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## EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Scientific Opinion on Dietary Reference Values for vitamin E as -tocopherol

Tetens, Inge; EFSA Journal

*Link to article, DOI:*  
[10.2903/j.efsa.2015.4149](https://doi.org/10.2903/j.efsa.2015.4149)

*Publication date:*  
2015

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
EFSA Journal (2015). EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Scientific Opinion on Dietary Reference Values for vitamin E as -tocopherol. Parma, Italy: European Food Safety Authority. (The EFSA Journal; No. 4149, Vol. 13(7)). DOI: 10.2903/j.efsa.2015.4149

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## SCIENTIFIC OPINION

### Scientific Opinion on Dietary Reference Values for vitamin E as $\alpha$ -tocopherol<sup>1</sup>

EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)<sup>2,3</sup>

European Food Safety Authority (EFSA), Parma, Italy

#### ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for vitamin E. In this Opinion, the Panel considers vitamin E as  $\alpha$ -tocopherol only. The Panel considers that Average Requirements (ARs) and Population Reference Intakes (PRIs) for vitamin E (as  $\alpha$ -tocopherol) cannot be derived for adults, infants and children, and therefore defines Adequate Intakes (AIs), based on observed intakes in healthy populations with no apparent  $\alpha$ -tocopherol deficiency in the EU. This approach considers the range of average intakes of  $\alpha$ -tocopherol and of  $\alpha$ -tocopherol equivalents estimated by EFSA from dietary surveys in children and adults in nine countries. The Panel notes the uncertainties in the available food composition and consumption data, the fact that most EU food composition databases contain values for vitamin E as  $\alpha$ -tocopherol equivalents, as well as the contribution of average  $\alpha$ -tocopherol intakes to average  $\alpha$ -tocopherol equivalent intakes in these countries. For adults, an AI for  $\alpha$ -tocopherol is set at 13 mg/day for men and 11 mg/day for women. For children aged 1 to < 3 years, an AI for  $\alpha$ -tocopherol is set at 6 mg/day for both sexes. For children aged 3 to < 10 years, an AI for  $\alpha$ -tocopherol is set at 9 mg/day for both sexes. For children aged 10 to < 18 years, an AI for  $\alpha$ -tocopherol is set at 13 mg/day for boys and 11 mg/day for girls. For infants aged 7–11 months, an AI for  $\alpha$ -tocopherol of 5 mg/day is derived by extrapolating upwards from the estimated  $\alpha$ -tocopherol intake in exclusively breast-fed infants aged 0–6 months and rounding. For pregnant or lactating women, the Panel considers that there is no evidence for an increased dietary  $\alpha$ -tocopherol requirement, and the same AI is set as for non-pregnant non-lactating women.

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#### KEY WORDS

vitamin E,  $\alpha$ -tocopherol,  $\alpha$ -tocopherol equivalent, Adequate Intake, Dietary Reference Value

<sup>1</sup> On request from the European Commission, Question No EFSA-Q-2011-01231, adopted on 11 June 2015.

<sup>2</sup> Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: [nda@efsa.europa.eu](mailto:nda@efsa.europa.eu)

<sup>3</sup> Acknowledgement: The Panel wishes to thank the members of the Working Group on Dietary Reference Values for vitamins: Christel Lamberg-Allardt, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Hildegard Przyrembel, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé and Dominique Turck for the preparatory work on this scientific opinion and EFSA staff: Sofia Ioannidou and Liisa Valsta for the support provided to this scientific opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Scientific Opinion on Dietary Reference Values for vitamin E as  $\alpha$ -tocopherol. EFSA Journal 2015;13(7):4149, 72 pp. doi:10.2903/j.efsa.2015.4149

Available online: [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal)

## SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a Scientific Opinion on Dietary Reference Values (DRVs) for the European population, including vitamin E.

Vitamin E is a fat-soluble vitamin. Previously, the term vitamin E was used as the generic term for four tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ) and four tocotrienols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ), which are organic compounds that possess antioxidant activity to a different degree. Factors have been used to convert food contents of tocopherols and tocotrienols to  $\alpha$ -tocopherol equivalents. In this Opinion, based on the available evidence and in line with other authoritative bodies, the Panel considers vitamin E as being  $\alpha$ -tocopherol only. Its naturally occurring form is RRR- $\alpha$ -tocopherol. Commercially available forms of  $\alpha$ -tocopherol include RRR- $\alpha$ -tocopherol, a synthetic form that contains in equal proportions the eight stereoisomers of  $\alpha$ -tocopherol (RRR-, RRS-, RSR-, RSS- and their enantiomers SSS-, SSR-, SRS-, SRR-) and is called all-rac- $\alpha$ -tocopherol, and their esterified forms.

Efficient  $\alpha$ -tocopherol absorption requires the presence of fat. The Panel considered that the average  $\alpha$ -tocopherol absorption from a usual diet is about 75 %. This is based on the means observed in two balance studies and in a kinetic study using a multi-compartmental model of  $\alpha$ -tocopherol metabolism. After its intestinal absorption,  $\alpha$ -tocopherol is incorporated into chylomicrons and transported to the liver. There, the  $\alpha$ -tocopherol transfer protein ( $\alpha$ -TTP), which preferentially binds  $\alpha$ -tocopherol rather than other tocopherols or tocotrienols, is responsible for its incorporation into nascent very low-density lipoproteins to be secreted by the liver into the circulation and distributed to body tissues.  $\alpha$ -Tocopherol not bound to  $\alpha$ -TTP is catabolised in the liver (to 2,5,7,8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman, i.e.  $\alpha$ -CEHC) by hepatic  $\omega$ -hydroxylase, which catabolises tocopherols and has a stronger activity towards tocopherols other than  $\alpha$ -tocopherol. Because of differences in activities of  $\alpha$ -TTP and  $\omega$ -hydroxylase towards  $\alpha$ -tocopherol and other tocopherols,  $\alpha$ -tocopherol predominantly accumulates in body tissues, whereas other tocopherols are preferentially catabolised in the liver.

Blood  $\alpha$ -tocopherol concentrations are maintained by the preferential binding of  $\alpha$ -tocopherol by  $\alpha$ -TTP. Among chemically synthesised  $\alpha$ -tocopherol forms, only 2R- $\alpha$ -tocopherol stereoisomers (i.e. RRR-, RRS-, RSR-, RSS-) were found to meet human requirements for the vitamin, because the 2S-stereoisomers (i.e. SSS-, SSR-, SRS-, SRR-) present in all-rac- $\alpha$ -tocopherol possess low affinity for  $\alpha$ -TTP and are rapidly metabolised in the liver. Currently, only RRR- $\alpha$ -tocopherol is considered to be the physiologically active vitamer.

$\alpha$ -Tocopherol is part of the antioxidant defence system and is a peroxy radical scavenger and especially protects polyunsaturated fatty acids (PUFAs) within membrane phospholipids and plasma lipoproteins. Primary  $\alpha$ -tocopherol deficiency, a result of mutations in the  $\alpha$ -TTP gene, is associated with neurological symptoms, including ataxia. Symptomatic  $\alpha$ -tocopherol deficiency in individuals without any disease and who consume diets 'low' in  $\alpha$ -tocopherol has not been reported.

The Panel considers that there is, at present, insufficient data on markers of  $\alpha$ -tocopherol intake/status/function (e.g. plasma/serum  $\alpha$ -tocopherol concentration, hydrogen peroxide-induced haemolysis, urinary  $\alpha$ -CEHC excretion, markers of oxidative damage) to derive the requirement for  $\alpha$ -tocopherol. The Panel notes the lack of convergence of the values that would be derived from the use of data on markers of  $\alpha$ -tocopherol intake/status or on  $\alpha$ -tocopherol kinetics and body pools. The Panel considers that available data on markers of  $\alpha$ -tocopherol intake/status/function, on  $\alpha$ -tocopherol kinetics and body pools, on the relationship between PUFA intake and  $\alpha$ -tocopherol intake/requirement can be used neither on their own nor in combination to derive the requirement for  $\alpha$ -tocopherol in adults. The Panel considers that data on the relationship between vitamin E (unspecified form) or  $\alpha$ -tocopherol intake and health consequences are inconsistent or limited and cannot be used to derive the requirement for  $\alpha$ -tocopherol. The Panel also considers that there are no data that can be used to derive the requirement for  $\alpha$ -tocopherol for infants or children.

The Panel considers that Average Requirements (ARs) and Population Reference Intakes (PRIs) cannot be set for  $\alpha$ -tocopherol. Therefore, the Panel proposes to set Adequate Intakes (AIs) for  $\alpha$ -tocopherol for all population groups.

For adults and children, the AIs are based on observed dietary intakes in healthy populations with no apparent  $\alpha$ -tocopherol deficiency and such intakes were estimated by EFSA using the EFSA Comprehensive European Food Consumption Database and the EFSA Food Composition Database. This intake assessment considered 13 dietary surveys in nine countries of the European Union (EU) (Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the United Kingdom). As most food composition databases in EU countries contain values for vitamin E as  $\alpha$ -tocopherol equivalents ( $\alpha$ -TEs) and only two countries (Finland and Sweden) considered in the intake assessment by EFSA have vitamin E values in their food composition databases as  $\alpha$ -tocopherol values, dietary intakes of both  $\alpha$ -tocopherol and  $\alpha$ -TE were estimated by EFSA for males and females for all included countries. The Panel noted the uncertainties in the available food composition and consumption data and dietary assessment methods, the contribution of average  $\alpha$ -tocopherol intakes to average  $\alpha$ -TE intakes in the nine EU countries considered, as well as the specific methodological uncertainties of the EFSA intake estimates for  $\alpha$ -tocopherol. The Panel considered the range of average EFSA intake estimates for  $\alpha$ -tocopherol as well as the range of average EFSA intake estimates for  $\alpha$ -TEs, and combined the approximate mid-points of both ranges of average EFSA intake estimates to set AIs for  $\alpha$ -tocopherol for children and adults, after rounding.

For adults, an AI for  $\alpha$ -tocopherol is set at 13 mg/day for men and 11 mg/day for women. For children aged 1 to < 3 years, an AI for  $\alpha$ -tocopherol is set at 6 mg/day for both sexes. For children aged 3 to < 10 years, an AI for  $\alpha$ -tocopherol is set at 9 mg/day for both sexes. For children aged 10 to < 18 years, an AI for  $\alpha$ -tocopherol is set at 13 mg/day for boys and 11 mg/day for girls.

For infants aged 7–11 months, an AI for  $\alpha$ -tocopherol of 5 mg/day is extrapolated upwards from the estimated  $\alpha$ -tocopherol intake in exclusively breast-fed infants aged 0–6 months, using allometric scaling (assuming that the requirement for this vitamin is related to metabolically active body mass) and rounding to the closest unit.

The Panel considers that the available data do not indicate an additional dietary  $\alpha$ -tocopherol requirement during pregnancy or during lactation, and that a full compensation of the transitory secretion of  $\alpha$ -tocopherol in breast milk is not justified for the derivation of DRVs for  $\alpha$ -tocopherol for lactating women. The Panel therefore considers that the AI for pregnant or lactating women is the same (11 mg/day of  $\alpha$ -tocopherol) as for non-pregnant non-lactating women.

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## BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example, such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and, if necessary, to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an Opinion on the nutrient and energy intakes for the European Community.<sup>4</sup> The report provided Reference Intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF Opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context the EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

## TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1)(a) and Article 31 of Regulation (EC) No. 178/2002,<sup>5</sup> the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically advice is requested on the following dietary components:

- Carbohydrates, including sugars;
- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;

<sup>4</sup> Scientific Committee for Food, Nutrient and energy intakes for the European Community, Reports of the Scientific Committee for Food 31<sup>st</sup> series, Office for Official Publication of the European Communities, Luxembourg, 1993.

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

- Protein;
- Dietary fibre.

Following on from the first part of the task, EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, EFSA is asked to provide guidance on the translation of nutrient based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

## ASSESSMENT

### 1. Introduction

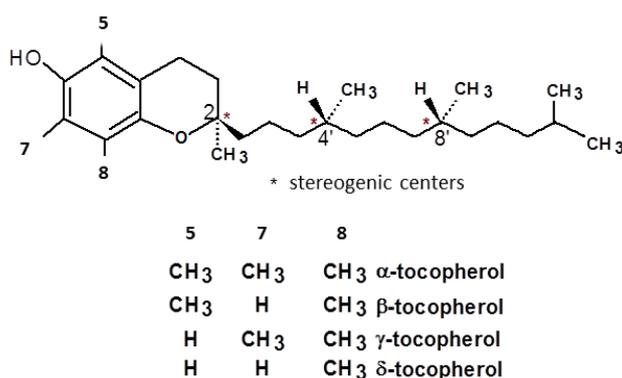
In 1993, the Scientific Committee for Food (SCF) adopted an Opinion on nutrient and energy intakes for the European Community, in which they did not set an Average Requirement (AR) or a Population Reference Intake (PRI) for vitamin E in absolute terms (SCF, 1993). Instead, the SCF considered an amount of 0.4 mg  $\alpha$ -tocopherol equivalents ( $\alpha$ -TEs) per gram of dietary polyunsaturated fatty acids (PUFAs) to fulfil the requirement of children and adults (including pregnant or lactating women), with a minimal intake of 4 mg  $\alpha$ -TE/day for men and 3 mg  $\alpha$ -TE/day for women regardless of PUFA intake.

The purpose of this Opinion is to review Dietary Reference Values (DRVs) for vitamin E. Previously, the term vitamin E was used as the generic term for four tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ) and four tocotrienols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ). In this Opinion, based on the available evidence and in line with other authoritative bodies (IOM, 2000; Nordic Council of Ministers, 2014), the Panel considers vitamin E as being  $\alpha$ -tocopherol only.

### 2. Definition/category

#### 2.1. Chemistry

$\alpha$ -Tocopherol is constituted by a trimethylated chromanol ring and a saturated phytyl side chain, and its molecular mass is 430.71 Da (Figure 1). Different methylation levels and positions on the chromanol ring define the other three members of the tocopherol family ( $\beta$ ,  $\gamma$ ,  $\delta$ ). Three double bonds present in the side chain characterise the four corresponding forms of the tocotrienol series ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ).  $\alpha$ -Tocopherol has three stereogenic centres, at position 2 on the ring and at positions 4' and 8' in the side chain; thus, there are potentially eight stereoisomers (identified by the configuration R or S of the three stereogenic centres). Commercially available forms of  $\alpha$ -tocopherol include natural RRR- $\alpha$ -tocopherol (formerly d- $\alpha$ -tocopherol), obtained by chemical methylation of by-products of soy oil production, a synthetic form that contains in equal proportions the eight stereoisomers of  $\alpha$ -tocopherol (RRR-, RRS-, RSR-, RSS- and their enantiomers SSS-, SSR-, SRS-, SRR-) and is called all-rac- $\alpha$ -tocopherol (formerly dl- $\alpha$ -tocopherol), and their esterified forms (e.g. RRR- $\alpha$ -tocopheryl acetate, all-rac- $\alpha$ -tocopheryl acetate). Bioactivity of each stereoisomer of  $\alpha$ -tocopheryl acetate has been determined using the resorption–gestation test in the rat (Weiser and Vecchi, 1982) and ranges from 21 % for the SSR isomer to 90 % for the RRS isomer, compared with RRR- $\alpha$ -tocopheryl acetate.



**Figure 1:** Structure of the four tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ )

Previously, the generic term vitamin E comprised tocopherols and tocotrienols, which are organic compounds that possess antioxidant activity to a different degree (Wang and Quinn, 1999). Currently, however, only the naturally occurring RRR- $\alpha$ -tocopherol is considered to be the physiologically active vitamers, as blood  $\alpha$ -tocopherol concentrations are maintained by the preferential binding of  $\alpha$ -tocopherol (compared to other tocopherols or tocotrienols) by the  $\alpha$ -tocopherol transfer protein

( $\alpha$ -TTP) (Hosomi et al., 1997; IOM, 2000). Among chemically synthesised  $\alpha$ -tocopherol forms, only 2R- $\alpha$ -tocopherol stereoisomers (i.e. RRR-, RRS-, RSR-, RSS-) were found to meet human vitamin E requirements (Weiser and Vecchi, 1982; IOM, 2000), because the 2S-stereoisomers (i.e. SSS-, SSR-, SRS-, SRR-) present in all-rac- $\alpha$ -tocopherol possess low affinity to  $\alpha$ -TTP and are rapidly metabolised in the liver (Acuff et al., 1994; Hosomi et al., 1997; Kiyose et al., 1997; Burton et al., 1998).

Contents of vitamin E have been presented in the literature in mg,  $\mu$ mol,  $\alpha$ -TEs or in international units (IU). The factors to convert tocopherols and tocotrienols to  $\alpha$ -TEs<sup>6</sup> are based on the bioactivity of these tocopherols and tocotrienols assessed using the resorption–gestation test in rats (IOM, 2000). The United States Pharmacopeia (USP) defined the IU for vitamin E (USP, 1979, 1980) and expressed it relative to the synthetic form, racemic all-rac- $\alpha$ -tocopheryl acetate.<sup>7</sup>

IOM (2000) considered that the difference in relative activity of all-rac- $\alpha$ -tocopherol compared with RRR- $\alpha$ -tocopherol is 50 % and defined 1 mg all-rac- $\alpha$ -tocopherol as equal to 0.5 mg RRR- $\alpha$ -tocopherol, 1 IU all-rac- $\alpha$ -tocopherol or its esters as equal to 0.45 mg 2R-stereoisomeric forms of  $\alpha$ -tocopherol and 1 IU RRR- $\alpha$ -tocopherol or its esters as equal to 0.67 mg 2R- $\alpha$ -tocopherol. The Panel agrees with this definition.

