugars and syrups	QS		1	2.05	3.42	FRCA	
12.1.2	Salt substitutes	QS		1	–	–	FRCA	No FoodEx linkage
12.2.2	Seasonings and condiments	QS		4	4.42	21.4	FRCA, FDE	
12.3	Vinegars	QS		1	0.15	0.25	FRCA	
12.4	Mustard	QS		1	0.1	0.2	FRCA	
12.5	Soups and broths	QS		20	11.9	101	FRCA, FDE	
12.6	Sauces	QS		10	36.5	327	FRCA, FDE	
12.7	Salads and savoury-based sandwich spreads	QS		1	10.0	20.0	FRCA	
12.8	Yeast and yeast products	QS		1	0.8	1.6	FRCA	
12.9	Protein products, excluding products covered in category 1.8	QS		1	16.8	33.6	FRCA	
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10		4	7.5	10.0	FRCA, SNE	
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10		4	6.5	10.0	FRCA, SNE	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	Only fat-containing cereal-based foods including biscuits and rusks and baby foods	2	3.0	100	FRCA, SNE	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels expressed on a whole-weight basis		Information provided by	Comments
					Typical mean	Highest maximum level		
13.1.4	Other foods for young children	100		2	10.0	100	FRCA, SNE	
13.2	Dietary foods for special medical purposes	QS		1	–	24.8	FRCA	
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual	QS		2	0.25	39.2	FRCA, FDE	
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	QS	Including dry pasta	1	–	24.8	FRCA	No FoodEx linkage
14.1.4	Flavoured drinks	QS		6	13.8	62.5	FDE	
14.1.5.2	Other than coffee and coffee extracts	QS	Excluding unflavoured leaf tea; including flavoured instant coffee	8	9.5	19.3	FDE	No FoodEx linkage
14.2.3	Cider and perry	QS		1	–	–	FRCA	No fat content reported for this food category
14.2.4	Fruit wine and made wine	QS		1	0.02	0.03	FRCA	No FoodEx linkage
14.2.5	Mead	QS		1	–	–	FRCA	No FoodEx linkage
14.2.6	Spirit drinks	QS		1	0.22	0.37	FRCA	
14.2.7.1/14.2.7.2	Aromatized wines/aromatized wine-product cocktails	QS		1	0.62	1.04	FRCA	No FoodEx linkage
14.2.8	Other alcoholic drinks including spirits with less than 15 % of alcohol and mixtures of alcoholic drinks with non-alcoholic drinks	QS	Except whisky or whiskey	1	–	–	FRCA	No fat content reported for this food category
15.1	Potato-, cereal-, flour- or starch-based snacks	QS		1	26.2	52.4	FRCA	
15.2	Processed nuts	QS		1	108	216	FRCA	
16	Desserts	QS		8	2.43	12.0	FRCA, FDE	

FCS category number	FCS food category	MPL	Restrictions/exceptions	Number of data	Reported use levels expressed on a whole-weight basis		Information provided by	Comments
					Typical mean	Highest maximum level		
17.1/17.2/17.3	Food supplements	QS		5	2505	5500	AESGP, FRCA	
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	QS		1	–	4.0	FRCA	

Appendix C. Summary of analytical results (mg/kg) of tocopherols provided by Members States

FCS category number	FCS food category	MPL	All data				Concentration (MB) (mg/kg)											Comments
			n	LC (%)	LOD Range	LOQ Range	All data					Positive values						
							Min	Mean	Median	P95 [a]	Max	n	Min	Mean	Median	P95 [a]	Max	
α-Tocopherol																		
01.3	Unflavoured fermented milk products, heat-treated after fermentation	QS	1	100	30–60	60–60	–	–	–	–	30.0	–	–	–	–	–	–	
01.4	Flavoured fermented milk products including heat-treated products	QS	3	100	30–30	60–60	15.0	25.0	30.0	–	30.0	–	–	–	–	–	–	
1.7.4	Whey cheese	n.a.	2	50	5.0–30	10–60	30	31.2	31.2	–	31.2	1	–	31.2	–	–	–	
02.1	Fats and oils essentially free from water	QS/200	266	1	0.2–4	0.6–10	0.6	261	225	640	766	264	0.6	263	226	640	766	
02.2.2	Other fat and oil emulsions including spreads	QS	62	2	0.2–30	0.6–60	5.0	223	183	448	473	61	56.0	227	183	448	473	
03	Edible ices	QS	3	0	10–10	30–30	44.1	64.3	44.9	–	104	3	44.1	64.3	44.9	–	104	
04.2.1	Dried fruit and vegetables	QS	1	0	0.2	0.6	–	–	–	–	215	1	–	–	–	–	215	
05.1	Cocoa and chocolate products		19	0	2.9–30	3.1–60	2.0	178	142	–	569	19	2.0	178	142	–	569	
05.2	Other confectionery including breath freshening microsweets	QS	46	4	0.04–20	0.04–20	10.0	508	447	–	3197	44	26.9	530	454	599	3197	
6.2.1	Flours	n.a.	1	0	–	–	–	3.0	–	–	–	1	–	3.0	–	–	–	
07.2	Fine bakery wares	QS	30	0	2.9–2.9	3.1–3.1	24.8	245	245	–	489	30	24.8	245	245	–	489	
09.2	Processed fish and fishery products including molluscs and crustaceans	QS	1	0	1.7	5.0	–	–	–	–	36.5	1	–	–	–	–	36.5	
12.5	Soups and broths	QS	1	0	20	20	–	–	–	–	88.6	1	–	–	–	–	88.6	
12.6	Sauces	QS	3	0	1.7–5.0	5.0–10	13.3	27.5	17.0	–	52.1	3	13.3	27.5	17.0	–	52.1	
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10	30	0	10–30	10–60	7.4	12.0	11.8	–	21.7	30	7.4	12.0	11.8	–	21.7	Diluted as in final product
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10	28	0	0.01–30	0.02–60	1.2	8.4	8.6	–	14.7	28	1.2	8.4	8.6	-	14.7	Diluted as in final product

FCS category number	FCS food category	MPL	All data				Concentration (MB) (mg/kg)											Comments
			n	LC (%)	LOD	LOQ	All data					Positive values						
					Range	Range	Min	Mean	Median	P95 [a]	Max	n	Min	Mean	Median	P95 [a]	Max	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	41	32	3–30	6–60	1.5	27.4	9.5	–	97.7	28	7.9	39.3	43.1	–	97.7	
13.1.5	Dietary foods for infants and young children for special medical purposes as defined by Commission Directive 1999/21/EC and special formulae for infants	n.a.	14	21	2.5–20	2.5–40	5.0	25.8	24.3	–	46.0	11	20.6	30.6	27.7	–	46.0	
13.2	Dietary foods for special medical purposes	QS	103	5	1.7–30	2.5–60	5.0	961	44.2	827	30040	98	14.3	1009	44.6	1320	30040	
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual	QS	11	0	1.7–30	5.0–60	62.8	150	111	–	618	11	62.8	150	111	–	618	
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	QS	11	36	1.7–5	2.5–5	1.25	21.4	24.9	–	46.3	7	20.4	32.5	27.7	–	46.3	
14.1.3	Fruit nectars as defined by Council Directive 2001/112/EC and vegetable nectars and similar products	QS	1	0	5	10	–	–	–	–	22.0	1	–	–	–	–	22.0	
14.1.4	Flavoured drinks	QS	67	16	1.7–5	2.5–10	0.71	40.6	19.3	220	480	56	0.7	48.2	26.8	–	480	
14.1.5.2	Other	QS	1	0	30	60	–	–	–	–	21.0	1	–	–	–	–	21.0	Diluted as in final product
15.2	Processed nuts	QS	18	0	2.9–2.9	3.1–3.1	81.7	328	336	–	490	18	81.7	328	336	–	490	
17	Food supplements	QS	420	15	1.7–30	2.5–450	1.25	17735	8168	51591	470000	358	2.6	20803	9373	57456	470000	
γ–Tocopherol																		
02.1	Fats and oils essentially free from water	QS/200	267	7	0.2–10	0.6–18	0.7	212	171	586	1357	249	0.7	227	202	596	1357	

FCS category number	FCS food category	MPL	All data				Concentration (MB) (mg/kg)											Comments
			n	LC (%)	LOD	LOQ	All data					Positive values						
					Range	Range	Min	Mean	Median	P95 [(a)]	Max	n	Min	Mean	Median	P95 [(a)]	Max	
02.2.2	Other fat and oil emulsions including spreads	QS	3	0	0.2–0.2	0.6–0.6	77.3	93.7	99.2	–	105	3	77.3	93.7	99.2	–	105	
04.2.1	Dried fruit and vegetables	QS	1	0	0.2	0.6	–	–	–	–	14.9	1	–	–	–	–	14.9	
05.1	Cocoa and chocolate products		17	0	0.03–0.03	0.03–0.03	3.2	41.0	20.7	–	122	17	3.2	41.0	20.7	–	122	
05.2	Other confectionery including breath freshening microsweets	QS	43	5	0.03–0.03	0.03–0.03	0.0	30.3	14.6	–	156	41	5.3	31.8	14.9	–	156	
6.2.1	Flours	n.a.	1	0	–	–	–	1.0	–	–	–	1	–	1.0	–	–	–	
07.2	Fine bakery wares	QS	30	3	0.03–0.03	0.03–0.03	0.0	14.4	11.3	–	57.4	29	2.0	14.9	11.4	–	57.4	
13.2	Dietary foods for special medical purposes	QS	3	0	–	–	6.0	19.0	8.0	–	43.0	3	6.0	19.0	8.0	–	43.0	
14.1.4	Flavoured drinks	QS	1	0	–	–	–	–	–	–	0.9	1	–	–	–	–	0.9	
15.2	Processed nuts	QS	22	0	0.03–0.03	0.03–0.03	0.94	14.6	13.4	–	28.9	22	0.94	14.6	13.4	–	28.9	
17	Food supplements	QS	2	0	–	–	8.0	82.3	82.3	–	157	2	8.0	82.3	82.3	–	157	
δ-Tocopherol																		
02.1	Fats and oils essentially free from water	QS/200	267	44	0.2–10	0.6–18	0.1	13.0	4.4	44.0	201	149	0.2	21.8	12.0	75.0	201	
02.2.2	Other fat and oil emulsions including spreads	QS	3	33	0.2–0.2	0.6–0.6	0.1	1.1	1.5	–	1.8	2	1.5	1.7	1.7	–	1.8	
05.1	Cocoa and chocolate products		11	55	0.04–0.04	0.05–0.05	0.0	2.1	0.02	–	15.7	5	0.9	4.6	1.4	–	15.7	
05.2	Other confectionery including breath freshening microsweets	QS	21	95	0.04–0.04	0.05–0.05	0.0	0.4	0.02	–	8.2	1	–	–	–	–	8.2	
07.2	Fine bakery wares	QS	16	81	0.04–0.04	0.05–0.05	0.0	0.1	0.02	–	0.9	3	0.4	0.5	0.4	–	0.9	
14.1.4	Flavoured drinks	QS	1	0	–	–	–	–	–	–	0.3	1	–	–	–	–	0.3	
15.2	Processed nuts	QS	14	100	0.04–0.04	0.05–0.05	0.02	0.02	0.02	0.02	0.02	–	–	–	–	–	–	
17	Food supplements	QS	2	0	–	–	0.1	1.3	1.3	–	2.4	2	0.1	1.3	1.3	–	2.4	

(a): The 95th percentile obtained on occurrence data with fewer than 60 analytical results may not be statistically robust (EFSA, 2011a) and therefore are not reported in the table.
LC, left-censored data; max, maximum; min, minimum; n, number of analytical results; n.a., not authorised as a food additive.

Appendix D. Concentration levels of α-tocopherol (E 307) used in the maximum level and refined exposure assessment scenarios (mg/kg bw/day) for exposure assessment of α-tocopherol (E 307) used as a food additive. Scenario based on usage data reported by industry. Data presented as used for exposure assessment

FCS category number	FCS food category	MPL	Maximum level scenario	Refined scenarios without loss factors applied		Refined scenarios with loss factors applied			Comments
			Maximum	Mean	Maximum	Loss factor (%)	Mean	Maximum	
01.3	Unflavoured fermented milk products, heat-treated after fermentation	QS	159	99.6	159	–	99.6	159	
01.4	Flavoured fermented milk products including heat-treated products	QS	159	99.6	159	–	99.6	159	
01.6.3	Other creams	QS	–	–	–	–	–	–	No FoodEx linkage
01.7.1	Unripened cheese excluding products falling in category 16	QS	121	48.4	121	–	48.4	121	
01.7.5	Processed cheese	QS	121	48.4	121	–	48.4	121	
01.7.6	Cheese products (excluding products falling in category 16)	QS	–	–	–	–	–	–	No FoodEx linkage
01.8	Dairy analogues, including beverage whiteners	QS	107	53.6	107	–	53.6	107	
02.1	Fats and oils essentially free from water (excluding anhydrous milkfat)	QS/200	726	308	726	30	216	508	
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	QS	–	–	–	–	–	–	No FoodEx linkage
02.3	Vegetable oil pan spray	QS	–	–	–	–	–	–	No FoodEx linkage
03	Edible ices	QS	48.7	7.36	48.7	–	7.36	48.7	
04.2.1	Dried fruit and vegetables	QS	2.50	1.05	2.50	30	0.74	1.75	
04.2.2	Fruit and vegetables in vinegar, oil, or brine	QS	3.0	0.39	3.0	30	0.27	2.1	
04.2.4.1	Fruit and vegetable preparations excluding compote	QS	3.0	0.39	3.0	30	0.27	2.1	
04.2.5.4	Nut butters and nut spreads	QS	160	80.1	160	30	56.1	112	
04.2.6	Processed potato products	QS	17.3	5.87	17.3	30	4.12	12.1	
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC		130	40.0	130	–	40.0	130	
05.2	Other confectionery including breath freshening microsweets	QS	30.0	18.0	30.0	–	18.0	30.0	
05.3	Chewing gum	QS	670	9.5	670	–	9.5	670	
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	QS	–	–	–	–	–	–	No FoodEx linkage