In this Opinion, the Panel considers  $\alpha$ -tocopherol, i.e. the naturally occurring form RRR- $\alpha$ -tocopherol and the other three synthetic 2R-stereoisomer forms (RSR-, RRS- and RSS-), to set DRVs for vitamin E. Contents in food and intakes are presented in this Opinion as milligrams of  $\alpha$ -tocopherol. The term ‘vitamin E’ is used in this Opinion when the papers cited do not report the form ingested (from foods or via supplementation), and, for example, the terms ‘ $\alpha$ -tocopherol as well as other tocopherols and tocotrienols’ when considerations apply to all these forms.

## 2.2. Function of $\alpha$ -tocopherol

### 2.2.1. Biochemical functions

$\alpha$ -Tocopherol is part of the antioxidant defence system, which is a complex network including endogenous and dietary antioxidants, antioxidant enzymes and repair mechanisms, with mutual interactions and synergetic effects among the various components.

$\alpha$ -Tocopherol mainly functions as a lipid-soluble non-specific chain-breaking antioxidant that prevents propagation of free-radical reactions. The vitamin is a peroxy radical scavenger and especially protects PUFAs within membrane phospholipids and plasma lipoproteins (Wang and Quinn, 1999; Traber and Atkinson, 2007; Niki, 2014). When peroxy radicals are formed, these react 1 000 times faster with  $\alpha$ -tocopherol than with PUFAs (Buettner, 1993). By protecting PUFAs within membrane phospholipids,  $\alpha$ -tocopherol preserves intracellular and cellular membrane integrity and stability, plays an important role in the stability of erythrocytes and the conductivity in central and peripheral nerves and prevents haemolytic anaemia and neurological symptoms (ataxia, peripheral neuropathy, myopathy, pigmented retinopathy) occurring in  $\alpha$ -tocopherol-deficient individuals (Muller, 1986).

The phenolic hydrogen at position 6 is the active site for scavenging radicals.  $\alpha$ -Tocopherol scavenges free radicals primarily by hydrogen atom transfer reaction to yield a non-radical product and  $\alpha$ -tocopherol radical.  $\alpha$ -Tocopherol may also scavenge radicals by a mechanism in which an electron is transferred from  $\alpha$ -tocopherol to give a vitamin cation radical, which undergoes rapid deprotonation to provide an  $\alpha$ -tocopherol radical. When  $\alpha$ -tocopherol scavenges lipid peroxy radicals, lipid hydroperoxide and  $\alpha$ -tocopherol radicals are formed (Niki et al., 1993; Yamauchi, 2007; Niki, 2014).

<sup>6</sup>  $\alpha$ -Tocopherol equivalents were defined as 1.0 mg  $\alpha$ -tocopherol, 0.5 mg  $\beta$ -tocopherol, 0.1 mg  $\gamma$ -tocopherol, 0.03 mg  $\delta$ -tocopherol, 0.3 mg  $\alpha$ -tocotrienol, 0.05 mg  $\beta$ -tocotrienol; the biological activities of  $\gamma$ - and  $\delta$ -tocotrienols were considered to be below the limit of detection (IOM, 2000; WHO/FAO, 2004).

<sup>7</sup> One IU was defined as equivalent to 1 mg of all-rac- $\alpha$ -tocopheryl acetate. One IU was provided by 0.91 mg of all-rac- $\alpha$ -tocopherol (thus, 1 mg of all-rac- $\alpha$ -tocopherol was equivalent to 1.10 IU) or 0.67 mg RRR- $\alpha$ -tocopherol (thus, 1 mg of RRR- $\alpha$ -tocopherol was equivalent to 1.49 IU) or 0.74 mg RRR- $\alpha$ -tocopheryl acetate (thus, 1 mg of RRR- $\alpha$ -tocopheryl acetate was equivalent to 1.35 IU).

The  $\alpha$ -tocopherol radical may react with another radical to give stable products, attack lipids or react with a reducing agent such as ascorbate or ubiquinol to regenerate the vitamin (Packer et al., 1979; Niki et al., 1982). The *in vivo* role of vitamin C and of selenium in sustaining the antioxidant capacity of  $\alpha$ -tocopherol is indicated by animal (Igarashi et al., 1991; Hill et al., 2001) and human (Bruno et al., 2006a) studies. The interaction of  $\alpha$ -tocopherol and vitamin C has led to the concept of ‘vitamin E recycling’, where the antioxidant function of oxidised  $\alpha$ -tocopherol is continuously restored by other antioxidants, and this antioxidant network depends on the supply of aqueous antioxidants and the metabolic activity of cells.

## 2.2.2. Health consequences of deficiency and excess

### 2.2.2.1. Deficiency

The classification of ‘vitamin E’ as an essential nutrient is based on animal studies and primary and secondary  $\alpha$ -tocopherol deficiency in humans. The need for  $\alpha$ -tocopherol in order to prevent fetal resorption in pregnant rats fed lard-containing diets is at the origin of the discovery of the vitamin (Evans and Bishop, 1922). The chemical name ‘tocopherol’ derives from its essentiality for normal reproduction in animals, even though the essentiality for this function has never been demonstrated in humans (Brigelius-Flohe et al., 2002). However, a human case report has been published on a woman with recurrent spontaneous abortions, that successfully delivered a health baby after administration of 300 mg/day of tocopherol nicotinate (Harada et al., 2005).

Primary  $\alpha$ -tocopherol deficiency, i.e. familial isolated  $\alpha$ -tocopherol deficiency, is associated with neurological symptoms, including ataxia. The primary defect is a result of mutations in the  $\alpha$ -TTP gene (Ouahchi et al., 1995). In carriers of variant alleles in the  $\alpha$ -TTP gene, serum  $\alpha$ -tocopherol concentrations even lower than 2.3  $\mu\text{mol/L}$  have been reported (Cavalier et al., 1998; IOM, 2000; Mariotti et al., 2004).

Secondary  $\alpha$ -tocopherol deficiency has been observed in patients with abetalipoproteinaemia, cholestatic liver diseases, severe malnutrition, fat malabsorption and cystic fibrosis (Farrell et al., 1977; Jeffrey et al., 1987; Eggermont, 2006; Zamel et al., 2008), in whom plasma/serum  $\alpha$ -tocopherol concentrations of about 2.5–12  $\mu\text{mol/L}$  have been reported.

Symptomatic  $\alpha$ -tocopherol deficiency in individuals without any disease and who consume diets ‘low’ in  $\alpha$ -tocopherol has not been reported (IOM, 2000).

### 2.2.2.2. Excess

In order to set a Tolerable Upper Intake Level (UL), SCF (2003) considered the impact on blood clotting as the critical adverse effect and identified a No Observed Adverse Effect Level (NOAEL) of 540 mg  $\alpha$ -TE/day from the study by Meydani et al. (1998). In this study, 88 healthy subjects over 65 years of age, who received for four months either a placebo, 40, 134 or 537 mg  $\alpha$ -TE/day (all-rac- $\alpha$ -tocopherol), were reported to develop no adverse effects, including bleeding time. SCF (2003) set a UL for adults of 270 mg  $\alpha$ -TE/day, rounded to 300 mg  $\alpha$ -TE/day using an uncertainty factor of 2. This UL also applies to pregnant and lactating women as there was no indication from animal studies of a specific risk for these population groups. The ULs for children were derived from the adult UL by allometric scaling on the basis of body weight to the power of 0.75, and ranged from 100 mg  $\alpha$ -TE/day (1–3 years) to 260 mg  $\alpha$ -TE/day (15–17 years).

## 2.3. Physiology and metabolism

### 2.3.1. Intestinal absorption

The absorption of tocopherols and tocotrienols is similar to that of other lipid compounds, takes place in the upper gastrointestinal tract and involves transporters non-specific to  $\alpha$ -tocopherol (Rigotti, 2007; Iqbal and Hussain, 2009; Reboul et al., 2011). Absorption includes emulsification, incorporation into micelles (or lipid droplets and vesicles), transport through the unstirred water layer, uptake by the

apical membrane of the enterocyte, solubilisation into intestinal lipoproteins and secretion out of the intestinal cell into the lymph or into the portal vein (Bender, 2003; Borel et al., 2013). Tocopherol esters are hydrolysed in the duodenum by pancreatic hydrolases and the bioavailability of the free and ester forms is similar (Cheeseman et al., 1995). The main fraction of absorbed tocopherols and tocotrienols is secreted in chylomicrons via the apolipoprotein B pathway, and only a small fraction via an apolipoprotein A I pathway (Reboul et al., 2009; Shichiri et al., 2010).

In eight healthy subjects consuming 150 mg  $^2\text{H}$ -labelled RRR- $\alpha$ -tocopheryl acetate with four different test meals (Jeanes et al., 2004), labelled  $\alpha$ -tocopherol uptake into chylomicrons and plasma up to nine hours after ingestion was highest after toasts with butter (17.5 g fat). It was significantly higher after ingestion of cereal with full-fat milk (17.5 g fat) than after cereal with semi-skimmed milk (2.7 g fat). It was lowest after water (no fat) intake or cereal with semi-skimmed milk (2.7 g fat) (not significantly different). Percentage absorption was not assessed as such. This study indicates that the amount of fat influenced absorption of  $\alpha$ -tocopherol.

A balance study using  $^3\text{H}$ -labelled all-rac- $\alpha$ -tocopherol (0.2 mg) in oily solution in humans reported a mean fractional absorption of  $\alpha$ -tocopherol of 75 % (range: 61–90 %) in normal adults who provided blood, urine and faecal samples for 14 days (Kelleher and Losowsky, 1968). In another balance study, mean fractional absorption of [ $^3\text{H}$ ]-all-rac- $\alpha$ -tocopherol (3–6  $\mu\text{g}$  in 1 mg unlabelled form, consumed with milk) was about 69 % (range: 55–79 %) in normal adults (blood, urine and faecal samples collected for 120 hours, three days and six days, respectively) (MacMahon and Neale, 1970).

A kinetic study involved 12 healthy adults, who ingested 0.78  $\mu\text{g}$   $^{14}\text{C}$ -labelled RRR- $\alpha$ -tocopherol mixed with milk (2 % fat) before breakfast (containing 8 g fat) and provided blood (for 70 days), urine and faecal samples (for 21 days) (Novotny et al., 2012).<sup>8</sup> A compartmental model of  $\alpha$ -tocopherol metabolism was developed to determine kinetic parameters, and mean absorption ( $\pm$  SD) of the labelled  $\alpha$ -tocopherol dose was calculated to be  $80.8 \pm 5.98$  %.<sup>9</sup>

Five healthy adults consumed apples, as a low-fat vitamin delivery system, fortified with D<sub>6</sub>-RRR- $\alpha$ -tocopheryl acetate<sup>10</sup> (22 mg per 80 g serving), in controlled breakfasts containing 0 %, 6 % or 21 % of energy from fat, then provided blood samples for 72 hours (Bruno et al., 2006b). Mean absorption of the labelled  $\alpha$ -tocopherol increased from 10 % after the 0 % fat meal to 20 % and 33 % after the 6 % and 21 % of energy from fat meals, respectively. The Panel notes that calculation of the area under the curve would have been a better method than the estimation from the plasma C<sub>max</sub> of the labelled  $\alpha$ -tocopherol multiplied by the plasma volume applied in this study, which is insufficient for an accurate estimation of  $\alpha$ -tocopherol absorption.

The Panel notes that studies on  $\alpha$ -tocopherol absorption used different models and techniques, with wide-ranging doses of labelled  $\alpha$ -tocopherol (0.78  $\mu\text{g}$  to 22 mg) embedded into different food matrices and test meals. The Panel also notes that there is a large range of reported mean  $\alpha$ -tocopherol absorption (from about 10 % to 80 %, for different fat intakes). Efficient  $\alpha$ -tocopherol absorption requires the presence of fat, but the precise quantity and quality of fat for optimising  $\alpha$ -tocopherol absorption are unknown. The Panel notes that, in a usual diet,  $\alpha$ -tocopherol is accompanied by fat and the mechanism of  $\alpha$ -tocopherol absorption is similar to that of lipid components. The Panel considers that the average  $\alpha$ -tocopherol absorption from a usual diet is about 75 %, which is based on the means observed in two balance studies (75 and 69 %) and in a kinetic study using a multi-compartmental model of  $\alpha$ -tocopherol metabolism (81 %). The Panel notes that such a value is consistent with the high efficiency of lipid absorption from the diet (EFSA NDA Panel, 2010).

<sup>8</sup> The dose of  $^{14}\text{C}$ -labelled RRR- $\alpha$ -tocopherol was reported to be 0.78 mg in Novotny et al. (2012), but 0.78  $\mu\text{g}$  in Chuang et al. (2011) (Section 2.3.3), and also expressed in both papers as 1.81 nmol. Thus, the value of 0.78  $\mu\text{g}$  is reported in this Opinion.

<sup>9</sup> Using the formula [dose – (faeces – faecal metabolic loss)]  $\times$  100/dose.

<sup>10</sup> Deuterium (i.e.  $^2\text{H}$ )-labelled  $\alpha$ -tocopherol molecules are called D<sub>0</sub>-, D<sub>3</sub>- or D<sub>6</sub>- according to the number of deuterium atoms on the ring (D<sub>0</sub>: no deuterium).

### 2.3.2. Transport in blood

After its intestinal absorption,  $\alpha$ -tocopherol is incorporated into chylomicrons, which, along the lymphatic pathway, are secreted into the systemic circulation. By the action of lipoprotein lipase (LPL), extra-hepatic tissues may take up part of the  $\alpha$ -tocopherol transported in chylomicrons, while the remnant chylomicrons transport  $\alpha$ -tocopherol to the liver. (Traber, 2007; Wu and Croft, 2007; Gee, 2011).

### 2.3.3. Distribution to tissues and estimation of body pools

In hepatocytes,  $\alpha$ -TTP binds RRR- $\alpha$ -tocopherol with the highest affinity and is responsible for the incorporation of this stereoisomer into nascent very low-density lipoproteins (VLDL), and thus for its preferential distribution to peripheral tissues (Traber and Kayden, 1989; Traber et al., 1992; Traber et al., 1994; Stocker and Azzi, 2000; Manor and Morley, 2007; Mustacich et al., 2007). Once secreted into the circulation, VLDL are converted into intermediate-density lipoproteins (IDL) and low-density lipoproteins (LDL) by the action of LPL, and the excess of VLDL surface components, including  $\alpha$ -tocopherol, is transferred to high-density lipoproteins (HDL) (Traber, 2007; Wu and Croft, 2007; Gee, 2011).

Humans discriminate between RRR- and SRR- $\alpha$ -tocopherol stereoisomers: after intake of equal amounts of D<sub>6</sub>-RRR- $\alpha$ -tocopheryl and D<sub>3</sub>-SRR- $\alpha$ -tocopheryl acetates, the chylomicrons contained similar concentrations of both forms, while VLDL, LDL and HDL were preferentially enriched in RRR- $\alpha$ -tocopheryl acetate (Traber et al., 1990). The rate of disappearance of SRR- $\alpha$ -tocopherol from plasma was similar to that of RRR- $\gamma$ -tocopherol and significantly quicker than that of RRR- $\alpha$ -tocopherol, after intake of D<sub>6</sub>-RRR- $\alpha$ -tocopheryl acetate, D<sub>3</sub>-SRR- $\alpha$ -tocopheryl acetate and D<sub>2</sub>-RRR- $\gamma$ -tocopherol (Traber et al., 1992).

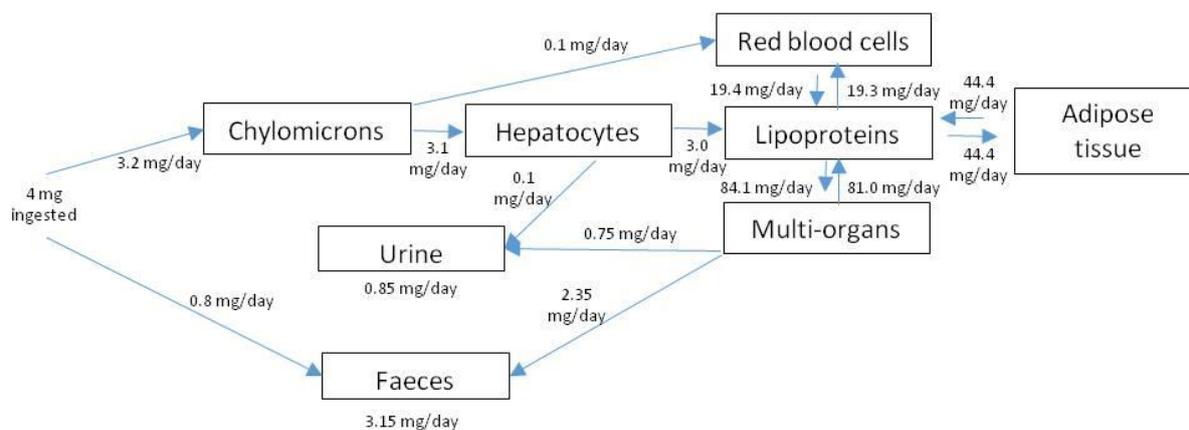
At least two mechanisms are responsible for  $\alpha$ -tocopherol delivery to tissues: the release during the hydrolysis of triglyceride-rich lipoproteins and the receptor uptake of LDL- and HDL-bound  $\alpha$ -tocopherol (Traber and Kayden, 1984; Rigotti, 2007; Parks et al., 2000). The LDL receptor pathway delivers to the cells the major part of  $\alpha$ -tocopherol (Traber and Kayden, 1984). Deficiency in the receptor, however, does not lead to a phenotype of  $\alpha$ -tocopherol deficiency: patients with homozygous familial hypercholesterolaemia do not manifest any biochemical or clinical evidence of  $\alpha$ -tocopherol deficiency (Traber and Kayden, 1984), so that other mechanisms are likely to be active (Rigotti, 2007).