FCS category number	FCS food category	MPL	Maximum level scenario	Refined scenarios without loss factors applied		Refined scenarios with loss factors applied			Comments
			Maximum	Mean	Maximum	Loss factor (%)	Mean	Maximum	
06.2.2	Starches	QS	0.35	0.35	0.35	–	0.35	0.35	Typical usage level not available, maximum usage level used for mean
06.3	Breakfast cereals	QS	10.0	0.04	10.0	–	0.04	10.0	
06.4.2	Dry pasta	QS	–	–	–	–	–	–	No FoodEx linkage
06.4.4	Potato Gnocchi	QS	–	–	–	–	–	–	No FoodEx linkage
06.4.5	Fillings of stuffed pasta (ravioli and similar)	QS	20.0	20.0	20.0	–	20.0	20.0	Typical usage level not available, maximum usage level used for mean
06.5	Noodles	QS	5.3	3.2	5.3	–	3.2	5.3	
06.6	Batters	QS	–	–	–	–	–	–	No FoodEx linkage
06.7	Pre-cooked or processed cereals	QS	–	–	–	–	–	–	No FoodEx linkage
07.1	Bread and rolls	QS	15.0	9.0	15.0	–	9.0	15.0	
07.2	Fine bakery wares	QS	68.8	6.2	68.8	–	6.2	68.8	
08.3.1	Non-heat-treated meat products	QS	1 500	1 000	1 500	25	750	1 125	
08.3.2	Heat-treated meat products	QS	1 500	1 000	1 500	25	750	1 125	
08.3.3	Casings and coatings and decorations for meat	QS	–	–	–	–	–	–	No FoodEx linkage
09.2	Processed fish and fishery products including molluscs and crustaceans	QS	52.5	21.0	52.5	–	21.0	52.5	
09.3	Fish roe	QS	49.5	19.8	49.5	–	19.8	49.5	
10.2	Processed eggs and egg products	QS	152	76.0	152	–	76.0	152	
11.2	Other sugars and syrups	QS	3.42	2.05	3.42	–	2.05	3.42	
12.1.2	Salt substitutes	QS	–	–	–	–	–	–	No FoodEx linkage
12.2.2	Seasonings and condiments	QS	21.4	4.42	21.4	–	4.42	21.4	
12.3	Vinegars	QS	0.25	0.15	0.25	–	0.15	0.25	

FCS category number	FCS food category	MPL	Maximum level scenario	Refined scenarios without loss factors applied		Refined scenarios with loss factors applied			Comments
			Maximum	Mean	Maximum	Loss factor (%)	Mean	Maximum	
12.4	Mustard	QS	0.2	0.1	0.2	–	0.1	0.2	
12.5	Soups and broths	QS	101	11.9	101	–	11.9	101	
12.6	Sauces	QS	327	36.5	327	–	36.5	327	
12.7	Salads and savoury-based sandwich spreads	QS	20.0	10.0	20.0	–	10.0	20.0	
12.8	Yeast and yeast products	QS	1.6	0.8	1.6	–	0.8	1.6	
12.9	Protein products, excluding products covered in category 1.8	QS	33.6	16.8	33.6	–	16.8	33.6	
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10	10	7.5	10.0	50	3.25	5.0	
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10	10	6.5	10.0	–	6.5	10.0	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	100	3.0	100	–	3.0	100	
13.1.4	Other foods for young children	100	100	10.0	100	–	10.0	100	
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	10							No FoodEx linkage
13.1.5.2	Dietary foods for babies and young children for special medical purposes as defined in Directive 1999/21/EC	10							No FoodEx linkage
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	QS	24.8	24.8	24.8	–	24.8	24.8	Typical usage level not available, maximum usage level used for mean
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)	QS	39.2	0.25	39.2	–	0.25	39.2	
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	QS	24.8	24.8	24.8	–	24.8	24.8	Typical usage level not available, maximum usage level used for mean
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	QS	–	–	–	–	–	–	No usage data reported
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	QS	–	–	–	–	–	–	No usage data reported; No FoodEx linkage
14.1.4	Flavoured drinks	QS	62.5	13.8	62.5	–	13.8	62.5	
14.1.5.2	Other than coffee and coffee extracts	QS	–	–	–	–	–	–	No FoodEx

FCS category number	FCS food category	MPL	Maximum level scenario	Refined scenarios without loss factors applied		Refined scenarios with loss factors applied			Comments
			Maximum	Mean	Maximum	Loss factor (%)	Mean	Maximum	
									linkage
14.2.3	Cider and perry	QS	–	–	–	–	–	–	No adequate data available

FCS category number	FCS food category	MPL	Maximum level scenario	Refined scenarios without loss factors applied		Refined scenarios with loss factors applied			Comments
			Maximum	Mean	Maximum	Loss factor (%)	Mean	Maximum	
14.2.4	Fruit wine and made wine	QS	–	–	–	–	–	–	No FoodEx linkage
14.2.5	Mead	QS	–	–	–	–	–	–	No FoodEx linkage
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	QS	0.37	0.22	0.37	–	0.22	0.37	
14.2.7.1	Aromatised wines	QS	1.04	0.62	1.04	–	–	–	
14.2.7.2	Aromatised wine-based drinks	QS	–	–	–	–	–	–	No FoodEx linkage
14.2.7.3	Aromatised wine-product cocktails	QS	–	–	–	–	–	–	No FoodEx linkage
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15 % of alcohol	QS	–	–	–	–	–	–	No adequate data available
15.1	Potato-, cereal-, flour- or starch-based snacks	QS	52.4	26.2	52.4	–	26.2	52.4	
15.2	Processed nuts	QS	216	108	216	–	108	216	
16	Desserts excluding products covered in categories 01, 03 and 04	QS	12.0	2.43	12.0	–	2.43	12.0	
17.1/17.2/ 17.3	Food supplements	QS	5 500	2 505	5 500	–	2 505	5 500	
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	QS	4.0	4.0	4.0	–	4.0	4.0	Typical usage level not available, maximum usage level used for mean

Appendix E. Concentration levels of α-tocopherol used in the refined exposure scenario (mg/kg bw/day) for exposure assessment to α-tocopherol from all sources (food additive, enzyme preparations, nutrient as vitamin and natural sources). Scenario based on analytical data (or usage data when no analytical data were available). Data presented as used for exposure assessment

FCS category number	FCS food category	MPL	Refined scenario		Comments
			Mean	Max	
01.3	Unflavoured fermented milk products, heat-treated after fermentation	QS	30.0	30.0	
01.4	Flavoured fermented milk products including heat-treated products	QS	25.0	30.0	
01.6.3	Other creams	QS	–	–	No FoodEx linkage
01.7.1	Unripened cheese excluding products falling in category 16	QS	48.4	121	Usage level used for this food category
01.7.4	Whey cheese	n.a.	–	–	No FoodEx linkage
01.7.5	Processed cheese	QS	48.4	121	Usage level used for this food category
01.7.6	Cheese products (excluding products falling in category 16)	QS	–	–	No FoodEx linkage
01.8	Dairy analogues, including beverage whiteners	QS	53.6	107	
02.1	Fats and oils essentially free from water (excluding anhydrous milkfat)	QS/200	261	766	
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	QS	–	–	No FoodEx linkage
02.3	Vegetable oil pan spray	QS	–	–	No FoodEx linkage
03	Edible ices	QS	64.3	104	
04.2.1	Dried fruit and vegetables	QS	215	215	
04.2.2	Fruit and vegetables in vinegar, oil, or brine	QS	0.27	2.1	Usage level with loss factor of 30 % used for this food category
04.2.4.1	Fruit and vegetable preparations excluding compote	QS	0.27	2.1	Usage level with loss factor of 30 % used for this food category
04.2.5.4	Nut butters and nut spreads	QS	56.1	112	Usage level with loss factor of 30 % used for this food category
04.2.6	Processed potato products	QS	4.12	12.1	Usage level with loss factor of 30 % used for this food category
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC		178	569	
05.2	Other confectionery including breath freshening microsweets	QS	508	3197	

FCS category number	FCS food category	MPL	Refined scenario		Comments
			Mean	Max	
05.3	Chewing gum	QS	9.5	670	Usage level used for this food category
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	QS	–	–	No FoodEx linkage
06.2.1	Flours	n.a.	3.0	3.0	Usage level used for this food category
06.2.2	Starches	QS	0.35	0.35	Usage level used for this food category
06.3	Breakfast cereals	QS	0.04	10.0	Usage level used for this food category
06.4.2	Dry pasta	QS	–	–	No FoodEx linkage
06.4.4	Potato Gnocchi	QS	–	–	No FoodEx linkage
06.4.5	Fillings of stuffed pasta (ravioli and similar)	QS	20.0	20.0	
06.5	Noodles	QS	3.20	5.30	
06.6	Batters	QS	–	–	No FoodEx linkage
06.7	Pre-cooked or processed cereals	QS	–	–	No FoodEx linkage
07.1	Bread and rolls	QS	9.0	15.0	
07.2	Fine bakery wares	QS	245	489	
08.3.1	Non-heat-treated meat products	QS	750	1125	Usage level with loss factor of 25 % used for this food category
08.3.2	Heat–treated meat products	QS	750	1125	Usage level with loss factor of 25 % used for this food category
08.3.3	Casings and coatings and decorations for meat	QS	–	–	No FoodEx linkage
09.2	Processed fish and fishery products including molluscs and crustaceans	QS	36.5	36.5	
09.3	Fish roe	QS	19.8	49.5	Usage level used for this food category
10.2	Processed eggs and egg products	QS	76.0	152	Usage level used for this food category
11.2	Other sugars and syrups	QS	2.05	3.42	Usage level used for this food category
12.1.2	Salt substitutes	QS	–	–	No FoodEx linkage

FCS category number	FCS food category	MPL	Refined scenario		Comments
			Mean	Max	
12.2.2	Seasonings and condiments	QS	4.42	21.4	Usage level used for this food category
12.3	Vinegars	QS	0.15	0.25	Usage level used for this food category
12.4	Mustard	QS	0.1	0.2	Usage level used for this food category
12.5	Soups and broths	QS	88.6	88.6	
12.6	Sauces	QS	27.5	52.1	
12.7	Salads and savoury-based sandwich spreads	QS	10.0	20.0	Usage level used for this food category
12.8	Yeast and yeast products	QS	0.80	1.60	Usage level used for this food category
12.9	Protein products, excluding products covered in category 1.8	QS	16.8	33.6	Usage level used for this food category
13.1.1	Infant formulae as defined by Directive 2006/141/EC	10	12.0 [(a)]	21.7 [(a)]	
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC	10	8.4	14.7	
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	100	27.4	97.7	
13.1.4	Other foods for young children	100	10.0	100	Usage level used for this food category
13.1.5	Dietary foods for infants and young children for special medical purposes as defined by Commission Directive 1999/21/EC and special formulae for infants				No FoodEx linkage
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	QS	961	30040	
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)	QS	150	618	
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	QS	24.8	24.8	Usage level used for this food category
14.1.2	Fruit juices as defined by Directive 2001/112/EC and vegetable juices	QS	21.4	46.3	
14.1.3	Fruit nectars as defined by Directive 2001/112/EC and vegetable nectars and similar products	QS	–	–	No FoodEx linkage
14.1.4	Flavoured drinks	QS	40.6	480	
14.1.5.2	Other than coffee and coffee extracts	QS	–	–	No FoodEx linkage
14.2.3	Cider and perry	QS	–	–	No adequate data

FCS category number	FCS food category	MPL	Refined scenario		Comments
			Mean	Max	
14.2.4	Fruit wine and made wine	QS	–	–	No FoodEx linkage
14.2.5	Mead	QS	–	–	No FoodEx linkage
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	QS	0.22	0.37	Usage level used for this food category
14.2.7.1	Aromatised wines	QS	0.62	1.04	Usage level used for this food category
14.2.7.2	Aromatised wine-based drinks	QS	–	–	No FoodEx linkage
14.2.7.3	Aromatised wine-product cocktails	QS	–	–	No FoodEx linkage
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15 % of alcohol	QS	–	–	No adequate data
15.1	Potato-, cereal-, flour- or starch-based snacks	QS	26.2	52.4	Usage level used for this food category
15.2	Processed nuts	QS	336	490	
16	Desserts excluding products covered in categories 01, 03 and 04	QS	2.43	12.0	Usage level used for this food category
17.1/17.2/17.3	Food supplements	QS	17 735	470 000	
18	Processed foods not covered by categories 1 to 17, excluding foods for infants and young children	QS	4.0	4.0	Usage level used for this food category

(a): Analytical values are higher than the MPL which may be explained by the presence of α-tocopherol (E 307) from sources other than the food additive (e.g. natural sources).
Max, maximum; n.a., not authorised as a food additive.