A kinetic study (Chuang et al., 2011) involved 12 healthy adults, who ingested 0.78  $\mu$ g <sup>14</sup>C-labelled RRR- $\alpha$ -tocopherol mixed with milk (2 % fat) before breakfast, provided blood (for 460 days), urine and faeces (for 21 days) samples, and had a mean ( $\pm$  SD)  $\alpha$ -tocopherol intake (assessed by a food frequency questionnaire (FFQ)) of 7.6  $\pm$  2.8 mg/day. The turnover of  $\alpha$ -tocopherol was slow: the mean half-life of the dose was 44 days in plasma and 96 days in red blood cells (RBC). However, high individual differences were observed.

In another publication about the first 70 days of the same kinetic study (Novotny et al., 2012),<sup>11</sup> a multi-compartmental model of  $\alpha$ -tocopherol metabolism was developed to determine mean transfer rates among body compartments (Figure 2). The model, with 11 compartments, three delay compartments and reservoirs for urine and faeces, took into account the observed plasma  $\alpha$ -tocopherol concentrations in these 12 healthy subjects (mean (range): 23 (19–27)  $\mu$ mol/L) and the intake of RRR- $\alpha$ -tocopherol necessary to maintain these values, which was estimated by the authors to be 4 mg/day. The model shows that  $\alpha$ -tocopherol is mainly absorbed via chylomicrons (81 % of ingested dose), transferred to hepatocytes (78 % of ingested dose) and from hepatocytes to plasma lipoproteins (75 % of ingested dose). Plasma lipoproteins distribute and exchange  $\alpha$ -tocopherol with three main compartments. Among these, the highest rate of transfer of  $\alpha$ -tocopherol is between plasma

<sup>11</sup> The dose of [<sup>14</sup>C]-labelled RRR- $\alpha$ -tocopherol was reported to be 0.78 mg in Novotny et al. (2012), but 0.78  $\mu$ g in Chuang et al. (2011), and also expressed in both papers as 1.81 nmol. Thus, the value of 0.78  $\mu$ g is reported in this Opinion.

lipoproteins and a multi-organ compartment (e.g. hepatic stellate cells, brain, spleen). The exchange flow and the net flux from plasma lipoproteins to this multi-organ compartment were estimated to be about 84 and 3 mg/day, respectively. The exchange flow and the net flux from RBC to plasma lipoproteins were estimated to be about 19 and 0.1 mg/day, respectively. The exchange flow and the net flux from the adipose tissue to plasma lipoproteins were estimated to be approximately 45 and 0 mg/day, respectively. Due to the very large compartment size of the adipose tissue, this flow was achieved with a very small fractional transfer rate of  $0.4 \pm 0.1$  % of the pool per day.



**Figure 2:**  $\alpha$ -Tocopherol exchanges between body compartments. Figures denote daily fluxes between compartments. Based on data from Novotny et al. (2012)

Traber and Kayden (1987) estimated that the adipose tissue contains about 90 % of the total body  $\alpha$ -tocopherol pool, and that 99 % of  $\alpha$ -tocopherol of the adipose tissue is in the bulk lipid. The compartmental model of Novotny et al. (2012) indicates a mean total body RRR- $\alpha$ -tocopherol pool of about 11 g (about 26 mmol), of which about 99 % was associated with a slowly turning-over compartment, which was assumed to be primarily adipose tissue.

Considering the average body weight (67 kg) and the estimated percentage of body fat (25 %) of the participants, Novotny et al. (2012) calculated that the  $\alpha$ -tocopherol concentration in adipose tissue was 657  $\mu\text{g/g}$  (1.53  $\mu\text{mol/g}$ ). However, measurements of  $\alpha$ -tocopherol concentrations in adipose tissue in adults provide variable results. Indeed,  $\alpha$ -tocopherol concentrations ranged from 61 to 811  $\mu\text{g/g}$  (0.14–1.89  $\mu\text{mol/g}$ ) (Parker, 1988), and means varied from 73 to 245  $\mu\text{g/g}$  (four groups studied post mortem) (0.17–0.57  $\mu\text{mol/g}$ ) (Dju et al., 1958), and from 83 to 268  $\mu\text{g/g}$  in men (0.19–0.62  $\mu\text{mol/g}$ ) and from 123 to 355  $\mu\text{g/g}$  in women (0.29–0.82  $\mu\text{mol/g}$ ) (biopsies) (Kardinaal et al., 1995; Su et al., 1998; El-Sohemy et al., 2001).

Changes in adipose tissue  $\alpha$ -tocopherol concentrations take years (Schaefer et al., 1983; Handelman et al., 1994). In adults, Handelman et al. (1994) found that adipose tissue  $\alpha$ -tocopherol concentration increased (10 to 60 % according to subjects) with 800 mg/day all-rac- $\alpha$ -tocopherol supplementation for one year compared with before supplementation, but that it did not decrease after one year of discontinuation of the supplement. Data suggest that efflux of  $\alpha$ -tocopherol from adipocytes may be tightly regulated, since during weight loss, the triglyceride content of adipocytes and their size significantly decreased (three subjects) without any change in ‘tocopherol’ content per cell (one subject) (Schaefer et al., 1983).

$\alpha$ -Tocopherol is transported in plasma lipoproteins and distributed to tissues. The Panel notes that 90 to 99 % of the total body RRR- $\alpha$ -tocopherol pool are contained in the adipose tissue and that the net flux of  $\alpha$ -tocopherol from the adipose tissue to plasma lipoproteins is very low (close to 0 mg/day).

#### 2.3.4. Metabolism

The liver plays a key role in the metabolism of tocopherols and tocotrienols, in the  $\alpha$ -tocopherol preference relative to the other tocopherols and tocotrienols, in determining the circulating concentrations of the various tocopherols and tocotrienols and in limiting  $\alpha$ -tocopherol accumulation in tissues (Traber, 2007; Wu and Croft, 2007; Traber, 2013).

In hepatocytes,  $\alpha$ -TTP binds RRR- $\alpha$ -tocopherol with the highest affinity and is responsible for the preferential secretion of this stereoisomer into nascent VLDL, and thus for its preferential distribution to peripheral tissues (Section 2.3.3). Oxidative stress may increase  $\alpha$ -TTP gene expression (Ulatowski et al., 2012), and it may be hypothesised that hepatic  $\alpha$ -TTP may increase with decreasing  $\alpha$ -tocopherol intake.

Tocopherols and tocotrienols are metabolised in the liver by  $\omega$ -hydroxylation, followed by  $\beta$ -oxidation, conjugation and excretion. Different metabolites from tocopherols and tocotrienols have been identified (Zhao et al., 2010). In particular,  $\alpha$ -tocopherol may be catabolised to 2,5,7,8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman ( $\alpha$ -CEHC) (Schultz et al., 1995). The enzyme cytochrome P (CYP)4F2  $\omega$ -hydroxylates tocopherols (Sontag and Parker, 2002), and its activity towards  $\alpha$ -tocopherol is lower than towards other tocopherols (Sontag and Parker, 2007).  $\beta$ -oxidation reactions may occur both in peroxisomes and mitochondria, but mitochondria were the only site for  $\alpha$ -CEHC production in rat liver homogenates (Mustacich et al., 2010).

Conjugates of  $\alpha$ -CEHC in plasma and in urine have been described, such as glucuronide conjugates of CEHC, CEHC sulfate and CEHC glycoside (Pope et al., 2002; Cho et al., 2009; Johnson et al., 2012),  $\alpha$ -CEHC glycine,  $\alpha$ -CEHC glycine glucuronide and  $\alpha$ -CEHC taurine (Johnson et al., 2012).

The Panel notes that both  $\alpha$ -TTP and  $\omega$ -hydroxylase play critical roles in controlling the metabolism of  $\alpha$ -tocopherol. The Panel notes that  $\alpha$ -TTP, which preferentially binds  $\alpha$ -tocopherol rather than to other tocopherols or tocotrienols, is responsible for its incorporation into nascent VLDL to be secreted by the liver into the circulation and distributed to body tissues, and that  $\alpha$ -tocopherol bound to  $\alpha$ -TTP is therefore not catabolised in the liver by the liver  $\omega$ -hydroxylase, which catabolises tocopherols and has a stronger activity towards tocopherols other than  $\alpha$ -tocopherol. Because of differences in activities of  $\alpha$ -TTP and  $\omega$ -hydroxylase towards  $\alpha$ -tocopherol and other tocopherols,  $\alpha$ -tocopherol is predominantly accumulated in body tissues, whereas other tocopherols are preferentially metabolised in the liver.

#### 2.3.5. Elimination

A kinetic study (Bruno et al., 2005) in 10 adult non-smokers, who consumed D<sub>3</sub>-RRR- $\alpha$ -tocopheryl acetate and D<sub>6</sub>-all-rac- $\alpha$ -tocopheryl acetate (one dose of 75 mg each, for six days) and provided blood and urine samples for up to 17 days, showed that tissue  $\alpha$ -tocopherol efflux rate was 0.191 pools/day. Considering this efflux rate, as well as the baseline plasma  $\alpha$ -tocopherol concentrations and plasma volume of the participants from another study (Bruno et al., 2006b) (Section 2.3.1), the authors considered that  $5.1 \pm 0.9$  mg  $\alpha$ -tocopherol was excreted daily from the body. Based on a compartmental model of  $\alpha$ -tocopherol metabolism and the assessment of both total and radioactive RRR- $\alpha$ -tocopherol concentration in samples, daily losses of  $\alpha$ -tocopherol in faeces and urine were estimated to be 4 mg, including 0.8 mg/day of non-absorbed fraction (Novotny et al., 2012) (Figure 2) (Section 2.3.3).

Excess  $\alpha$ -tocopherol (i.e. not incorporated into nascent VLDL or entering the liver by reverse lipoprotein uptake), other tocopherols and tocotrienols are secreted in the bile. Considering a mean  $\alpha$ -tocopherol concentration in human bile of  $8.4 \pm 0.9$   $\mu$ mol/L (Leo et al., 1995), and a bile production in humans of about 750 mL/day (Boyer and Bloomer, 1974; Boyer, 2013), about 2.7 mg (6.3  $\mu$ mol) of  $\alpha$ -tocopherol is secreted in the bile per day. Oxidative metabolites of  $\alpha$ -tocopherol are also secreted in the bile (Schultz et al., 1995; Wu and Croft, 2007).

#### 2.3.5.1. Faeces

In the kinetic study in adults who ingested  $0.78 \mu\text{g }^{14}\text{C}$ -labelled-RRR- $\alpha$ -tocopherol and provided faecal samples over 21 days (Chuang et al., 2011) (Section 2.3.3),  $23.2 \pm 5.8 \%$  of the labelled dose was eliminated via the faeces. In another publication on the same study, but based on a compartmental model of  $\alpha$ -tocopherol metabolism and assessment of both total and radioactive RRR- $\alpha$ -tocopherol concentration in the samples, Novotny et al. (2012) found mean faecal losses of  $\alpha$ -tocopherol to be about 3.15 mg/day (Figure 2) (Section 2.3.3).

#### 2.3.5.2. Urine

$\alpha$ -CEHC is formed directly from  $\alpha$ -tocopherol by side-chain oxidation and is eliminated in the urine (Schultz et al., 1995). In the kinetic study in adults who provided urine samples over 21 days (Chuang et al., 2011) (Sections 2.3.3 and 2.3.5.1),  $4.26 \pm 1.38 \%$  of the radioactive dose was eliminated via urine. In the other publication on the same study based on a compartmental model of  $\alpha$ -tocopherol metabolism, Novotny et al. (2012) found mean daily total urine losses of  $\alpha$ -tocopherol to be about 0.85 mg/day (Figure 2) (Sections 2.3.3 and 2.3.5.1).

#### 2.3.5.3. Skin

$\alpha$ -Tocopherol is secreted by sebaceous glands, though dermal losses have not been quantified (Wu and Croft, 2007).

#### 2.3.5.4. Breast milk

Lactating women secrete  $\alpha$ -tocopherol via their breast milk.  $\alpha$ -Tocopherol content in human milk of about 3.5 mg/L has been noted (EFSA NDA Panel, 2013), based on Antonakou et al. (2011). A comprehensive search of the literature published after January 2000 was performed as preparatory work to the present Opinion in order to identify data on breast milk  $\alpha$ -tocopherol concentration (LASER Analytica, 2014). Considering the amount of available data, the Panel excluded studies explicitly undertaken in non-European countries and/or on a mixed population of infants born pre-term or at term. Finally, Appendix A reports on the mean  $\alpha$ -tocopherol concentration of human milk from healthy lactating mothers in 14 studies. Among them, seven studies did not explicitly indicate whether the infants were born pre-term or at term (Romeu-Nadal et al., 2008a; Romeu-Nadal et al., 2008b; Duda et al., 2009; Molto-Puigmarti et al., 2009; Molto-Puigmarti et al., 2011; Kasparova et al., 2012; Martysiak-Zurowska et al., 2013), and two studies in mothers of full-term infants were not undertaken in the European Union (EU) (Tokusoglu et al., 2008; Orhon et al., 2009). These nine studies are listed in Appendix A, for completeness.

The other five studies (Schweigert et al., 2004; Quiles et al., 2006; Romeu-Nadal et al., 2006; Sziklai-Laszlo et al., 2009; Antonakou et al., 2011) were conducted in mothers of full-term infants in the EU. In these studies, mean  $\alpha$ -tocopherol concentration in human milk, measured by high-performance liquid chromatography (HPLC), ranged from about 3 mg/L to about 25 mg/L (including all stages of lactation). The highest value (25 mg/L) was observed in colostrum samples (three days post partum) (Quiles et al., 2006). Mean maternal 'vitamin E' intake was reported in two studies (Quiles et al., 2006; Antonakou et al., 2011) and ranged from about 6 to 11 mg/day. It was explicitly indicated that the women did not receive supplements in two studies (Schweigert et al., 2004; Antonakou et al., 2011) ( $n = 85$  women in total at baseline). The remaining two studies did not mention a possible  $\alpha$ -tocopherol supplementation. Focusing more specifically on the two studies in the EU (Schweigert et al., 2004; Antonakou et al., 2011) in unsupplemented women, the mean  $\alpha$ -tocopherol concentration in mature milk ranged between 3.5 and 5.7 mg/L (mid-point of 4.6 mg/L).

Considering a mean milk transfer of 0.8 L/day during the first six months of lactation in exclusively breastfeeding women (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), and a concentration of  $\alpha$ -tocopherol in mature human milk of 4.6 mg/L, the secretion of  $\alpha$ -tocopherol into milk during lactation is estimated to be 3.7 mg/day.

### 2.3.5.5. Conclusions on elimination

The Panel notes that the main route of  $\alpha$ -tocopherol excretion is via the faeces. The Panel notes that daily losses of  $\alpha$ -tocopherol in healthy non-lactating adults are about 4–5 mg/day based on two kinetic studies (Bruno et al., 2006b; Novotny et al., 2012). The Panel also considers that secretion of  $\alpha$ -tocopherol into breast milk during the first six months of exclusive breastfeeding is about 4 mg/day.

## 2.3.6. Interaction with other nutrients

### 2.3.6.1. Interaction with PUFAs

$\alpha$ -Tocopherol is needed to prevent oxidation of PUFAs in membrane phospholipids and plasma lipoproteins.

Based on data on  $\alpha$ -tocopherol depletion and supplementation in men consuming diets with different PUFA content and the effect on the percentage of hydrogen peroxide-induced haemolysis (Horwitt et al., 1956; Horwitt, 1960) (Section 2.4.2), Harris and Embree (1963) considered that the minimum intake ratio needed to prevent  $\alpha$ -tocopherol deficiency was in the range 0.5–0.8 mg  $\alpha$ -tocopherol/g PUFAs. The authors also noted a ratio of 0.6 mg  $\alpha$ -tocopherol/g PUFAs (mainly linoleic acid) in the American diet and considered this ratio to be protective against  $\alpha$ -tocopherol deficiency.

In the 1970s, in the USA, the ratio of milligrams of  $\alpha$ -tocopherol per gram of PUFAs<sup>12</sup> in typical breakfasts, lunches and dinners ranged from 0.16 to 0.71, with a mean at 0.43 (Bieri and Evarts, 1973). In female students consuming a repetitive series of diets over about nine months in the USA, Witting and Lee (1975) observed a mean plasma total tocopherol concentration of 1.09 mg/dL<sup>13</sup> for a daily mean intake of 17.9 g of 18:2 n-6, 1.6 g of 18:3 n-3 and 7.5 mg RRR- $\alpha$ -tocopherol. The authors thus proposed a ratio of 0.4 mg  $\alpha$ -tocopherol/g PUFAs to describe the relationship between both nutrients in a diet. The Panel notes that these ratios of milligrams of  $\alpha$ -tocopherol per gram of PUFAs, which have been used in the past to set DRVs (Section 4.1), were not related to a functional outcome.

In order to define the compositional requirement for RRR- $\alpha$ -tocopherol in infant formulae, the SCF (1997) considered the results of an *in vitro* study (Holman, 1954) and an animal study (Witting and Horwitt, 1964). The *in vitro* study (Holman, 1954) found that the relative rate of oxidation of fatty acids was 0.025: 1: 2: 4: 6: 8 for the number of double bonds in fatty acids increasing from 1 to 6. The animal study in tocopherol-deficient rats showed that the relative ratio of fatty acid oxidation was slightly different: 0.3, 2, 3, 4, 5, 6 for mono-, di-, tri-, tetra-, penta- and hexaenoic fatty acids (Witting and Horwitt, 1964). Thus, SCF (1997) proposed the relative requirement of RRR- $\alpha$ -tocopherol in infant formulae according to the degree of unsaturation of PUFAs to be: 0.5 mg/g linoleic acid, 0.75 mg/ $\alpha$ -linolenic acid, 1 mg/g arachidonic acid, 1.25 mg/g eicosapentaenoic acid and 1.50 mg/g docosahexaenoic acid.

### 2.3.6.2. Interaction with vitamin C

The interactions of  $\alpha$ -tocopherol and vitamin C depend on their roles as antioxidants, and vitamin C can reduce the oxidised form of  $\alpha$ -tocopherol. Smokers had higher plasma F<sub>2</sub>-isoprostane concentrations and faster plasma  $\alpha$ -tocopherol disappearance rates than non-smokers and, when they received vitamin C supplementation (500 mg twice daily) for two weeks,  $\alpha$ -tocopherol disappearance rates were normalised (Bruno et al., 2005; Bruno et al., 2006a).