Appendix F. Summary of total estimated exposure to α-tocopherol (E 307) from its use as a food additive for refined exposure scenarios per population group and survey: mean and high level (mg/kg bw/day)

	Number of subjects	Exposure to α-tocopherol (E 307) from its use as a food additive without loss factors				Exposure to α-tocopherol (E 307) from its use as a food additive with loss factors			
		Brand-loyal scenario		Non-brand-loyal scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level	Mean	High level
Infants									
Bulgaria (NUTRICHILD)	659	1.5	4.4	0.4	1.4	1.4	4.0	0.3	1.1
Denmark (IAT 2006_2007)	826	4.2	8.6	1.5	4.5	1.9	5.1	1.2	3.5
Finland (DIPP_2001_2009)	496	2.4	6.5	0.8	2.1	0.7	2.2	0.5	1.5
Germany (VELS)	159	1.1	3.0	0.9	2.6	4.0	8.4	0.8	2.1
Italy (INRAN_SCAI_2005_06)	12	2.2	–	0.7	–	2.2	–	0.5	–
United Kingdom (DNSIYC_2011)	1 362	2.3	5.3	0.9	2.0	1.9	4.8	0.7	1.6
Toddlers									
Belgium (Regional_Flanders)	36	4.5	–	3.1	–	3.8	–	2.6	–
Bulgaria (NUTRICHILD)	428	3.6	8.4	2.5	5.6	3.2	7.8	2.2	5.3
Finland (DIPP)	497	2.1	5.6	1.5	4.1	1.9	4.7	1.3	3.5
Germany (DONALD_2006_2008)	261	3.5	7.9	2.0	5.1	2.9	6.5	1.6	4.0
Italy (INRAN_SCAI_2005_06)	36	2.7	–	1.8	–	2.2	–	1.5	–
Spain (EnKid)	17	4.3	–	3.0	–	3.6	–	2.5	–
The Netherlands (VCP_kids)	322	4.4	9.7	3.1	7.2	3.8	8.1	2.7	5.9
Children									
Belgium (Regional_Flanders)	625	4.1	8.8	2.9	6.3	3.5	7.2	2.4	5.2
Bulgaria (NUTRICHILD)	433	3.3	8.3	2.4	6.0	2.7	6.6	2.0	4.8
Czech Republic (SISP04)	389	2.8	6.7	2.0	4.6	2.3	5.2	1.6	3.7
Denmark (Danish_Dietary_Survey)	490	2.5	5.2	1.8	3.6	2.0	4.0	1.5	3.0
Finland (DIPP)	933	3.3	8.0	2.3	5.7	2.6	6.3	1.9	4.6
Finland (STRIP)	250	4.1	9.5	2.9	6.5	3.3	7.2	2.3	5.0
France (INCA2)	482	2.5	5.2	1.9	3.7	2.1	4.0	1.5	3.0
Germany (DONALD_2006_2008)	660	3.0	6.8	2.1	4.7	2.4	5.3	1.7	3.7
Greece (Regional_Crete)	839	1.6	5.6	1.1	3.8	1.4	4.3	0.9	2.9
Italy (INRAN_SCAI_2005_06)	193	2.2	5.1	1.5	3.7	1.7	3.9	1.2	2.8
Latvia (EFSA_TEST)	189	2.3	6.0	1.5	4.2	1.9	4.6	1.2	3.3
Spain (enKid)	156	3.8	8.6	2.8	6.1	3.0	6.6	2.2	4.9
Spain (NUT_INK05)	399	3.6	7.8	2.7	5.5	2.9	6.1	2.2	4.5
Sweden (NFA)	1 473	3.2	6.7	2.3	4.8	2.7	5.4	1.9	3.9
The Netherlands (VCP_kids)	957	3.8	7.9	2.8	6.0	3.3	6.8	2.4	5.0

	Number of subjects	Exposure to α-tocopherol (E 307) from its use as a food additive without loss factors				Exposure to α-tocopherol (E 307) from its use as a food additive with loss factors			
		Brand-loyal scenario		Non-brand-loyal scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level	Mean	High level
Adolescents									
Belgium (Diet_National_2004)	584	1.3	2.9	0.8	2.0	1.1	2.5	0.7	1.6
Cyprus (Childhealth)	303	0.7	1.7	0.5	1.2	0.6	1.3	0.4	0.9
Czech Republic (SISP04)	298	2.5	6.6	1.8	4.5	2.0	5.2	1.4	3.4
Denmark (Danish_Dietary_Survey)	479	1.3	2.9	0.9	2.0	1.1	2.4	0.8	1.6
France (INCA2)	973	1.3	2.7	1.0	2.0	1.1	2.2	0.8	1.6
Germany (National_Nutrition_Survey_II)	1011	1.4	3.8	0.9	2.5	1.2	3.0	0.7	1.9
Italy (INRAN_SCAI_2005_06)	247	1.4	3.4	1.0	2.4	1.1	2.5	0.8	1.8
Latvia (EFSA_TEST)	470	1.7	4.3	1.2	3.0	1.4	3.3	0.9	2.4
Spain (AESAN_FIAB)	86	1.8	3.7	1.3	2.7	1.4	2.9	1.0	2.1
Spain (enKid)	209	2.4	6.5	1.7	4.4	1.9	5.0	1.4	3.4
Spain (NUT_INK05)	651	2.2	5.0	1.6	3.5	1.7	3.8	1.3	2.7
Sweden (NFA)	1 018	1.9	4.2	1.4	3.0	1.6	3.3	1.1	2.4
Adults									
Belgium (Diet_National_2004)	1 304	1.1	2.8	0.7	1.9	1.0	2.3	0.6	1.5
Czech Republic (SISP04)	1 666	1.9	5.0	1.3	3.4	1.5	3.8	1.0	2.6
Denmark (Danish_Dietary_Survey)	2 822	0.8	1.8	0.6	1.3	0.7	1.5	0.5	1.0
Finland (FINDIET_2007)	1 575	1.2	3.2	0.9	2.2	1.0	2.5	0.7	1.8
France (INCA2)	2 276	1.1	2.2	0.8	1.6	0.9	1.8	0.6	1.2
Germany (National_Nutrition_Survey_II)	10 419	1.3	3.3	0.9	2.2	1.1	2.5	0.7	1.7
Hungary (National_Repr_Surv)	1 074	1.8	4.1	1.2	2.8	1.4	3.1	1.0	2.1
Ireland (NSIFCS)	958	1.3	3.0	0.9	2.1	1.0	2.3	0.7	1.6
Italy (INRAN_SCAI_2005_06)	2 313	1.0	2.2	0.7	1.6	0.8	1.7	0.5	1.2
Latvia (EFSA_TEST)	1 306	1.2	3.3	0.8	2.3	1.0	2.5	0.6	1.8
Spain (AESAN)	410	1.5	3.7	1.1	2.5	1.2	2.8	0.8	1.9
Spain (AESAN_FIAB)	981	1.5	3.1	1.1	2.2	1.1	2.4	0.8	1.7
Sweden (Riksmaten_1997_98)	1 210	1.2	2.4	0.8	1.7	1.0	1.9	0.7	1.4
The Netherland (DNFCS_2003)	750	1.5	3.4	1.0	2.4	1.3	2.7	0.9	2.0
United Kingdom (NDNS)	1 724	0.9	1.9	0.6	1.3	0.7	1.5	0.5	1.0
Elderly and very elderly									
Belgium (Diet_National_2004)	1 230	1.0	2.5	0.7	1.7	0.8	1.9	0.5	1.3
Denmark (Danish_Dietary_Survey)	329	0.7	1.8	0.5	1.3	0.6	1.4	0.4	1.0
Finland (FINDIET_2007)	463	1.0	2.9	0.7	2.0	0.9	2.4	0.6	1.7
France (INCA2)	348	0.9	2.0	0.7	1.4	0.7	1.5	0.5	1.1

	Number of subjects	Exposure to α-tocopherol (E 307) from its use as a food additive without loss factors				Exposure to α-tocopherol (E 307) from its use as a food additive with loss factors			
		Brand-loyal scenario		Non-brand-loyal scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level	Mean	High level
Germany (National_Nutrition_Survey_II)	2 496	1.1	2.6	0.8	1.8	0.9	2.0	0.6	1.4
Hungary (National_Repr_Surv)	286	1.4	3.3	1.0	2.3	1.1	2.5	0.7	1.7
Italy (INRAN_SCAI_2005_06)	518	0.8	1.7	0.5	1.3	0.6	1.4	0.4	1.0

Appendix G. Summary of total estimated exposure to α-tocopherol from all sources (food additive, enzyme preparations, nutrient as vitamin and natural sources) per population group and survey: mean and high level (mg/kg bw/day)

	Number of subjects	Exposure to α-tocopherol from all sources	
		Mean	High level
Infants			
Bulgaria (NUTRICHILD)	659	0.8	2.2
Denmark (IAT 2006_2007)	826	1.5	3.7
Finland (DIPP_2001_2009)	496	1.3	2.7
Germany (VELS)	159	1.4	3.2
Italy (INRAN_SCAI_2005_06)	12	1.0	–
United Kingdom (DNSIYC_2011)	1 362	1.3	2.4
Toddlers			
Belgium (Regional_Flanders)	36	3.7	–
Bulgaria (NUTRICHILD)	428	2.4	5.1
Finland (DIPP)	497	1.2	3.6
Germany (DONALD_2006_2008)	261	2.1	4.9
Italy (INRAN_SCAI_2005_06)	36	2.1	–
Spain (EnKid)	17	2.5	–
The Netherlands (VCP_kids)	322	3.2	6.3
Children			
Belgium (Regional_Flanders)	625	3.2	6.2
Bulgaria (NUTRICHILD)	433	2.7	5.9
Czech Republic (SISP04)	389	2.4	4.9
Denmark (Danish_Dietary_Survey)	490	1.9	3.7
Finland (DIPP)	933	2.1	4.8
Finland (STRIP)	250	4.0	9.7
France (INCA2)	482	2.4	4.3
Germany (DONALD_2006_2008)	660	2.4	4.4
Greece (Regional_Crete)	839	1.6	3.6
Italy (INRAN_SCAI_2005_06)	193	1.8	3.7
Latvia (EFSA_TEST)	189	2.1	4.7
Spain (enKid)	156	2.6	5.5
Spain (NUT_INK05)	399	2.5	4.6
Sweden (NFA)	1 473	3.1	5.7
The Netherlands (VCP_kids)	957	2.9	5.2
Adolescents			
Belgium (Diet_National_2004)	584	1.3	2.7

	Number of subjects	Exposure to α-tocopherol from all sources	
		Mean	High level
Cyprus (Childhealth)	303	0.6	1.4
Czech Republic (SISP04)	298	2.0	4.4
Denmark (Danish_Dietary_Survey)	479	1.1	2.4
France (INCA2)	973	1.3	2.5
Germany (National_Nutrition_Survey_II)	1 011	1.2	2.7
Italy (INRAN_SCAI_2005_06)	247	1.1	2.5
Latvia (EFSA_TEST)	470	1.5	3.1
Spain (AESAN_FIAB)	86	1.3	2.7
Spain (enKid)	209	1.7	4.1
Spain (NUT_INK05)	651	1.6	3.0
Sweden (NFA)	1 018	1.8	3.5
Adults			
Belgium (Diet_National_2004)	1 304	1.0	2.1
Czech Republic (SISP04)	1 666	1.3	3.0
Denmark (Danish_Dietary_Survey)	2 822	0.6	1.3
Finland (FINDIET_2007)	1 575	1.0	2.5
France (INCA2)	2 276	0.9	1.6
Germany (National_Nutrition_Survey_II)	10 419	1.1	2.3
Hungary (National_Repr_Surv)	1 074	1.1	2.2
Ireland (NSIFCS)	958	1.1	2.3
Italy (INRAN_SCAI_2005_06)	2 313	0.7	1.6
Latvia (EFSA_TEST)	1 306	0.9	2.2
Spain (AESAN)	410	1.1	2.4
Spain (AESAN_FIAB)	981	1.1	2.1
Sweden (Riksmaten_1997_98)	1 210	1.0	1.8
The Netherland (DNFCS_2003)	750	1.2	2.4
United Kingdom (NDNS)	1 724	0.9	1.8
Elderly and very elderly			
Belgium (Diet_National_2004)	1 230	0.9	1.8
Denmark (Danish_Dietary_Survey)	329	0.5	1.0
Finland (FINDIET_2007)	463	0.9	2.5
France (INCA2)	348	0.7	1.3
Germany (National_Nutrition_Survey_II)	2 496	0.9	1.8
Hungary (National_Repr_Surv)	286	0.8	1.9
Italy (INRAN_SCAI_2005_06)	518	0.6	1.3