### 2.3.6.3. Interaction with selenium, niacin and vitamin K

Both selenium and niacin are required to maintain glutathione peroxidase activity. The membrane-specific isoenzyme of glutathione peroxidase catalyses the reduction of the tocopheroxyl radical back to tocopherol. Glutathione peroxidase reduces hydrogen peroxide and thereby lowers the amount of

<sup>12</sup> PUFAs considered in this publication: 18:2 and 20:4.

<sup>13</sup> This would be equivalent to about 25  $\mu$ mol  $\alpha$ -tocopherol/L.

peroxide available for the generation of radicals, whereas  $\alpha$ -tocopherol is involved in removing the products of attack by these radicals on lipids (Bender, 2003).

A competitive inhibition was described between tocopherol quinone and the phyloquinone hydroquinone for the vitamin K-dependent gamma-carboxylase. This carboxylase is required for the conversion of specific glutamyl residues to  $\gamma$ -carboxyglutamyl residues in certain proteins, including factors II, VII, IX and X, and proteins C and S involved in normal haemostatic function (Furie et al., 1999).

#### 2.3.6.4. Conclusions on interactions with other nutrients

The Panel considers that  $\alpha$ -tocopherol, as a lipid-soluble antioxidant, prevents PUFA oxidation and that PUFA intake should be associated with an adequate  $\alpha$ -tocopherol intake. However, the Panel notes that the required amount of  $\alpha$ -tocopherol may differ according to the degree of saturation of the various PUFAs, the intakes of which are variable in the EU (EFSA NDA Panel, 2010). The Panel considers that there is little evidence to support the ratios of 0.4 mg or 0.6 mg of  $\alpha$ -tocopherol per gram of dietary PUFAs, and that there were uncertainties in the intake measurements based on which both ratios were proposed.

The Panel therefore considers that data on interactions of  $\alpha$ -tocopherol with PUFAs, vitamin C, selenium, niacin and vitamin K cannot be used for deriving the requirement for  $\alpha$ -tocopherol.

## 2.4. Biomarkers

### 2.4.1. Plasma/serum $\alpha$ -tocopherol concentration

Dietary  $\alpha$ -tocopherol intake (assessed six times over 13 weeks by 24-hour dietary recall) was significantly correlated with plasma  $\alpha$ -tocopherol in 233 adults (men and women). This was observed without or with adjustment for plasma cholesterol and triglycerides, body mass index (BMI), age, sex, ethnicity and total energy intake (respectively, correlation coefficient  $r = 0.40$  and  $r = 0.43$ ,  $p = 0.001$ ) (Lebold et al., 2012). The (unadjusted) correlation was also significant in the sub-group with plasma  $\alpha$ -tocopherol concentrations  $\leq 33 \mu\text{mol/L}$ <sup>14</sup> ( $p = 0.001$ ,  $n = 200$ , non-supplement users, median  $\alpha$ -tocopherol intake 8.6 mg/day). There was no significant association in the sub-group with plasma  $\alpha$ -tocopherol concentrations  $> 33 \mu\text{mol/L}$  ( $n = 33$ , including supplement users, median  $\alpha$ -tocopherol intake: 17.8 mg/day).

Dietary  $\alpha$ -tocopherol intake adjusted for energy intake (and measured by a FFQ) correlated weakly with plasma  $\alpha$ -tocopherol concentration (adjusted for plasma triacylglycerol) in 361 men and 121 women ( $r = 0.16$ , 95 % confidence interval (CI): 0.07–0.25), after adjustments for age, sex, BMI and smoking (El-Sohemy et al., 2001). In non-supplement users ( $n = 458$ ),  $\alpha$ -tocopherol intake (mean  $\pm$  standard error of the mean (SEM)) was  $8.7 \pm 0.2$  mg/day for men and  $9.7 \pm 0.6$  mg/day for women, adjusted for energy intake.

$\alpha$ -Tocopherol intake, as assessed by a 180-item FFQ (median, P25–P75: 11.4, 7.7–15.5 mg/day, including supplements), and serum  $\alpha$ -tocopherol concentration (expressed either in  $\mu\text{mol/L}$  or  $\alpha$ -tocopherol/cholesterol) were not associated in 135 healthy men (Andersen et al., 1999). In addition, plasma  $\alpha$ -tocopherol concentration did not correlate with intake assessed by a 24-hour dietary recall in the Third National Health and Nutrition Examination Survey (IOM, 2000).

In seven healthy men receiving a controlled diet ( $\alpha$ -tocopherol content:  $2.1 \pm 1.9$  mg/day), and supplemented with 50 (week 2), 150 (week 3), 350 (week 4) and 800 (week 5) mg/day RRR- $\alpha$ -tocopherol, average plasma  $\alpha$ -tocopherol concentration increased with supplementation dose (from  $24.6 \pm 3.6$  to  $61.8 \pm 18.1 \mu\text{mol/L}$ ) (Schultz et al., 1995). The curve of plasma  $\alpha$ -tocopherol concentration showed saturation features (levelling-off) for the two highest doses.

<sup>14</sup> based on the mean and median serum  $\alpha$ -tocopherol concentrations of the US adult population.

In adults (supplement users included), mean plasma/serum  $\alpha$ -tocopherol concentrations were between 27 and 38  $\mu\text{mol/L}$ , in the UK National Diet and Nutrition Survey (Bates et al., 1999) or at baseline in the study Supplémentation en vitamines et minéraux antioxydants (SU.VI.MAX) (Preziosi et al., 1998) and the Alpha-Tocopherol Beta-Carotene Cancer (ATBC) Prevention Study (Wright et al., 2006). In children aged 9–17 years, mean/median serum  $\alpha$ -tocopherol concentration was between about 15 and 30  $\mu\text{mol/L}$  in seven European countries (Valtuna et al., 2011)

Plasma or serum  $\alpha$ -tocopherol concentrations (after 12–14 hours of fasting) are commonly used to assess  $\alpha$ -tocopherol status. Clinical symptoms, such as impaired skeletal muscle function and accumulation of ceroid pigments in smooth muscle tissue, have been reported at plasma  $\alpha$ -tocopherol concentrations below 12  $\mu\text{mol/L}$  (Stamp and Evans, 1987), and ataxia below 8  $\mu\text{mol/L}$  (IOM, 2000). Plasma/serum  $\alpha$ -tocopherol concentrations of about 2.5–12  $\mu\text{mol/L}$  have been reported in primary or secondary  $\alpha$ -tocopherol deficiency (see Section 2.2.2.1). Change in plasma/serum  $\alpha$ -tocopherol concentration has also been related to the percentage of RBC haemolysis (see Section 2.4.2).

The Panel notes that an association between dietary  $\alpha$ -tocopherol intake and plasma/serum  $\alpha$ -tocopherol concentrations has not consistently been observed, and that, when observed, this correlation was weak. The Panel thus considers that plasma/serum  $\alpha$ -tocopherol concentration is not a sensitive marker of dietary  $\alpha$ -tocopherol intake. As regards  $\alpha$ -tocopherol status, the Panel notes that there is a lack of data on the relationship between plasma/serum  $\alpha$ -tocopherol concentrations and  $\alpha$ -tocopherol concentrations in peripheral tissues. The Panel notes that data show that plasma/serum  $\alpha$ -tocopherol concentrations below about 12  $\mu\text{mol/L}$  may be indicative of  $\alpha$ -tocopherol deficiency, but that there is a lack of data to set a precise cut-off value above which  $\alpha$ -tocopherol status may be considered as adequate.

#### **2.4.2. Hydrogen peroxide-induced haemolysis and its relationship with plasma $\alpha$ -tocopherol concentration**

Red blood cells (RBC) are incapable of *de novo* lipid synthesis, and peroxidative damage resulting from oxidative stress can lead to shortening of RBC life and possibly precipitate haemolysis in  $\alpha$ -tocopherol deficiency. This has been exploited as a method of assessing  $\alpha$ -tocopherol status by measuring the degree of haemolysis induced by hydrogen peroxide (or dialuric acid) *in vitro*.

In a depletion–repletion study of over eight years (Horwitt et al., 1956; Horwitt, 1960, 1962; Horwitt et al., 1963), 38 men received either a basal diet providing about 3 mg/day of  $\alpha$ -tocopherol ('depletion',  $n = 19$ ), the basal diet supplemented with RRR- $\alpha$ -tocopheryl acetate<sup>15</sup> ( $n = 9$ ) or a hospital diet *ad libitum* ( $n = 10$ ). In the depleted group (over 70 months), plasma 'tocopherol' concentration decreased from about 23  $\mu\text{mol/L}$  to about 4.5  $\mu\text{mol/L}$  and haemolysis increased from about 0 % to remain at about 80 % after approximately 28 months, while, in the supplemented group, haemolysis remained close to 0 % for about 60 months (Horwitt, 1960). In some subjects who had been on the depleted diet for 54 months, haemolysis and plasma 'tocopherol' concentration responded to supplementation (at varying doses between 7.5 and 320 mg/day RRR- $\alpha$ -tocopheryl acetate for 138 days, one subject per dose) (Horwitt, 1960). In four subjects depleted for 72–76 months (Horwitt et al., 1963), haemolysis was 80–97 % and plasma 'tocopherol' concentration was about 1.5–5  $\mu\text{mol/L}$ . However, in one subject on the basal diet supplemented for 74 months and five subjects on the hospital diet for 74–76 months, haemolysis was 1–12 % and plasma 'tocopherol' concentration was 11.5–21.5  $\mu\text{mol/L}$  (average at about 16  $\mu\text{mol/L}$ ). The authors stated that percentages of haemolysis between 3 and 12 % should be considered as similar, as precautions regarding the age and standardisation of the peroxide solutions were not taken. The Panel notes that the increase in the percentage of RBC haemolysis up to 'high' values took several months in depleted men receiving a basal diet providing about 3 mg/day of  $\alpha$ -tocopherol. From this study, the Panel considers that the dose–response relationship between  $\alpha$ -tocopherol intake and hydrogen peroxide-induced haemolysis remains unclear.

<sup>15</sup> Supplementation with 15 mg/day of RRR- $\alpha$ -tocopherol acetate for 46 months, then 30, 105 or 140 mg/day for seven months, then supplementation was discontinued after the fifth year.

In 31 cystic fibrosis patients (males and females aged 1–42 years) with pancreatic insufficiency, not receiving  $\alpha$ -tocopherol supplements or salicylates and not iron-deficient (Farrell et al., 1977), mean ( $\pm$  standard error (SE)) RBC haemolysis ( $78 \pm 4.5$  %, range: 5–98 %) was significantly higher than that of 32 adult controls (aged 18–40 years) (mean =  $0.53 \pm 0.12$  %; range = 0–2 %,  $p < 0.001$ ). Haemolysis in patients was close to 0 % for a plasma  $\alpha$ -tocopherol concentration above about 11.5–14  $\mu\text{mol/L}$ , was approximately below 2 % for a concentration higher than about 9  $\mu\text{mol/L}$  and below 10 % for a concentration higher than about 8  $\mu\text{mol/L}$ , and increased sharply for a concentration below about 4.5  $\mu\text{mol/L}$ .

Eight children (age range: 1–17 years) with  $\alpha$ -tocopherol deficiency secondary to chronic severe liver disease were compared with five healthy controls (age range: 7–17 years) (Refat et al., 1991). Serum ‘vitamin E’ concentrations of the patients ranged from  $< 1$  to 4 mg/L (which would be equivalent to about 2.3–9.3  $\mu\text{mol/L}$   $\alpha$ -tocopherol) and RBC haemolysis induced by peroxide was 100 % for five subjects, and 96, 41 and 0 % for the three others. In the controls, serum ‘vitamin E’ concentrations were 10–13 mg/L (mean  $\pm$  standard deviation (SD):  $11 \pm 1$  mg/L) and RBC haemolysis 0–2 %, for the three subjects for whom it was determined. This study did not report  $\alpha$ -tocopherol intake of these children

The Panel considers that, while *in vitro* hydrogen peroxide-induced haemolysis is used to identify  $\alpha$ -tocopherol deficiency, it is not useful as a criterion for deriving the requirement for  $\alpha$ -tocopherol.

### 2.4.3. Urinary $\alpha$ -CEHC excretion

A cross-sectional study investigated the relationship between  $\alpha$ -tocopherol intake and urinary  $\alpha$ -CEHC excretion in 76 free-living healthy Japanese women (18–33 years) consuming their usual diet without dietary supplements (Imai et al., 2011). Intake of  $\alpha$ -tocopherol was assessed by a four-day weighed food record (mean:  $5.9 \pm 1.6$  mg/day) and  $\alpha$ -CEHC excretion was measured in a single 24-hour urine sample collected on day 4. Intake of  $\alpha$ -tocopherol was significantly related ( $r = 0.29$ ,  $p = 0.0147$ ) to urinary  $\alpha$ -CEHC excretion.

Other studies investigated the response of urinary  $\alpha$ -CEHC excretion to  $\alpha$ -tocopherol supplementation. Indeed, seven healthy men received a controlled diet providing  $2.1 \pm 1.9$  mg/day of  $\alpha$ -tocopherol (week 1), and were then supplemented with 50 (week 2), 150 (week 3), 350 (week 4) and 800 (week 5) mg/day of RRR- $\alpha$ -tocopherol (Schultz et al., 1995).  $\alpha$ -CEHC in 24-hour urine was not detectable in case of no supplementation or supplementation with 50 mg/day and increased with higher supplementation doses (150–800 mg/day). Urinary  $\alpha$ -CEHC appeared in detectable concentrations above a plasma  $\alpha$ -tocopherol concentration of 30–50  $\mu\text{mol/L}$ .

Healthy men and women (18–35 years, non-smokers and smokers,  $n = 10$  per group), with a baseline  $\alpha$ -tocopherol intake (assessed by a three-day food record) of 5.3–5.5 mg/day, received D<sub>3</sub>-RRR- $\alpha$ -tocopheryl acetate and D<sub>6</sub>-all-rac- $\alpha$ -tocopheryl acetate (one dose of 75 mg each, for six days) (Bruno et al., 2005) (Section 2.3.5).  $\alpha$ -CEHC concentrations in 24-hour urine were variable between subjects, were not different between groups before supplementation, increased 4–5.5-fold after six days of supplementation, then decreased to pre-study concentrations, or even below, after 17 days.

Ten apparently healthy Japanese men (18–25 years) who consumed the same basal diet providing 8.7 mg/day of  $\alpha$ -tocopherol for five days per week<sup>16</sup> for four weeks, also took  $\alpha$ -tocopheryl acetate supplements in the last three weeks (Imai et al., 2011). This supplementation was about 10 mg/day<sup>17</sup> in week 2, about 30 mg/day<sup>17</sup> in week 3 and about 59 mg/day<sup>17</sup> in week 4. Total  $\alpha$ -tocopherol intake was associated with mean 24-hour urinary excretion of  $\alpha$ -CEHC measured once each week ( $r = 0.99$ ,  $p = 0.0043$ ).

<sup>16</sup> Subjects were free to eat what they wished on the two remaining days.

<sup>17</sup> Intakes of  $\alpha$ -tocopheryl acetate expressed in  $\mu\text{mol/day}$  in the publication were converted to mg/day using a molecular mass of 472.74 Da.

A study in 233 adults (median age  $\pm$  SD: 33.3  $\pm$  12.5 years) (Lebold et al., 2012) (Section 2.4.1) investigated the relationship between plasma  $\alpha$ -tocopherol, urinary excretion of  $\alpha$ -tocopherol metabolites ( $\alpha$ -CEHC and  $\alpha$ -carboxymethylbutyl hydrochroman), averaged from two 24-hour urine collections) and dietary  $\alpha$ -tocopherol intake (assessed six times over 13 weeks by 24-hour dietary recall). The sub-group with plasma  $\alpha$ -tocopherol concentrations  $>$  33  $\mu$ mol/L ( $n = 33$ ) had a significantly higher urinary  $\alpha$ -CEHC concentration than the sub-group with plasma  $\alpha$ -tocopherol concentrations  $\leq$  33  $\mu$ mol/L ( $n = 200$ ). Median  $\alpha$ -tocopherol intake and urinary  $\alpha$ -CEHC concentration were 17.8 mg/day and 4.1  $\mu$ mol/g creatinine, respectively, in the sub-group with plasma  $\alpha$ -tocopherol concentrations  $>$  33  $\mu$ mol/L, and 8.6 mg/day and 1.6  $\mu$ mol/g creatinine, respectively, in the other sub-group. Urinary  $\alpha$ -CEHC excretion was significantly correlated with plasma  $\alpha$ -tocopherol (mmol/mol cholesterol) in the whole population (with or without adjustments,<sup>18</sup>  $p = 0.001$ ) and in both sub-groups (without adjustments,  $p \leq 0.01$ ). Urinary  $\alpha$ -CEHC excretion was also significantly correlated with usual  $\alpha$ -tocopherol intake in the whole population (with or without adjustments,  $r_{\text{adjusted}} = 0.39$ ,  $p = 0.001$ ), and in both sub-groups (without adjustments,  $p \leq 0.01$ ). Multiple regression with adjustment for confounders showed that urinary  $\alpha$ -CEHC excretion increased by 0.086  $\mu$ mol/g creatinine for every 1 mg increase in dietary  $\alpha$ -tocopherol. From a spline curve of median daily urinary  $\alpha$ -CEHC excretion according to dietary  $\alpha$ -tocopherol, the authors visually estimated that the median excretion remained at a plateau of about 1.39  $\mu$ mol/g creatinine until an intake of about 9 mg  $\alpha$ -tocopherol/day, then the slope of the curve increased. The Panel notes that the derivation of a cut-off for urinary  $\alpha$ -CEHC excretion and the related  $\alpha$ -tocopherol intake by visual inspection remains uncertain.