Appendix H. Main food categories contributing to exposure to α-tocopherol (E 307) based on reported use levels

Table H1: Main food categories contributing to exposure to α-tocopherol (E 307) from its use as a food additive using the maximum exposure scenario (> 5 % to the total mean exposure) and number of surveys in which each food category is contributing

FCS category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	5.7–43.7 (4)	5.2–25.9 (8)	5.7–7.6 (5)	5.5–11.1 (8)	7.4–16.4 (3)
01.4	Flavoured fermented milk products	7.7–10.4 (2)	7.3–26.1 (6)	5.1–21.0 (10)	6.1–9.1 (2)	5.1–8.5 (2)	5.4 (1)
01.7.1	Unripened cheese excluding products falling in category 16	10.7 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	10.6–23.5 (4)	8.4–23.0 (4)	7.7–30.2 (7)	5.5–27.2 (7)	6.6–31.3 (6)	11.6–36.4 (3)
07.2	Fine bakery wares	–	–	5.4–8.0 (3)	6.2 (1)	–	–
08.3	Meat products	6.5–48.1 (6)	22.9–55.5 (7)	39.8–62.9 (15)	41.4–64.2 (12)	47.0–71.2 (15)	46.2–68.4 (7)
12.5	Soups and broths	7.0 (1)	7.8 (1)	5.3–13.5 (3)	5.4–11.0 (2)	7.7–12.4 (2)	6.0–15.3 (2)
12.6	Sauces	–	–	5.9–7.6 (4)	5.1–11.4 (6)	5.3–12.8 (7)	5.5–6.9 (3)
13.1	Foods for infants and young children	25.2–76.3 (6)	5.3–24.9 (4)	–	–	–	–
14.1.4	Flavoured drinks	–	6.8–15.6 (2)	6.3–15.2 (10)	6.0–24.0 (8)	5.7–16.8 (9)	–
17	Food supplements	–	–	–	–	5.3–7.0 (2)	11.1 (1)
18	Processed foods not covered by categories 1 to 17	–	–	–	–	–	–

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

Table H2: Main food categories contributing to exposure to α-tocopherol (E 307) from its use as a food additive using the brand-loyal refined exposure scenario (> 5 % to the total mean exposure) without loss factors and number of surveys in which each food category is contributing

FCS category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	5.6–52.6 (4)	5.3–25.4 (8)	5.9–6.8 (4)	5.3–10.8 (8)	6.6–16.0 (3)
01.4	Flavoured fermented milk products	7.7–10.3 (2)	6.7–29.8 (6)	6.4–23.3 (9)	5.9–8.9 (2)	6.3–7.8 (2)	–
01.7.1	Unripened cheese excluding products falling in category 16	7.1 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	8.8–17.7 (4)	9.4–19.7 (3)	5.1–27.3 (7)	5.8–21.5 (5)	5.3–26.6 (6)	7.6–32.9 (3)
08.3	Meat products	8.0–54.6 (6)	27.7–66.9 (7)	50.9–80.6 (15)	59.1–79.9 (12)	63.4–83.3 (15)	55.3–81.5 (7)
12.5	Soups and broths	8.7 (1)	–	7.8 (1)	5.4 (1)	6.6 (1)	8.3 (1)
12.6	Sauces	–	–	–	5.3–6.5 (2)	5.1–5.5 (2)	–
13.1	Foods for infants and children	24.0–82.9 (6)	10.5–23.1 (3)	–	–	–	–
14.1.4	Flavoured drinks	–	9.8 (1)	5.2–7.9 (5)	8.3–21.2 (5)	5.1–14.1 (5)	–
17	Food supplements	–	–	–	–	5.6–5.9 (2)	9.4 (1)
18	Processed foods not covered by categories 1 to 17	–	–	–	–	5.7 (1)	5.7 (1)

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

Table H3: Main food categories contributing to exposure to α-tocopherol (E 307) from its use as a food additive following the non-brand-loyal exposure scenario (> 5 % to the total mean exposure) without loss factors and number of surveys in which each food category is contributing

FCS category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	6.4–48.4 (4)	5.9–26.3 (8)	6.6–8.6 (5)	6.9–12.9 (8)	8.2–16.7 (3)
01.4	Flavoured fermented milk products	5.3–14.8 (5)	9.1–26.4 (6)	5.7–24.1 (10)	5.2–11.2 (4)	7.8–8.8 (2)	5.4 (1)
01.7.1	Unripened cheese excluding products falling in category 16	13.2 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	6.6–35.4 (5)	6.0–19.3 (4)	6.2–24.1 (7)	5.7–21.3 (6)	6.3–24.1 (6)	8.7–28.4 (3)
07.1	Bread and rolls	5.1 (1)	–	–	–	–	–
08.3	Meat products	15.7–58.1 (6)	24.6–68.9 (7)	48.6–77.1 (15)	66.1–77.8 (12)	63.1–80.2 (15)	56.6–78.3 (7)
13.1	Foods for infants and children	15.1–45.5 (6)	8.1 (1)	–	–	–	–
14.1.4	Flavoured drinks	–	7.3 (1)	5.9–6.6 (2)	5.6–12.7 (5)	5.0–8.1 (3)	–
17	Food supplements	–	–	–	–	5.3 (1)	8.2 (1)
18	Processed foods not covered by categories 1 to 17	–	5.8–11.5 (2)	–	5.6 (1)	5.2–8.2 (3)	6.3–7.8 (2)

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

Table H4: Main food categories contributing to exposure to α-tocopherol (E 307) from its use as a food additive using the brand-loyal refined exposure scenario (> 5 % to the total mean exposure) with loss factors and number of surveys in which each food category is contributing