The comparison of urinary  $\alpha$ -CEHC concentration in three patients with ‘ataxia with vitamin E deficiency’ (AVED) lacking  $\alpha$ -TTP (two adults, one child, with or without supplementation with all-*rac*- $\alpha$ -tocopheryl acetate or RRR- $\alpha$ -tocopherol), and in six healthy unsupplemented controls, indicates that  $\alpha$ -CEHC excretion in urine reflects the amount of liver  $\alpha$ -tocopherol which has exceeded the capacity of binding to  $\alpha$ -TTP (Schuelke et al., 2000). Two of the controls were supplemented with 400 mg RRR or all-*rac*- $\alpha$ -tocopherol for five days. Combining all available data on urinary  $\alpha$ -CEHC in healthy supplemented or unsupplemented subjects, the curve of urinary  $\alpha$ -CEHC according to plasma  $\alpha$ -tocopherol concentration showed that urinary  $\alpha$ -CEHC was close to 0 mg/day for plasma concentrations below about 30–40  $\mu$ mol/L, above which urinary  $\alpha$ -CEHC excretion increased.

The Panel considers that urinary  $\alpha$ -CEHC excretion responds to  $\alpha$ -tocopherol supplementation and is a marker of saturation of the liver  $\alpha$ -TTP binding capacity. The Panel also considers that insufficient evidence is available, on its relationship with dietary  $\alpha$ -tocopherol intake and saturation of body tissues with  $\alpha$ -tocopherol, for urinary  $\alpha$ -CEHC excretion to be a criterion for deriving the requirement for  $\alpha$ -tocopherol.

#### 2.4.4. Adipose tissue $\alpha$ -tocopherol concentration

In 85 healthy Dutch adults (men and women, aged 50–70 years) who were not taking vitamin supplements (Kardinaal et al., 1995), ‘vitamin E’ intake, assessed by FFQ, was significantly correlated with  $\alpha$ -tocopherol concentrations in adipose tissue from biopsies of the buttock ( $r = 0.24$ , adjusted for age and sex,  $p < 0.05$ ,  $n = 74$ ).

In Costa Rican men ( $n = 361$ , mean age  $\pm$  SD: 56  $\pm$  11 years) and women ( $n = 121$ , mean age  $\pm$  SD: 60  $\pm$  10 years) (El-Sohemy et al., 2001) (Section 2.4.1), dietary  $\alpha$ -tocopherol intake adjusted for energy intake (assessed by FFQ) was significantly correlated with  $\alpha$ -tocopherol concentrations in adipose tissue from biopsies of the buttock, after adjustments for age, sex, BMI and smoking. However, correlations were low either for the whole sample ( $r = 0.15$ ,  $p < 0.01$ ) or when vitamin supplement users ( $n = 24$ ) were excluded ( $r = 0.10$ ,  $p < 0.05$ ).

A study in healthy men (aged 20–55 years) from Norway found no association between  $\alpha$ -tocopherol intake, assessed by FFQ (median, P25–P75: 11.4, 7.7–15.5 mg/day, including supplements), and the

<sup>18</sup> Adjustments for total plasma cholesterol, plasma triglycerides, BMI, age, sex, ethnicity and energy intake.

concentration of  $\alpha$ -tocopherol in adipose tissue ( $\mu\text{g/g}$  total fatty acid methyl esters,  $n = 119$  biopsies from the buttock) (Andersen et al., 1999).

Changes in adipose tissue  $\alpha$ -tocopherol concentrations take years (Schaefer et al., 1983; Handelman et al., 1994) (Section 2.3.3).

The Panel considers that adipose tissue  $\alpha$ -tocopherol concentration is not a good marker of either  $\alpha$ -tocopherol intake or  $\alpha$ -tocopherol status.

#### 2.4.5. Biomarkers of function

##### 2.4.5.1. Markers of oxidative damage

Oxidative damage to DNA, proteins and lipids can be measured *in vivo* using biomarkers validated for that purpose, e.g. plasma or preferably urinary F2-isoprostanes (EFSA NDA Panel, 2011).

Athlete runners consumed at dinner, before each trial, 75 mg each of D<sub>3</sub>-RRR and D<sub>6</sub>-all rac- $\alpha$ -tocopheryl acetates: deuterated  $\alpha$ -tocopherol disappearance rates and plasma F2-isoprostane concentrations increased during a marathon race as compared with a rest period in the same subjects one month later (Mastaloudis et al., 2001). All-rac- $\alpha$ -tocopheryl acetate supplementation was found to decrease urinary F2-isoprostanes in subjects with hypercholesterolaemia (Davi et al., 1997) and in diabetics (Davi et al., 1999). Roberts et al. (2007) found a significant linear trend between the dosage of RRR- $\alpha$ -tocopherol and the percentage reduction in plasma F2-isoprostane concentrations in subjects with polygenic hypercholesterolaemia supplemented with RRR- $\alpha$ -tocopherol (0–2 144 mg/day) for 16 weeks. In a randomised controlled trial (RCT) in 30 healthy men and women, who received for eight weeks either a placebo or  $\alpha$ -tocopherol (at five different doses ranging from 134 to 1 340 mg/day,  $n = 5$  in each group), followed by an eight-week washout period, supplementation had no effect on two urinary isoprostanes, iPF(2 $\alpha$ )-III and iPF(2 $\alpha$ )-VI, measured *in vivo* at baseline and at 4, 8 and 16 weeks (Meagher et al., 2001).

The Panel considers that these markers of oxidative damage are not specific to the antioxidative effect of  $\alpha$ -tocopherol, that information on the relationship between  $\alpha$ -tocopherol intake and these markers is missing and that these markers cannot be considered suitable biomarkers of function for  $\alpha$ -tocopherol.

##### 2.4.5.2. Other biomarkers of function

In healthy subjects, supplementation with 'vitamin E' for two weeks up to 400 IU/day (which would be equivalent to 267 mg/day of  $\alpha$ -tocopherol) resulted in a significant dose-dependent decrease in platelet adhesion (Richardson and Steiner, 1993). In normal subjects, oral supplementation with  $\alpha$ -tocopherol (267–805 mg/day) resulted in an increase in platelet  $\alpha$ -tocopherol concentration that correlated with a marked inhibition of platelet aggregation (Freedman et al., 1996).

The Panel notes that there are limited data on other functions of  $\alpha$ -tocopherol and considers that markers of these functions are not specific to effects of  $\alpha$ -tocopherol.

#### 2.5. Effects of genotypes

In a cohort of 128 volunteers, single-nucleotide polymorphisms in SCARB1, the gene coding for scavenger receptor B type 1 (SR-BI), were related to plasma  $\alpha$ -tocopherol concentration, suggesting an effect of these variants on  $\alpha$ -tocopherol distribution in the body (Borel et al., 2007). Some polymorphisms of the cluster of differentiation 36 (CD36) might modestly influence plasma  $\alpha$ -tocopherol concentrations, especially in people with low triglyceride concentrations (Lecompte et al., 2011). Variants in genes involved in lipid absorption, transport, uptake and metabolism may modulate  $\alpha$ -tocopherol absorption, transport and intracellular metabolism and may influence plasma  $\alpha$ -tocopherol concentrations (Zingg et al., 2008). The CYP4F2 variant Rs2108622 was associated with increased serum  $\alpha$ -tocopherol in subjects from the ATBC trial, suggesting that this variant has reduced  $\omega$ -hydroxylation activity (Major et al., 2012).

The Panel considers that data on the effect of genotypes on  $\alpha$ -tocopherol absorption and distribution are insufficient to be used for deriving the requirement for  $\alpha$ -tocopherol according to genotype variants.

### 3. Dietary sources and intake data

#### 3.1. Dietary sources

The main dietary sources of  $\alpha$ -tocopherol include vegetable oils, fat spreads from vegetable oils, nuts and seeds, some fatty fish, egg yolk and whole grain cereals. The proportions of the four tocopherols vary according to the food source, the more abundant being  $\alpha$ -tocopherol and  $\gamma$ -tocopherol. In particular, vegetable oils vary in their content of the different tocopherol forms: wheat germ, sunflower, olive and rapeseed oils are good sources of  $\alpha$ -tocopherol, wheat germ oil of  $\beta$ -tocopherol, soybean, corn and rapeseed oils of  $\gamma$ -tocopherol and soybean oil of  $\delta$ -tocopherol.

Currently, d- $\alpha$ -tocopherol, dl- $\alpha$ -tocopherol, d- $\alpha$ -tocopheryl acetate, dl- $\alpha$ -tocopheryl acetate and d- $\alpha$ -tocopheryl acid succinate (Section 2.1 on chemistry) may be added to foods<sup>19</sup> and food supplements,<sup>20</sup> whereas mixed tocopherols<sup>21</sup> and ‘tocotrienol tocopherol’<sup>22</sup> may be added to food supplements only.<sup>20</sup> The vitamin E (milligrams of  $\alpha$ -TE) content of infant and follow-on formulae and of processed cereal-based foods and baby foods for infants and children is regulated.<sup>23</sup>

#### 3.2. Dietary intake

Published data suggest that mean  $\alpha$ -tocopherol intakes in adults in some European countries (Finland, Sweden) (Amcoff et al., 2012; Helldán et al., 2013) are higher than those observed in the USA, where  $\gamma$ -tocopherol intakes are generally reported to be higher than in the EU (Gao et al., 2004; Maras et al., 2004; Dixon et al., 2006; Mahabir et al., 2008; Signorello et al., 2010; Yang et al., 2014a; Yang et al., 2014b).

In this context, the Panel aimed at presenting in this section observed  $\alpha$ -tocopherol intakes in Europe, estimated by EFSA using the EFSA Comprehensive European Food Consumption Database (EFSA, 2011b) and the EFSA Food Composition Database. However, most food composition databases in EU countries still contain values for ‘vitamin E’ as  $\alpha$ -tocopherol equivalents ( $\alpha$ -TEs). For only two countries, Finland and Sweden, the national database compilers indicated to EFSA that the vitamin E values in their food composition databases were  $\alpha$ -tocopherol values, contrary to the other countries considered in this intake assessment. Therefore, this section reports on both estimated dietary intakes of  $\alpha$ -tocopherol and  $\alpha$ -TEs.

This assessment includes food consumption data from 13 dietary surveys (Appendix B) from nine countries (Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK). Individual data from these nationally representative (except for the Finnish surveys in children) surveys undertaken between 2000 and 2012 were available to EFSA, and classified according to the FoodEx2 food classification system (EFSA, 2011a). Nutrient intake calculations were performed only on subjects with at least two reporting days. The EFSA Food Composition Database was compiled during a procurement project (Roe et al., 2013) involving fourteen national food database compiler

<sup>19</sup> 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.

<sup>20</sup> 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.

<sup>21</sup>  $\alpha$ -Tocopherol < 20 %,  $\beta$ -tocopherol < 10 %,  $\gamma$ -tocopherol 50–70 % and  $\delta$ -tocopherol 10–30 %.

<sup>22</sup> Typical levels of individual tocopherols and tocotrienols: 115 mg/g  $\alpha$ -tocopherol (101 mg/g minimum), 5 mg/g  $\beta$ -tocopherol (< 1 mg/g minimum), 45 mg/g  $\gamma$ -tocopherol (25 mg/g minimum), 12 mg/g  $\delta$ -tocopherol (3 mg/g minimum), 67 mg/g  $\alpha$ -tocotrienol (30 mg/g minimum), < 1 mg/g  $\beta$ -tocotrienol (< 1 mg/g minimum), 82 mg/g  $\gamma$ -tocotrienol (45 mg/g minimum), 5 mg/g  $\delta$ -tocotrienol (< 1 mg/g minimum), according to Directive 2002/46/EC.

<sup>23</sup> Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p. 1. and Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children, OJ L 339, 06.12.2006, p. 16.

organisations, who were allowed to borrow compatible data from other countries in case no original composition data were available. Food composition information of Finland, France, Germany, Italy, the Netherlands, Sweden and the UK were used to calculate  $\alpha$ -tocopherol and  $\alpha$ -TE intakes in these countries. It was assumed that the best intake estimates would be obtained when both the consumption data and the composition data are from the same country. EFSA estimates are based on consumption of foods, either fortified or not, but without taking dietary supplements into account. The data covers all age groups from infants to adults. The Panel notes the limitations in the methods used for assessing breast milk consumption in infants (table footnotes of Appendices C–F) and related uncertainties in the  $\alpha$ -tocopherol and  $\alpha$ -TE intake estimates for infants.

### 3.2.1. Dietary intake of $\alpha$ -tocopherol

For this intake assessment of  $\alpha$ -tocopherol, the average values of the food contents in the Finnish and Swedish databases were used to calculate  $\alpha$ -tocopherol intake in France, Germany, Italy, the Netherlands and the UK, using the food consumption data from these five countries.

Appendices C (males) and D (females) show the  $\alpha$ -tocopherol intake estimates for all included countries, expressed in mg/day and mg/MJ. In infants (1–11 months), the average  $\alpha$ -tocopherol intakes ranged between 2.9 and 4.9 mg/day in girls and between 3.2 and 5.4 mg/day in boys. In children aged 1 to < 3 years, they ranged between 4 and 5 mg/day in girls and between 4.5 and 5.7 mg/day in boys. In children aged 3 to < 10 years, they ranged between 5.4 and 10.3 mg/day in girls and between 5.8 and 10.9 mg/day in boys. In children aged 10 to < 18 years, they ranged between 8.2 and 13.2 mg/day in girls and between 9.1 and 14.3 mg/day in boys. In adults ( $\geq$  18 years), the average  $\alpha$ -tocopherol intakes ranged between 7.8 and 12.5 mg/day in women and between 8.2 and 16 mg/day in men.

The overall number of values (including '0' values) in the included national databases ranged between 2 183 and 2 204 for  $\alpha$ -tocopherol in Finland and Sweden.  $\alpha$ -Tocopherol values were specified to be based on analyses in < 1 %.  $\alpha$ -Tocopherol values were missing for 796 foods, for which imputation of missing composition values was undertaken by EFSA.

The Finnish  $\alpha$ -tocopherol values of the EFSA Food Composition Database originated from Finland in 29 % of the cases and were borrowed from Sweden in 6 % of the cases. Only 16 % of Swedish  $\alpha$ -tocopherol values of the EFSA Food Composition Database originated from Sweden, and 18 % were borrowed from Finland. The main source of borrowed values was Germany, i.e. 46–50 % for Finland and Sweden, which means that  $\alpha$ -tocopherol and  $\alpha$ -TE data may have been combined, in the case of Finland and Sweden, in the composition data provided to EFSA. Further evaluation of the EFSA Food Composition Database and contacts of the national database compilers for Finland and Sweden showed that only about 200 Swedish foods out of the about 2 000 foods with non-missing information for 'vitamin E' in the EFSA Food Composition database originated from Sweden and were fully compatible with the original Swedish composition database for  $\alpha$ -tocopherol. Similarly, for Finland, there were about 650 foods fully compatible and originating from the Finnish database.

The Panel notes that these methodological limitations may induce uncertainty in the  $\alpha$ -tocopherol intake estimates for the included European countries.

### 3.2.2. Dietary intake of $\alpha$ -tocopherol equivalents ( $\alpha$ -TEs)

For the  $\alpha$ -TE intake assessment, for countries not having a food composition database, i.e. Ireland and Latvia,  $\alpha$ -TE food composition data from the UK and Germany, respectively, were used. To calculate  $\alpha$ -TE intake in Finland and Sweden, the average values of the food contents in France, Germany, Italy, the Netherlands and the UK were used, with the food consumption data from Finland and Sweden.

Appendices E (males) and F (females) show the  $\alpha$ -TE intake estimates for all included countries, expressed in mg/day and mg/MJ. In infants (1–11 months), average  $\alpha$ -TE intakes ranged between 3.2 and 5.3 mg/day in girls and between 3.4 and 5.9 mg/day in boys. In children aged 1 to < 3 years,

they ranged between 4.4 and 6.8 mg/day in girls and between 4.7 and 7.3 mg/day in boys. In children aged 3 to < 10 years, they ranged between 6.5 and 11.8 mg/day in girls and between 7.1 and 12.4 mg/day in boys. In children aged 10 to < 18 years, they ranged between 8.8 and 13.8 mg/day in girls and between 9.6 and 15.9 mg/day in boys. In adults ( $\geq 18$  years), the average  $\alpha$ -TE intakes ranged between 8.9 and 13.5 mg/day in females and between 10.1 and 16.0 mg/day in males.

Vegetable fats and oils, grains and grain-based products and the sum of fruits and vegetables and derived products were among the main food groups contributing to  $\alpha$ -TE intakes in all sex and age groups (Appendices G and H), as well as to  $\alpha$ -tocopherol intakes (data not shown). Differences between sexes in the main contributors to intakes were minor.

The overall number of values (including '0' values) in the included national databases ranged between 2 322 and 2 414 for  $\alpha$ -TE. For 63–93 % of the  $\alpha$ -TE values, the analytical or estimation/calculation method (e.g. recipe calculations, scientific publications or borrowed from other composition databases) applied for the determination of the values was not specified by the data provider of the EFSA Food Composition Database.  $\alpha$ -TE values were specified to be based on analyses for 1–21 % of the values. The amount of borrowed values in the  $\alpha$ -TE datasets of the EFSA Food Composition Database varied between 12 and 92 %. Most of the borrowed  $\alpha$ -TE values, 35–56 %, originated from Germany.  $\alpha$ -TE values were missing for 796 foods, for which imputation of missing composition values was undertaken by EFSA.

$\alpha$ -TE intake estimates of this assessment were compared with published  $\alpha$ -TE intake estimates when they were available from the same survey and dataset: for the Dutch national survey (van Rossum et al., 2011), the French INCA2 survey (Afssa, 2009), the German EsKiMo study (Mensink et al., 2007), the German VELs study (Kersting and Clausen, 2003), the Irish NANS (IUNA, 2011), the Italian INRAN-SCAI survey (Sette et al., 2010) and the UK NDNS (Bates et al., 2012). No published  $\alpha$ -TE intake data were available from the DNSIYC-2011 surveys of UK children (Lennox et al., 2013). Publication was not available for the dataset of the Latvian survey of pregnant women. The EFSA estimates were found to deviate by < 10 % in the Dutch, French and German surveys (excluding infants) and were higher by > 10 % and in some age groups by > 20 % in the Italian, Irish and UK surveys and in German infants (Table 1).

**Table 1:** EFSA's average  $\alpha$ -TE intake estimates, expressed as percentages of published intakes

Country	% of published intake, range over different age classes in a specific survey
France	92–107 % (INCA2)
Germany	80–86 % (VELS infants), 106–108 % (VELS children), 90–101 % (EsKiMo)
Ireland	118–128 % (NANS)
Italy	126 % (INRAN-SCAI, infants and children aged 1–< 3 years), 113–117 % (other age classes)
Netherlands	102–105 % (Dutch National Dietary Survey)
UK	108–119 % (NDNS Rolling Programme Years 1–3)

Comparing the EFSA  $\alpha$ -tocopherol intake estimates (Section 3.2.1) with the EFSA  $\alpha$ -TE intake estimates per each age class in each country (i.e. comparing exactly both intakes in the same population sub-groups), suggests that  $\alpha$ -tocopherol intake is the major contributor to  $\alpha$ -TE intake in these EU countries. However, methodological limitations in the  $\alpha$ -tocopherol data used for this intake assessment may have induced uncertainty in the intake estimates for the included European countries (Section 3.2.1).

Additional uncertainties in the intake estimates may be caused by inaccuracies in mapping food consumption data according to the FoodEx2 classification, analytical errors or errors in the estimation of the concentration in foods in the food composition databases, the use of borrowed values from other countries in the food composition databases and the replacement of missing composition values by available values for similar foods or food groups in the intake estimation process by EFSA. These

uncertainties may, in principle, result in estimates that are too high or too low. Regarding vitamin losses from processed foods, the losses in this intake assessment were based on data available in the individual national food composition databases (Roe et al., 2013).

The Panel notes that the EFSA  $\alpha$ -tocopherol intake estimates and the EFSA  $\alpha$ -TE intake estimates per each age class in each country are close. The Panel also notes the sources of uncertainty in the  $\alpha$ -TE intake estimates for the included European countries.

## 4. Overview of Dietary Reference Values and recommendations

### 4.1. Adults

The German-speaking countries (D-A-CH, 2015) derived Adequate Intakes (AIs) of 12–15 mg  $\alpha$ -TE/day for men and 11–12 mg  $\alpha$ -TE/day for women according to age. This was based on a ‘basal requirement’ of 4 mg  $\alpha$ -TE/day for adults independently of unsaturated fat intake, to which varying amounts of  $\alpha$ -TE were added based on the guiding value for total fat and the percentage contributions of fatty acids with one to three double bonds and assuming that 0.06, 0.4 and 0.6 mg  $\alpha$ -TE are required to protect 1 g of fatty acid with one, two or three double bonds, respectively, from oxidation (Horwitt, 1974; Witting and Lee, 1975). Intake of PUFAs with more double bonds would increase the AI by about 0.5 mg  $\alpha$ -TE/day.

The Nordic countries (Nordic Council of Ministers, 2014) maintained their previous Recommended Intake (RI), underlining that RIs apply to 2R-isomers of  $\alpha$ -tocopherol only (RRR-, RSR-, RRS- and RSS). In the absence of data on deficiency due to low dietary intake in healthy people, the Nordic countries considered possible cut-off values for plasma  $\alpha$ -tocopherol concentration to assess status (12 or 16.2  $\mu$ mol/L) (Horwitt et al., 1963; Morrissey and Sheehy, 1999), mean  $\alpha$ -tocopherol intakes and plasma concentrations in Nordic populations (Pironen et al., 1984; Wallstrom et al., 2001; Ylonen et al., 2003; Tomten and Hostmark, 2009) and possible ratios of 0.6 mg  $\alpha$ -TE/g PUFAs (Valk and Hornstra, 2000) or 0.4 mg  $\alpha$ -TE/g PUFAs (SCF, 1993). Based on a ratio of 0.4 mg  $\alpha$ -TE/g PUFAs and an average PUFA intake of 5 % of energy intake, ARs and RIs were set at, respectively, 5 and 8 mg  $\alpha$ -TE/day for women, and 6 and 10 mg  $\alpha$ -TE/day for men. A lower intake level was set at 3 and 4 mg  $\alpha$ -TE/day for women and men, respectively.

The World Health Organization (WHO/FAO, 2004) considered that the data were not sufficient to set a PRI for ‘vitamin E’, mentioned median intakes in the UK (10 and 7 mg  $\alpha$ -TE/day for men and women, respectively (DH, 1991)) and the USA (10 and 8 mg  $\alpha$ -TE/day for men and women, respectively (NRC, 1989)), and proposed ‘best estimates of requirements’ of 10 and 7.5 mg  $\alpha$ -TE/day for men and women, respectively.

The French Food Safety Agency (Afssa, 2001) retained its previous reference value from 1992 of 12 mg/day ‘vitamin E (tocopherol)’ for men and women. For adults aged 75 years and over, it derived a reference value of 20–50 mg/day in relation to possible benefits with respect to age-related diseases like cancer and cardiovascular diseases.

IOM (2000) set a Recommended Dietary Allowance (RDA) for the naturally occurring form (RRR-) and the synthetic 2R-stereoisomers (RSR-, RRS- and RSS-) of  $\alpha$ -tocopherol, because the other naturally occurring tocopherols and tocotrienols ( $\beta$ -,  $\gamma$ - and  $\delta$ -tocopherols and the tocotrienols) are not converted to  $\alpha$ -tocopherol by humans and are recognised poorly by the  $\alpha$ -TTP in the liver. Data investigating the relationship of the intake of the vitamin to chronic diseases were reviewed but could not be used to set DRVs. The Estimated Average Requirement (EAR) of 12 mg  $\alpha$ -tocopherol/day was based on data on induced deficiency in men (Horwitt et al., 1956; Horwitt, 1960, 1962; Horwitt et al., 1963; Horwitt et al., 1972; Horwitt, 1974; Farrell et al., 1977). In particular, IOM used and adapted data from Horwitt et al. (1963) (instead of Farrell et al. (1977)) to consider that a plasma  $\alpha$ -tocopherol concentration of 12  $\mu$ mol/L was associated with *in vitro* hydrogen peroxide-induced haemolysis below 12 % (which was considered normal). Using data from Horwitt (1960), i.e. estimating  $\alpha$ -tocopherol intake from food and supplements and plotting the intake against plasma  $\alpha$ -tocopherol concentration of

each subject averaged on four different days of measurement,<sup>24</sup> IOM determined that plasma  $\alpha$ -tocopherol concentration was above the cut-off of 12  $\mu\text{mol/L}$  for an intake of at least 12 mg  $\alpha$ -tocopherol/day. Similar data were not available for women or for older adults. IOM concluded that there was no scientific basis for assuming different requirements for these population groups. The amount of  $\alpha$ -tocopherol required daily, based on the ratio of at least 0.4 mg  $\alpha$ -tocopherol per gram of PUFAs for adults (Bieri and Evarts, 1973; Horwitt, 1974; Witting and Lee, 1975) and mean PUFA intakes from National Health and Nutrition Examination Survey (NHANES) II (Murphy et al., 1990), was considered to be covered by the EAR of 12 mg  $\alpha$ -tocopherol/day. As no information was available on the standard deviation of the requirement, the RDA of 15 mg  $\alpha$ -tocopherol/day for adults was derived from the EAR by assuming a coefficient of variation (CV) of 10 %.

SCF (1993) considered that concentrations higher than 11.6  $\mu\text{mol/L}$  for plasma tocopherol or 2.25  $\mu\text{mol}$  serum tocopherol/mmol cholesterol (values below which the erythrocytes tend to have a reduced survival time *in vivo* (Horwitt, 1980a)) are maintained in men on low PUFA intakes for intakes of about 3 mg  $\alpha$ -TE/day (Bunnell et al., 1975). Noting the lack of evidence on 'vitamin E' deficiency due to inadequate intake, the SCF (1993) defined the requirement as 0.4 mg  $\alpha$ -TE/g PUFAs (Bieri and Evarts, 1973; Witting and Lee, 1975). SCF (1993) also considered that the intake of the vitamin should be above 4 mg  $\alpha$ -TE/day for men and 3 mg  $\alpha$ -TE/day for women, as women were considered to have lower PUFA amounts in their tissues because of their smaller body size than men.

The Netherlands Food and Nutrition Council (1992) considered that the 'vitamin E' amount to attain a plasma 'vitamin E' concentration of at least 11.6  $\mu\text{mol/L}$  would be the requirement, corresponding to about 0.4 mg  $\alpha$ -TE/g PUFAs (Horwitt et al., 1972; Horwitt, 1974; Farrell, 1980; Horwitt, 1980b), and that, at low PUFA intake, the diet should provide at least 4 mg  $\alpha$ -TE/day. The PRI was defined as the quantity to maintain plasma 'vitamin E' concentrations considered as normal by the Council, i.e. on average 24.4  $\mu\text{mol/L}$  (range: 11.6–37.1  $\mu\text{mol/L}$ ). This average concentration was maintained by an average intake of 0.67 mg  $\alpha$ -TE/g PUFAs (Horwitt et al., 1972; Horwitt, 1974; Farrell, 1980; Horwitt, 1980b).

The UK COMA (DH, 1991) could not set DRVs for 'vitamin E', but considered that intakes above 4 mg  $\alpha$ -TE/day (men) and 3 mg  $\alpha$ -TE/day (women) could be adequate, based on observed intakes in the UK (Black et al., 1986; Gregory et al., 1990). It was noted that the range of PUFA intake was wide in the UK, and that average 'vitamin E' amounts required for adults consuming the DRVs for PUFAs (calculated using a ratio of 0.4 mg  $\alpha$ -TE/g PUFAs) were below average UK intakes (Gregory et al., 1990).

An overview of DRVs for 'vitamin E' for adults is presented in Table 2.

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<sup>24</sup> Reported by IOM as days 13, 21, 30 and 138.

**Table 2:** Overview of Dietary Reference Values for ‘vitamin E’ for adults

	<b>D-A-CH (2015)</b> <sup>(a)</sup>	<b>NCM (2014)</b> <sup>(b)(c)</sup>	<b>WHO/FAO (2004)</b> <sup>(d)</sup>	<b>Afssa (2001)</b>	<b>IOM (2000)</b> <sup>(b)(c)</sup>	<b>SCF (1993)</b> <sup>(e)(f)</sup>	<b>NL (1992)</b> <sup>(c)(f)</sup>	<b>DH (1991)</b> <sup>(g)</sup>
<b>Age</b> (years)	19–< 25	≥ 18	≥ 19	20–74	≥ 19–50	≥ 18	≥ 18	> 18
<b>Men</b> (mg/day)	15	10	10	12	15	0.4	0.67	> 4
<b>Women</b> (mg/day)	12	8	7.5	12	15	0.4	0.67	> 3
<b>Age</b> (years)	25–< 51							
<b>Men</b> (mg/day)	14							
<b>Women</b> (mg/day)	12							
<b>Age</b> (years)	51–< 65							
<b>Men</b> (mg/day)	13							
<b>Women</b> (mg/day)	12							
<b>Age</b> (years)	≥ 65			≥ 75				
<b>Men</b> (mg/day)	12			20–50				
<b>Women</b> (mg/day)	11			20–50				

DRVs in  $\alpha$ -tocopherol equivalents except for IOM. NL, Netherlands Food and Nutrition Council; NCM, Nordic Council of Ministers.

(a): Adequate Intake.

(b): Applicable to RRR-, RSR-, RRS- and RSS-isomers of  $\alpha$ -tocopherol only.

(c): Population Reference Intake.

(d): Data were insufficient to set PRIs; the indicated figures represent the ‘best estimates of requirements’ (WHO/FAO, 2004).

(e): ‘vitamin E requirement’.

(f): mg  $\alpha$ -TE/g PUFA.

(g): ‘Safe’ intakes.

#### 4.2. Infants and children

For children aged 1–14 years, D-A-CH (2015) set AIs in mg  $\alpha$ -TE/day by interpolation between the AI for infants and that for adults.

The Nordic countries (Nordic Council of Ministers, 2014) based their RIs for infants and children on the ‘vitamin E’ concentration of human milk, the relationship between  $\alpha$ -TE, linoleic acid or total PUFAs (Aggett et al., 1998), a ratio of at least 0.6 mg  $\alpha$ -TE/g PUFAs and an average PUFA intake corresponding to 5 % of energy intake.

WHO/FAO (2004) set an AI of 2.7 mg  $\alpha$ -TE/day for infants, based on the average concentration of 3.2 mg  $\alpha$ -TE/mL of human milk (Kelly et al., 1990) and a breast milk consumption of 0.85 L/day. For children, only ‘best estimates of requirements’ could be proposed.

Afssa (2001) derived PRIs for children from the adult value, adjusted for energy requirement.

For infants aged 7–11 months, the IOM (2000) derived an AI of 5 mg  $\alpha$ -tocopherol/day by allometric scaling (body weight to the power of 0.75, using reference body weights from NHANES III 1988–1994, and rounding up) from the intake of younger infants calculated considering a breast milk consumption of 0.78 L/day and an average  $\alpha$ -tocopherol concentration in breast milk of 4.9 mg/L (Jansson et al., 1981; Chappell et al., 1985; Lammi-Keefe et al., 1985; Lammi-Keefe et al., 1990; Boersma et al., 1991). For children aged 1–18 years, no data were available on which to base EARs, which were thus derived from the adult EAR by allometric scaling (body weight to the power of 0.75, using reference body weights from NHANES III 1988–1994 and growth factors). The RDAs were derived from the EARs by assuming a CV of 10 %.

The SCF (1993) stated that a diet containing 0.4 mg  $\alpha$ -TE/g PUFAs (as for adults) seemed also adequate for infants aged 6–11 months and children, but that there was no information on the basal requirement for the vitamin in case of a very low PUFA intake.

For infants older than six months and children, the Netherlands Food and Nutrition Council (1992) set the same PRI of 0.67 mg  $\alpha$ -TE/g PUFAs as for adults.

The UK COMA (DH, 1991) set a ‘safe intake’ of 0.4 mg  $\alpha$ -TE/g PUFAs and explained that infant formulae should not contain less than this amount (DHSS, 1980). No DRVs were set for children.

An overview of DRVs for ‘vitamin E’ for infants and children is presented in Table 3.

**Table 3:** Overview of Dietary Reference Values for ‘vitamin E’ for infants and children

	D-A-CH (2015) <sup>(a)</sup>	NCM (2014) <sup>(b)(c)</sup>	WHO/FAO (2004)	Afssa (2001)	IOM (2000) <sup>(a)</sup>	SCF (1993) <sup>(e)(f)</sup>	NL (1992) <sup>(f)</sup>	DH (1991) <sup>(f)(g)</sup>
<b>Age</b> (months)	6–< 12	6–11	7–12	6–12	6–12	6–11	6–11	Infants
<b>All</b> (mg/day)	4	3	2.7 <sup>(a)</sup>	4	5 <sup>(a)</sup>	0.4	0.67	0.4
<b>Age</b> (years)	1–< 4	1–< 2	1–3	1–3	1–3	1–18	1–18	
<b>Boys</b> (mg/day)	6	4	5 <sup>(d)</sup>	6	6 <sup>(c)</sup>	0.4	0.67	
<b>Girls</b> (mg/day)	5	4	5 <sup>(d)</sup>	6	6 <sup>(c)</sup>	0.4	0.67	
<b>Age</b> (years)	4–< 7	2–5	4–6	4–6	4–8			
<b>All</b> (mg/day)	8	5	5 <sup>(d)</sup>	7.5	7 <sup>(c)</sup>			
<b>Age</b> (years)	7–< 10	6–9	7–9	7–9	9–13			
<b>Boys</b> (mg/day)	10	6	7 <sup>(d)</sup>	9	11 <sup>(c)</sup>			
<b>Girls</b> (mg/day)	9	6	7 <sup>(d)</sup>	9	11 <sup>(c)</sup>			
<b>Age</b> (years)	10–< 13	10–13	10–18	10–12	14–18			
<b>Boys</b> (mg/day)	13	8	10 <sup>(d)</sup>	11	15 <sup>(c)</sup>			
<b>Girls</b> (mg/day)	11	7	7.5 <sup>(d)</sup>	11	15 <sup>(c)</sup>			
<b>Age</b> (years)	13–< 15	14–17		13–19				
<b>Boys</b> (mg/day)	14	10		12				
<b>Girls</b> (mg/day)	12	8		12				
<b>Age</b> (years)	15–< 19							
<b>Boys</b> (mg/day)	15							
<b>Girls</b> (mg/day)	12							

DRVs in  $\alpha$ -tocopherol equivalents except for IOM. NL, Netherlands Food and Nutrition Council; NCM, Nordic Council of Ministers.

(a): Adequate Intake.

(b): Applicable to RRR-, RSR-, RRS- and RSS isomers of  $\alpha$ -tocopherol only.

(c): Population Reference Intake.

(d): Data were insufficient to set PRIs; the indicated figures represent the ‘best estimates of requirements’ (WHO/FAO, 2004).

(e): ‘vitamin E requirement’.

(f): mg  $\alpha$ -TE/g PUFA.

(g): ‘Safe’ intakes.

### 4.3. Pregnancy and lactation

D-A-CH (2015) set an AI of 13 mg  $\alpha$ -TE/day for pregnant women and of 17 mg  $\alpha$ -TE/day for lactating women, resulting from the increased energy requirement and concomitant higher intake of unsaturated fatty acids. For lactating women, the AI was considered to cover the additional requirement of 0.26 mg  $\alpha$ -TE/100 g of secreted milk.