FCS category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	7.0–59.5 (4)	6.3–31.4 (8)	5.7–9.0 (5)	7.1–13.8 (8)	5.2–20.0 (4)
01.4	Flavoured fermented milk products	8.9–13.4 (2)	8.3–35.1 (6)	5.3–28.6 (10)	5.4–11.1 (3)	7.6–9.7 (2)	5.8 (1)
01.7.1	Unripened cheese excluding products falling in category 16	8.6 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	6.4–19.2 (4)	7.3–16.7 (3)	5.1–24.2 (6)	5.0–19.4 (4)	8.4–23.6 (4)	6.5–29.4 (3)
08.3	Meat products	6.4–60.3 (6)	23.5–59.4 (7)	45.2–74.9 (15)	49.4–76.1 (12)	55.8–81.3 (15)	54.5–79.7 (7)
12.5	Soups and broths	9.2 (1)	–	5.4–10.1 (2)	7.2 (1)	5.3–8.7 (2)	11.8 (1)
12.6	Sauces	–	–	–	7.4–7.9 (2)	5.6–7.8 (3)	–
13.1	Foods for infants and children	19.1–85.9 (6)	9.2–28.7 (3)	–	–	–	–
14.1.4	Flavoured drinks	–	5.4–11.7 (2)	5.3–10.8 (7)	5.2–27.5 (7)	5.3–18.0 (6)	–
17	Food supplements	–	–	–	–	7.0–7.4 (2)	11.5 (1)
18	Processed foods not covered by categories 1 to 17	–	–	–	–	6.9 (1)	5.3–6.9 (2)

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

Table H5: Main food categories contributing to exposure to α-tocopherol (E 307) from its use as a food additive following the non-brand-loyal exposure scenario (> 5 % to the total mean exposure) with loss factors and number of surveys in which each food category is contributing

FCS category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	5.3–56.2 (5)	5.3–31.3 (10)	5.6–10.7 (6)	8.5–15.7 (8)	5.8–19.9 (5)
01.4	Flavoured fermented milk products	6.5–18.7 (5)	12.0–35.0 (6)	5.5–28.1 (13)	6.3–13.7 (4)	5.1–10.7 (7)	6.5 (1)
01.7.1	Unripened cheese excluding products falling in category 16	16.7 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	5.5–30.5 (5)	5.3–17.5 (4)	5.3–21.9 (7)	6.3–19.4 (5)	5.6–21.9 (6)	7.6–25.7 (3)
07.1	Bread and rolls	6.2 (1)	–	–	–	–	–
08.3	Meat products	14.8–58.1 (6)	24.6–67.9 (7)	43.5–71.8 (15)	59.6–72.9 (12)	58.1–77.5 (15)	51.3–75.7 (7)
13.1	Foods for infants and children	12.1–43.2 (6)	6.1–6.2 (2)	–	–	–	–
14.1.4	Flavoured drinks	–	8.7 (1)	5.2–8.0 (4)	5.2–15.4 (6)	5.1–9.9 (5)	–
17	Food supplements	–	–	–	–	6.0–6.4 (2)	9.8 (1)
18	Processed foods not covered by categories 1 to 17	–	–	5.3 (1)	6.7 (1)	6.3–9.9 (3)	7.5–9.4 (2)

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

Appendix I. Main food categories contributing to exposure to α-tocopherol based on analytical levels

Table I1: Main food categories contributing to exposure to α-tocopherol (E 307) from all sources (> 5 % to the total mean exposure) and number of surveys in which each food category is contributing

FCS Category number	FCS food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of contribution (%) to the total exposure (number of surveys) [(a)]					
01.3	Unflavoured fermented milk products	–	6.6–16.1 (2)	7.0 (1)	–	–	–
01.4	Flavoured fermented milk products	–	5.2–9.3 (3)	5.8 (1)	–	–	–
01.7.1	Unripened cheese excluding products falling in category 16	9.2 (1)	–	–	–	–	–
02.1	Fats and oils essentially free from water	8.1–19.4 (4)	6.4–14.9 (4)	5.3–17.5 (6)	5.4–16.2 (5)	5.2–19.2 (6)	7.4–21.6 (3)
05.1	Cocoa and chocolate products	–	5.6 (1)	5.1–5.9 (4)	5.5–5.8 (3)	–	–
05.2	Other confectionery including breath freshening microsweets	–	6.9 (1)	6.7–14.0 (6)	10.9–16.9 (2)	5.2–12.3 (2)	5.5 (1)
07.2	Fine bakery wares	6.5–33.2 (3)	12.3–32.2 (6)	11.4–38.5 (13)	14.5–32.4 (11)	5.2–25.3 (13)	7.1–24.3 (6)
08.3	Meat products	8.2–42.6 (6)	24.2–59.0 (7)	29.2–58.0 (15)	31.1–56.0 (12)	33.2–70.0 (15)	36.1–67.3 (7)
12.5	Soups and broths	17.5 (1)	11.9 (1)	6.3–17.7 (3)	7.1–15.3 (3)	5.3–17.9 (4)	8.3–20.5 (2)
13.1	Foods for infants and children	21.5–45.0 (6)	6.2–14.3 (2)	–	–	–	–
14.1.4	Flavoured drinks	7.6 (1)	7.9–17.8 (2)	5.1–15.5 (11)	5.0–23.4 (11)	5.1–18.8 (10)	5.5 (1)
17	Food supplements	7.2–25.1 (3)	–	8.2–16.1 (2)	–	5.7–32.7 (6)	13.9–46.9 (2)
18	Processed foods not covered by categories 1 to 17	8.1–17.0 (5)	6.0–16.2 (2)	–	–	7.5 (1)	5.1–8.6 (2)

(a): The total number of surveys may be greater than the total number of countries, as listed in Table 8, as some countries submitted more than one survey for a specific age range.

ABBREVIATIONS

ADI	Acceptable Daily Intake
AESGP	Association of the European Self-Medication Industry
AFC Panel	EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
ANS Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
bw	body weight
CAS	Chemical Abstract Service
CEHC	2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-hydroxychroman
CI	confidence interval
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
EC	European Commission
EINECS	European Inventory of Existing Commercial chemical Substances
ERNA	European Responsible Nutrition Alliance
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organization
FCRA	Food Chemical Risk Analysis
FCS	Food Categorisation System
FDA	US Food and Drug Administration
FDE	FoodDrinkEurope
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
GLP	Good Laboratory Practice
HPLC	high performance liquid chromatography
ICGA	International Chewing Gum Association
ICSI	intra-cytoplasmic sperm injection
INS	International Numbering System

IOM	Institute of Medicine
ISO	International Organization for Standardization
IU	international units
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	lethal dose, 50 % (i.e. the dose that causes death among 50 % of treated animals)
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of Detection
LOQ	Limit of Quantification
MB	medium-bound
MPL	Maximum Permitted Level
NDA Panel	EFSA Panel on Dietetic products, Nutrition and Allergies
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
PIVKA-II	proteins induced by vitamin K absence-factor II
QL	quinone lactone
QS	*quantum satis*
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
SNE	Specialised Nutrition Europe
TG	Test Guideline
α-TTP	α-tocopherol transport protein
ucOC	undercarboxylated osteocalcin
UL	Tolerable Upper Intake Level
UV	ultraviolet

VLDL	very-low-density lipoprotein
WHO	World Health Organization