The Nordic countries (Nordic Council of Ministers, 2014) set an RI of 10 mg  $\alpha$ -TE/day for the last two trimesters of pregnancy, to cover the increased intake of energy and PUFAs, and an RI of 11 mg  $\alpha$ -TE/day for lactating women, to cover secretion of the vitamin in human milk.

IOM (2000) considered the increase in blood concentrations of  $\alpha$ -tocopherol and total lipids during pregnancy (Horwitt et al., 1972), the constant placental transfer of the vitamin (Abbasi et al., 1990), and the lack of reported deficiency of the vitamin during pregnancy, and set the same EAR and RDA as for non-pregnant women. The IOM set an RDA of 19 mg  $\alpha$ -tocopherol/day for lactating women, adding to the EAR for non-lactating women the average amount of about 4 mg  $\alpha$ -tocopherol/day secreted in human milk (see Section 4.2), and using a CV of 10 %.

For pregnancy, the Netherlands Food and Nutrition Council (1992) mentioned the increased plasma concentrations of ‘vitamin E’ and lipids during pregnancy and the low placental transfer of the vitamin (Takahashi et al., 1978; Haga et al., 1982), and considered the same PRI as for other adults (0.67 mg  $\alpha$ -TE/g PUFA). For lactation, they added to this PRI an extra 2.7 mg  $\alpha$ -TE/day to compensate for ‘vitamin E’ secretion in human milk, based on a breast milk volume of 0.8 L/day (Jansson et al., 1981; Van Zoeren-Grobbe et al., 1987)).

WHO/FAO (2004) did not report specific reference values for pregnant or lactating women. WHO/FAO (2004) stated that other authorities (e.g. DH (1991)) considered that there was no evidence that the requirement for the vitamin was different in pregnant or lactating women compared with other women and that their increased energy intake would likely compensate for the increased needs for infant growth and milk synthesis. Afssa (2001) and SCF (1993) did not identify evidence for a different requirement for the vitamin in pregnant or lactating women compared with other women. DH (1991) did not set specific DRVs for pregnant or lactating women; thus, the minimal intake set for non-pregnant non-lactating women (i.e. above 3 mg  $\alpha$ -TE/day) applies.

An overview of DRVs for ‘vitamin E’ for pregnant and lactating women is presented in Table 4.

**Table 4:** Overview of Dietary Reference Values for ‘vitamin E’ for pregnant and lactating women

	<b>D-A-CH (2015)</b> <sup>(a)</sup>	<b>NCM (2014)</b> <sup>(b)(c)</sup>	<b>WHO/FAO (2004)</b> <sup>(e)</sup>	<b>Afssa (2001)</b>	<b>IOM (2000)</b> <sup>(b)(c)</sup>	<b>SCF (1993)</b> <sup>(f)(g)</sup>	<b>NL (1992)</b>	<b>DH (1991)</b> <sup>(g)(h)</sup>
<b>Pregnancy</b> (mg/day)	13	10 <sup>(d)</sup>	–	12	15	0.4	0.67 <sup>(g)</sup>	> 3
<b>Lactation</b> (mg/day)	17	11	–	12	19	0.4	+ 2.7	> 3

DRVs in  $\alpha$ -tocopherol equivalents except for IOM. NL, Netherlands Food and Nutrition Council; NCM, Nordic Council of Ministers.

(a): Adequate Intake.

(b): Applicable to RRR-, RSR-, RRS- and RSS isomers of  $\alpha$ -tocopherol only.

(c): Population Reference Intake.

(d): For the last two trimesters of pregnancy.

(e): No values.

(f): ‘vitamin E requirement’.

(g): mg  $\alpha$ -TE/g PUFA.

(h): ‘Safe’ intakes.

## 5. Criteria (endpoints) on which to base Dietary Reference Values

### 5.1. Indicators of $\alpha$ -tocopherol requirement

#### 5.1.1. Adults

##### 5.1.1.1. PUFA intake

The requirement for  $\alpha$ -tocopherol has been previously related to the amount and degree of unsaturation of dietary PUFAs (Horwitt, 1960; Harris and Embree, 1963; Witting and Horwitt, 1964) (Section 2.3.6.1).

Based on the available data (Sections 2.3.6.1 and 2.3.6.4), the Panel considers that no conclusions can be drawn on the relationship between PUFA intake and  $\alpha$ -tocopherol requirement.

##### 5.1.1.2. Markers of $\alpha$ -tocopherol intake/status/function

Based on the available data (Section 2.4) on plasma/serum  $\alpha$ -tocopherol concentration, hydrogen peroxide-induced haemolysis and its relationship with plasma  $\alpha$ -tocopherol concentration, urinary  $\alpha$ -CEHC excretion, adipose tissue  $\alpha$ -tocopherol concentration, markers of oxidative damage and other biomarkers of function, the Panel considers that there is, at present, insufficient data on biomarkers to derive  $\alpha$ -tocopherol requirement.

##### 5.1.1.3. Kinetic studies

Data on  $\alpha$ -tocopherol kinetics and body pools are limited (Sections 2.3.1 and 2.3.5). Daily losses of  $\alpha$ -tocopherol in healthy non-lactating adults were estimated to be about 4–5 mg/day based on two kinetic studies (Bruno et al., 2006b; Novotny et al., 2012). However, the Panel notes that the estimation of these daily losses of  $\alpha$ -tocopherol was based on observed plasma  $\alpha$ -tocopherol concentrations (mean of about 20–23  $\mu\text{mol/L}$ ) of the participants included in the two studies. The Panel considers that there is no indication that such plasma  $\alpha$ -tocopherol concentrations should be a target for  $\alpha$ -tocopherol sufficiency.

The Panel considers that the available data on  $\alpha$ -tocopherol kinetics and body pools cannot be used to derive  $\alpha$ -tocopherol requirement.

##### 5.1.1.4. Conclusions on indicators of $\alpha$ -tocopherol requirement for adults

The Panel considers that data on markers of  $\alpha$ -tocopherol intake/status/function, available data on  $\alpha$ -tocopherol kinetics and body pools, as well as on the relationship between PUFA intake and  $\alpha$ -tocopherol intake/requirement cannot be used to derive DRVs for  $\alpha$ -tocopherol.

The Panel also investigated whether the limitations mentioned above suggest that a combination of (some of) these biomarkers/criteria could be used to derive DRVs for  $\alpha$ -tocopherol.

IOM (2000) considered the long-term depletion–repletion study in men by Horwitt et al. (Sections 2.4.2 and 4.1) to set DRVs for  $\alpha$ -tocopherol. Based on data from Horwitt et al. (1963), it concluded that a plasma  $\alpha$ -tocopherol concentration of 12  $\mu\text{mol/L}$  was associated with *in vitro* hydrogen peroxide-induced haemolysis below 12 %, which was considered normal by the IOM. Using data from Horwitt (1960), i.e. estimating  $\alpha$ -tocopherol intake from food and supplements and plotting the intake against plasma  $\alpha$ -tocopherol concentration of each subject averaged on four different days of measurement,<sup>25</sup> plasma  $\alpha$ -tocopherol concentration was shown to be above the cut-off of 12  $\mu\text{mol/L}$  for an intake of at least 12 mg  $\alpha$ -tocopherol/day (IOM, 2000).

<sup>25</sup> Reported by the IOM as days 13, 21, 30 and 138.

From a spline curve of median daily urinary  $\alpha$ -CEHC excretion according to dietary  $\alpha$ -tocopherol, Lebold et al. (2012) visually estimated that the median excretion remained at a plateau of about 1.39  $\mu\text{mol/g}$  creatinine until an intake of about 9 mg  $\alpha$ -tocopherol/day, then the slope of the curve increased (Section 2.4.3).

Taking into account the estimation of daily losses of  $\alpha$ -tocopherol of about 4–5 mg/day in healthy adults (with mean plasma  $\alpha$ -tocopherol concentrations of about 20–23  $\mu\text{mol/L}$ ) from two kinetic studies (Bruno et al., 2006b; Novotny et al., 2012) (Sections 2.3.5 and 5.1.1.3), and an average  $\alpha$ -tocopherol absorption from a usual diet of about 75 % (Section 2.3.1), about 6 mg  $\alpha$ -tocopherol/day would need to be consumed to provide an amount of absorbed  $\alpha$ -tocopherol to compensate these total daily losses.

The Panel notes the lack of convergence of the values that would be derived from the use of data on markers of  $\alpha$ -tocopherol intake/status or on  $\alpha$ -tocopherol kinetics and body pools. Thus, the Panel concludes that a combination of these biomarkers/criteria cannot be used to derive DRVs for  $\alpha$ -tocopherol.

### 5.1.2. Infants and children

The Panel notes the lack of data in infants aged 7–11 months and children on  $\alpha$ -tocopherol requirement.

### 5.2. Pregnant or lactating women

The presence of  $\alpha$ -TTP in the placenta has been shown (Kaempf-Rotzoll et al., 2003; Muller-Schmehl et al., 2004). Based on immunohistochemical localisation of  $\alpha$ -TTP and estimated staining intensity, it was found that  $\alpha$ -TTP expression in the placenta doubled from the first trimester (six to eight weeks) to term (Rotzoll et al., 2008).

Four prospective cohort studies investigated the association between maternal ‘vitamin E’ intake from foods and supplements during pregnancy and the risk of wheeze, asthma, eczema and/or hay fever (Martindale et al., 2005; Devereux et al., 2006; Litonjua et al., 2006; Allan et al., 2015) in children at various ages over the first 10 years with, overall, inconsistent results.

In an RCT (Pressman et al., 2003), pregnant women received from week 35 of gestation onwards a daily prenatal vitamin C- and ‘vitamin E’-containing supplement (containing 120 mg vitamin C and 30 IU ‘vitamin E’, which would be equivalent to 20.1 mg/day of  $\alpha$ -tocopherol), either with or without additional 500 mg vitamin C and ‘vitamin E’ (400 IU, which would be equivalent to 268 mg/day of  $\alpha$ -tocopherol). Mean maternal plasma  $\alpha$ -tocopherol concentrations were 31.3  $\mu\text{mol/L}$  and 50.4  $\mu\text{mol/L}$  at delivery in each group, while cord plasma  $\alpha$ -tocopherol at delivery was only 6.97  $\mu\text{mol/L}$  in both groups (differences between groups not statistically significant). In addition, maternal plasma and chorioamnion  $\alpha$ -tocopherol concentrations were correlated ( $r = 0.87$ ,  $p < 0.001$ ).

An observational study followed 19 pregnant women with  $\alpha$ -tocopherol intakes (mean (range)) of 8.1 (1.4–22.7) mg/day from foods and consuming ‘vitamin E’ supplements (mean of 30 IU/day, range of 11–100 IU/day, which would be equivalent to about 20 (7.4–67) mg/day of  $\alpha$ -tocopherol) (Didenco et al., 2011). Mean ( $\pm$  SD) maternal  $\alpha$ -tocopherol concentration measured during the course of pregnancy (exact period not specified) was significantly higher than mean  $\alpha$ -tocopherol cord blood concentration ( $33.4 \pm 7.7 \mu\text{mol/L}$  vs.  $6.7 \pm 2.5 \mu\text{mol/L}$ ,  $p < 0.001$ ). This suggests that the placenta limits  $\alpha$ -tocopherol transfer to the fetus (Didenco et al., 2011). There was no significant correlation between maternal and cord blood  $\alpha$ -tocopherol concentrations, but a significant correlation was observed between maternal and cord blood  $\alpha$ -CEHC concentrations ( $r = 0.70$ , log transformed  $\alpha$ -CEHC,  $p < 0.002$ ). Mean concentration of umbilical cord blood  $\alpha$ -CEHC ( $30.2 \pm 28.9 \text{ nmol/L}$ ) was not significantly different from maternal  $\alpha$ -CEHC concentration.

In 26 mothers at delivery, mean ( $\pm$  SE) maternal plasma  $\alpha$ -tocopherol concentration was significantly higher than mean cord plasma  $\alpha$ -tocopherol concentration, expressed as  $\mu\text{mol/L}$  ( $26.1 \pm 1.1$  vs.  $5.5 \pm 0.4$   $\mu\text{mol/L}$ ,  $p = 0.0001$ ) or  $\mu\text{mol/mol}$  total lipids ( $2.6 \pm 0.1$  vs.  $1.9 \pm 0.1$   $\mu\text{mol/mol}$ ,  $p = 0.0001$ ). Maternal plasma and cord plasma  $\alpha$ -tocopherol concentrations were significantly correlated after adjustment for total lipids ( $r = 0.54$ ,  $p = 0.007$ ), but not when expressed as  $\mu\text{mol/L}$  ( $r = 0.09$ ,  $p = 0.64$ ) (Jain et al., 1996).

In another study on 66 mothers and 40 samples of umbilical cord blood of full-term newborns, mean ( $\pm$  SD)  $\alpha$ -tocopherol concentration in maternal blood measured between 10 and 20 weeks of gestation was significantly higher than cord blood  $\alpha$ -tocopherol at delivery ( $20.6 \pm 4.0$   $\mu\text{mol/L}$  vs.  $7.2 \pm 1.9$   $\mu\text{mol/L}$ ,  $p < 0.02$ ) (Kiely et al., 1999). There was no correlation between maternal and cord blood  $\alpha$ -tocopherol concentrations as well as lipid-adjusted  $\alpha$ -tocopherol concentrations (Kiely et al., 1999).

Fifteen pregnant women were supplemented with 30 mg/day of all-rac- $\alpha$ -tocopheryl acetate during pregnancy, and with different doses (15, 30, 75, 150 or 300 mg/day,  $n = 3$  per dose) of  $\text{D}_3$ -RRR- $\alpha$ -tocopheryl acetate and  $\text{D}_6$ -all-rac- $\alpha$ -tocopheryl acetate (1:1 by weight,  $n = 3$  per dose) within five to nine days before delivery (Acuff et al., 1998). Maternal plasma total (i.e. deuterated or not)  $\alpha$ -tocopherol concentrations of the five groups at delivery (mean  $\pm$  SEM) were between  $39.35 \pm 2.86$   $\mu\text{mol/L}$  and  $59.03 \pm 0.73$   $\mu\text{mol/L}$ , while corresponding mean total  $\alpha$ -tocopherol concentrations in cord blood were between  $6.71 \pm 0.49$   $\mu\text{mol/L}$  and  $9.52 \pm 0.90$   $\mu\text{mol/L}$ . Maternal plasma and cord plasma at delivery had significantly higher concentrations of  $\text{D}_3$ -RRR- $\alpha$ -tocopherol than  $\text{D}_6$ -all-rac- $\alpha$ -tocopherol ( $p < 0.05$ ), whatever the dose received. Maternal  $\text{D}_3$ -RRR- $\alpha$ -tocopherol concentrations were significantly higher with the two highest doses (150 and 300 mg/day) than with the three lowest ones, and cord plasma  $\text{D}_3$ -RRR- $\alpha$ -tocopherol concentrations were significantly higher with the two highest doses than with the lowest one (15 mg/day) ( $p < 0.05$ ).

Placental transfer was investigated by analysis of  $\alpha$ -tocopherol concentration according to gestational age, in 52 fetal blood samples (umbilical cord) and maternal blood (Abbasi et al., 1990). Mean  $\alpha$ -tocopherol concentration was  $9.2 \pm 3.3$   $\mu\text{mol/L}$  in samples from 13 fetuses with a gestational age up to 22 weeks,  $9.2 \pm 4.9$   $\mu\text{mol/L}$  in 12 fetuses at 23–27 weeks of gestation and  $8.6 \pm 4.2$   $\mu\text{mol/L}$  in 27 fetuses with a gestational age of 28–38 weeks. Maternal plasma  $\alpha$ -tocopherol concentrations were measured in six mothers at  $\leq 22$  weeks and also at 23–27 weeks of gestation, and in 20 mothers at  $\geq 28$  weeks of gestation. Maternal plasma  $\alpha$ -tocopherol concentrations correlated significantly with those in the fetus ( $r = 0.551$ ,  $p < 0.002$ ). There were no significant differences in plasma  $\alpha$ -tocopherol concentrations in samples from early, mid or late gestation in either the mother or the fetus. This study suggests that placental transfer of  $\alpha$ -tocopherol is relatively constant throughout gestation.

The Panel notes that, despite the presence of  $\alpha$ -TTP in the placenta and the existence of a correlation between maternal plasma and chorioamnion  $\alpha$ -tocopherol concentrations, the  $\alpha$ -tocopherol concentration of cord blood is much lower than that of maternal blood. In addition, maternal 'vitamin E' supplementation increases maternal but not cord plasma  $\alpha$ -tocopherol concentrations. The Panel also notes that placental transfer of  $\alpha$ -tocopherol is relatively constant throughout gestation. The Panel considers that the available data do not indicate an additional dietary  $\alpha$ -tocopherol requirement during pregnancy.

For lactating women, the secretion of  $\alpha$ -tocopherol in mature human milk during the first six months of exclusive breastfeeding was estimated by the Panel to be 3.7 mg/day (Section 2.3.5.4). However, the Panel notes the scarcity of data in lactating women on  $\alpha$ -tocopherol requirement. The Panel also notes the size of the theoretical  $\alpha$ -tocopherol store in adipose tissue (Section 2.3.3), and that the increase in the percentage of RBC haemolysis up to 'high' values took several months in depleted men receiving a basal diet providing about 3 mg/day of  $\alpha$ -tocopherol (Section 2.4.2). The Panel considers that the available data do not indicate an additional dietary  $\alpha$ -tocopherol requirement during lactation.

### 5.3. 'Vitamin E'/ $\alpha$ -tocopherol intake and health consequences

The relationship between  $\alpha$ -tocopherol/'vitamin E' intakes and chronic disease outcomes has been investigated in systematic reviews, RCTs and also in observational (prospective cohort, case-control, cross-sectional) studies, where associations between intakes and disease outcomes may be confounded by uncertainties inherent in the methodology used for the assessment of 'vitamin E'/ $\alpha$ -tocopherol intakes and by the effect of other dietary, lifestyle or undefined factors on the disease outcomes investigated. Systematic reviews, RCTs and observational studies are discussed in this section.

IOM (2000) reviewed the available evidence (*in vitro*, animal, observational, intervention studies) in relation to 'vitamin E'/ $\alpha$ -tocopherol intake and the risk of cardiovascular diseases, diabetes mellitus, cancer, cataract, and central nervous system disorders (e.g. risk of Parkinson's disease, Alzheimer's disease or tardive dyskinesia) or markers of immune function. Although useful in the generation of hypotheses about the role of 'vitamin E'/ $\alpha$ -tocopherol in chronic disease development, the results from these studies were insufficient to set reference values for the vitamin and it was noted that even positive outcomes from trials targeting high-risk groups may not necessarily lead to a change in reference values for the healthy population (IOM, 2000).

A comprehensive search of the literature published between 1990 and 2011 was performed as preparatory work to this assessment in order to identify new data on health outcomes upon which DRVs for 'vitamin E' may potentially be based (Heinonen et al., 2012). An additional literature search (in PubMed) was performed to identify new data published afterwards and until the end of 2014 on  $\alpha$ -tocopherol intake and health outcomes.

The relationship between supplementation with all-*rac*- $\alpha$ -tocopherol and markers of immune function has been investigated in RCTs by Meydani et al. (1997; 2004). Outcome measures were delayed-type hypersensitivity skin response, antibody responses to hepatitis B, tetanus and diphtheria and pneumococcal vaccines, autoantibodies to DNA and thyroglobulin before and after supplementation, incidence of respiratory tract infections, number of persons and number of days with respiratory tract infections (upper and lower) and number of new antibiotic prescriptions for respiratory tract infections. The Panel considers that the available evidence does not establish that modulation of any of these markers is in itself a health outcome, which could be considered as a suitable criterion for deriving a DRV for  $\alpha$ -tocopherol. Other studies also investigated the relationship between 'vitamin E'/ $\alpha$ -tocopherol and diabetes mellitus (cohort studies (Arnlov et al., 2009; Song et al., 2011)), osteoporosis (one case-control study (Zhang et al., 2006)) and hearing loss (one cohort study (Shargorodsky et al., 2010)). One study (Song et al., 2011) investigated the relationship between the frequency of use (i.e. number of times per week of supplement use, and not doses as such) of single or multivitamin supplements, including 'vitamin E', on diabetes mellitus risk, from which no conclusions can be drawn to set DRVs for  $\alpha$ -tocopherol. In addition, the small number of studies available for these outcomes does not allow conclusions to be drawn on a putative role of  $\alpha$ -tocopherol in the pathogenesis of these conditions.

Since the reports by SCF (1993) and IOM (2000), more data have become available on the relationship between 'vitamin E'/ $\alpha$ -tocopherol intake and the risk of cardiovascular disease-related outcomes, cancer, Parkinson's and Alzheimer's diseases and vision-related outcomes, as well as on all-cause mortality.

#### 5.3.1. Cardiovascular disease-related outcomes

The relationship between 'vitamin E' or  $\alpha$ -tocopherol through diet or supplementation (alone or in combination) and cardiovascular disease-related outcomes has been investigated in a number of systematic reviews, RCTs, prospective cohort studies and case-control studies (Heinonen et al., 2012).

In an RCT, the effect of aspirin or 300 mg/day of 'synthetic  $\alpha$ -tocopherol' supplementation compared with a placebo was investigated in the primary prevention of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (de Gaetano and Collaborative Group of the Primary

Prevention, 2001). The Panel notes the high dose of supplementation and the specific population (including diseased subjects) investigated in this study, and considers that this study cannot be used to set DRVs for  $\alpha$ -tocopherol. In RCTs,  $\alpha$ -tocopherol supplementation of at least 50 mg/day did not have an effect on intermittent claudication (Tornwall et al., 1997; Tornwall et al., 1999), abdominal aortic aneurysm (Tornwall et al., 2001), intima–media thickness (Hodis et al., 2002) and cardiovascular events (fatal and non-fatal) (Tornwall et al., 2004b).  $\alpha$ -Tocopherol supplementation (50 mg/day, background  $\alpha$ -tocopherol intake not reported) did not have any significant effect on primary stroke incidence or mortality in normotensive male smokers (50–69 years at inclusion) during an RCT (median duration: six years) or post trial (Leppala et al., 2000b; Leppala et al., 2000a; Tornwall et al., 2004a).

In a prospective cohort study in 34 492 post-menopausal women followed for 11 years and whose intake from foods and supplements was assessed by a FFQ, 215 deaths from stroke were identified (Yochum et al., 2000). Overall, after adjustments, there was no relationship between risk of death from stroke and quintiles of intake of ‘vitamin E’ from food and supplements, food only or supplements only. In another prospective cohort study in 559 men (mean age: 72 years), who were free of chronic diseases in 1985, mean  $\alpha$ -tocopherol intake ( $\pm$  SD), without dietary supplements, was  $9.1 \pm 4.6$  mg/day at baseline (Buijsse et al., 2008). After 15 years of follow-up, 197 men had died from cardiovascular disease.  $\alpha$ -Tocopherol dietary intake at baseline was not associated with 15-year cardiovascular disease mortality after adjustments, in all the models tested.

### 5.3.2. Cancer

The World Cancer Research Fund (WCRF/AICR, 2007) considered that there is limited evidence suggesting that foods containing ‘vitamin E’ protect against oesophageal cancer or prostate cancer (mostly case–control studies) and also limited evidence suggesting that  $\alpha$ -tocopherol supplements protect against prostate cancer in smokers (one RCT).

The relationship between ‘vitamin E’ or  $\alpha$ -tocopherol intake through diet or supplementation (alone or in combination) and various types of cancers has been investigated in a number of systematic reviews, RCTs, prospective cohort studies and case–control studies (Heinonen et al., 2012). The Panel notes the high dose of supplementation in some of the studies investigated.

No relationship was observed between ‘vitamin E’ or  $\alpha$ -tocopherol intake and breast cancer (Yuan et al., 1995; Freudenheim et al., 1996; Do et al., 2003; Nissen et al., 2003; Frazier et al., 2004; Nagel et al., 2010), bladder cancer (Riboli et al., 1991; Albanes et al., 1995; Jacobs et al., 2002; Brinkman et al., 2010), cervical, endometrial and ovarian cancers (Fairfield et al., 2001; Xu et al., 2007; Ghosh et al., 2008; Kim et al., 2010), renal cancer (Hu et al., 2009), pancreatic cancer (Rautalahti et al., 1999), stomach cancer (Alkhenizan and Hafez, 2007), testicular cancer (Bonner et al., 2002), skin carcinomas (Kirkpatrick et al., 1994; Fung et al., 2002) as well as lung cancer (1994; Albanes et al., 1995; Ocke et al., 1997; Alkhenizan and Hafez, 2007).

Inconsistent results were observed between studies (RCTs and observational studies) on intake of the vitamin and risk of colorectal carcinoma (Bostick et al., 1993; Ferraroni et al., 1994; Albanes et al., 1995; Slattery et al., 1998; Malila et al., 1999; Jacobs et al., 2001; Wu et al., 2002; Chiu et al., 2003; Satia-Abouta et al., 2003; Murtaugh et al., 2004; Kune and Watson, 2006; Arain and Abdul Qadeer, 2010).

Inconsistent results were also observed between studies (RCTs and observational studies) on intake of ‘vitamin E’ or  $\alpha$ -tocopherol and risk of prostate cancer (Albanes et al., 1995; Rautalahti et al., 1999; Alkhenizan and Hafez, 2007; Wright et al., 2007; Bidoli et al., 2009; Gaziano et al., 2009; Lippman et al., 2009; Klein et al., 2011; Kristal et al., 2014; Wang et al., 2014).

### 5.3.3. Other health outcomes

The relationship between 'vitamin E' or  $\alpha$ -tocopherol intake through diet or supplementation (alone or in combination) and a variety of other health outcomes (e.g. risk of Parkinson's and Alzheimer's diseases, vision-related outcomes) has been investigated in a number of systematic reviews, RCTs, prospective cohort studies and case-control studies, reviewed in Heinonen et al. (2012).

In a case-control study in Japan (Miyake et al., 2011), 'vitamin E' intake from food only was assessed by a diet history questionnaire. After adjustments, 'vitamin E' intake was significantly associated with a reduced risk of Parkinson's disease (e.g. quartile 4, > 9.8 mg/day, compared with quartile 1, < 7.2 mg/day: odds ratio (OR) (95 % CI): 0.45 (0.25–0.79), *p* for trend 0.009). A systematic review with meta-analysis of observational studies considered seven studies (five case-control, one cohort and one cross-sectional) investigating the relationship between 'vitamin E' intake and the risk of Parkinson's disease (Etminan et al., 2005). ORs or relative risks (RRs) were pooled by the authors by 'moderate' or 'high' intakes: 'moderate' was defined as intake in the second or third quartiles or second, third or fourth quintiles in each study, and 'high' was defined as intake in the last quartile or quintile. Only 'moderate' dietary intake of 'vitamin E' (value not given) was associated with a significantly reduced risk of Parkinson's disease (RR: 0.81, 95 % CI: 0.67–0.98, *p* heterogeneity = 0.68). In a systematic review with meta-analysis of seven observational studies (Li et al., 2012), there was a significant inverse association between dietary intake of 'vitamin E' from food and the risk of Alzheimer's disease (pooled RR (95 % CI): 0.76 (0.67–0.84),  $I^2 = 43.2$  %, *p* = 0.103). The Panel notes that no quantitative data can be derived from these meta-analyses in order to set DRVs for  $\alpha$ -tocopherol.

Meta-analysis of two RCTs providing more than 50 mg/day of supplemental  $\alpha$ -tocopherol did not show a significant effect of supplementation on the risk of age-related maculopathy compared with placebo ( $I^2 = 19$  %) (Evans, 2008). In a pooled analysis combining two large prospective cohort studies (one in men and the other in women,  $\geq 40$  years of age at baseline), overall, no significant association was found between 'vitamin E' intake (total or from food only, assessed by FFQs) and the risk of primary open-angle glaucoma (Kang et al., 2003).

### 5.3.4. All-cause mortality

Three meta-analyses of RCTs (Miller et al., 2005; Bjelakovic et al., 2007; Abner et al., 2011) investigated the relationship between 'vitamin E' supplementation, alone or in combination with other micronutrients, and all-cause mortality.

The Panel notes that the trials included in these meta-analyses were often performed in patients with chronic diseases, that the form of 'vitamin E' was often unknown and that the trials often used doses of the vitamin exceeding the UL.

### 5.3.5. Conclusions on $\alpha$ -tocopherol intake and health consequences

The Panel considers that the data available on  $\alpha$ -tocopherol/vitamin E intakes and health consequences are inconsistent or limited and cannot be used to derive DRVs for  $\alpha$ -tocopherol.

## 6. Data on which to base Dietary Reference Values

The Panel considers that available data on markers of  $\alpha$ -tocopherol intake/status/function, on  $\alpha$ -tocopherol kinetics and body pools, on the relationship between PUFA intake and  $\alpha$ -tocopherol intake/requirement can be used neither on their own nor in combination to derive the requirement for  $\alpha$ -tocopherol in adults. The Panel also considers that there are no data that can be used to derive the requirement for  $\alpha$ -tocopherol for infants or children, and that data on the relationship between 'vitamin E'/ $\alpha$ -tocopherol intake and health consequences are inconsistent or limited and cannot be used to derive DRVs for  $\alpha$ -tocopherol (Section 5).

The Panel chose to set an Adequate Intake (AI) for  $\alpha$ -tocopherol for all population groups based on observed intakes in healthy populations with no apparent  $\alpha$ -tocopherol deficiency, suggesting that current intake levels are adequate. Except for infants aged 7–11 months (Section 6.2), the Panel considered the range of average EFSA intake estimates for  $\alpha$ -tocopherol as well as the range of average EFSA intake estimates for  $\alpha$ -tocopherol equivalents ( $\alpha$ -TEs). As these average intakes were estimated by sex, age class and survey for nine EU countries (Sections 3.2.1 and 3.2.2, Appendix B), the Panel combined the approximate mid-points of both ranges of average EFSA intake estimates (and rounded) to set AIs for  $\alpha$ -tocopherol for children and adults. It was not considered necessary to set sex-specific AIs for infants and children aged less than 10 years. The Panel notes the uncertainties in the food composition and consumption data and dietary assessment methods used to estimate dietary intakes, and the specific methodological uncertainties of the EFSA intake estimates for  $\alpha$ -tocopherol (Section 3.2).

### 6.1. Adults

In adults ( $\geq 18$  years) in EU countries (eight surveys), average  $\alpha$ -tocopherol intakes ranged between 7.8 and 12.5 mg/day in women and between 8.2 and 16 mg/day in men, and average  $\alpha$ -TE intakes ranged between 8.9 and 13.5 mg/day in women and between 10.1 and 16.0 mg/day in men. The Panel considered the approximate mid-points of the range of mean intakes for  $\alpha$ -tocopherol and for  $\alpha$ -TEs and, after rounding, set an AI for  $\alpha$ -tocopherol at 13 mg/day for men and 11 mg/day for women.

The Panel notes that these AIs are close to or above the intakes that are suggested from available studies on markers of  $\alpha$ -tocopherol intake/status or on  $\alpha$ -tocopherol kinetics and body pools (Section 5.1.1.4).

### 6.2. Infants

Because of the methodological uncertainties of the EFSA intake estimates in infants (Appendices C–F and Section 3.2), the Panel considers it preferable to set an AI for older infants (7–11 months) based on estimated  $\alpha$ -tocopherol intakes of breast-fed younger infants and upwards extrapolation.

Assuming an average breast milk  $\alpha$ -tocopherol concentration of 4.6 mg/L in mature human milk of unsupplemented mothers of term infants (Section 2.3.5.5) and an average breast milk intake of infants aged 0–6 months of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the estimated  $\alpha$ -tocopherol intake of infants in the first half-year of life is 3.7 mg/day. Averages of the median weight-for-age of male and female infants aged three months (6.1 kg) and nine months (8.6 kg) according to the WHO Growth Standards (WHO Multicentre Growth Reference Study Group, 2006) are used for the calculation. The AI for  $\alpha$ -tocopherol for infants aged 7–11 months is derived by allometric scaling, assuming that the requirement for this vitamin is related to metabolically active body mass, using the formula below. Rounding to the nearest unit, the AI for  $\alpha$ -tocopherol for infants aged 7–11 months is 5 mg/day.

$$AI_{\text{infants 7–11 months}} = \alpha\text{-tocopherol intake}_{\text{infants 0–6 months}} \times \left( \frac{\text{weight}_{\text{infants 9 months}}}{\text{weight}_{\text{infants 3 months}}} \right)^{0.75}$$

### 6.3. Children

In children aged 1 to < 3 years in EU countries (five surveys), average  $\alpha$ -tocopherol intakes ranged between 4 and 5 mg/day in girls and between 4.5 and 5.7 mg/day in boys, and average  $\alpha$ -TE intakes ranged between 4.4 and 6.8 mg/day in girls and between 4.7 and 7.3 mg/day in boys. The Panel considered the approximate mid-points of the range of mean intakes for  $\alpha$ -tocopherol and for  $\alpha$ -TEs and, after rounding, set an AI for  $\alpha$ -tocopherol at 6 mg/day for both sexes for children aged 1 to < 3 years.

In children aged 3 to < 10 years in EU countries (seven surveys), average  $\alpha$ -tocopherol intakes ranged between 5.4 and 10.3 mg/day in girls and between 5.8 and 10.9 mg/day in boys, and average  $\alpha$ -TE intakes ranged between 6.5 and 11.8 mg/day in girls and between 7.1 and 12.4 mg/day in boys. The Panel considered the approximate mid-points of the range of mean intakes for  $\alpha$ -tocopherol and for

$\alpha$ -TEs and, after rounding, set an AI for  $\alpha$ -tocopherol at 9 mg/day for both sexes for children aged 3 to < 10 years.

In children aged 10 to < 18 years in EU countries (seven surveys), average  $\alpha$ -tocopherol intakes ranged between 8.2 and 13.2 mg/day in girls and between 9.1 and 14.3 mg/day in boys, and average  $\alpha$ -TE intakes ranged between 8.8 and 13.8 mg/day in girls and between 9.6 and 15.9 mg/day in boys. The Panel considered the approximate mid-points of the range of mean intakes for  $\alpha$ -tocopherol and for  $\alpha$ -TEs and, after rounding, set an AI for  $\alpha$ -tocopherol at 11 mg/day for girls and 13 mg/day for boys aged 10 to < 18 years.

#### 6.4. Pregnancy

The Panel considers that there is no evidence for an increased dietary  $\alpha$ -tocopherol requirement in pregnancy (Section 5.2), and the same AI for  $\alpha$ -tocopherol is set as for non-pregnant women, i.e. 11 mg/day. The Panel also notes that the mean  $\alpha$ -tocopherol and  $\alpha$ -TE intakes from the EFSA intake assessment for the Latvian survey on pregnant adult women are, respectively, 12.4 and 12.5 mg/day (Appendices D and F).

#### 6.5. Lactation

The secretion of  $\alpha$ -tocopherol in milk during the first six months of lactation in exclusively breastfeeding women is about 3.7 mg/day (Sections 2.3.5.4 and 6.2). Considering an average  $\alpha$ -tocopherol absorption from a usual diet of about 75 % (Section 2.3.1), an additional intake of 4.9 mg  $\alpha$ -tocopherol/day would be assumed with the aim of fully compensating the amount of  $\alpha$ -tocopherol secreted in human milk. However, the Panel notes that the proposed AI for (non-lactating) women, derived from observed intakes in the EU, is close to or above the intakes suggested from available studies on markers of  $\alpha$ -tocopherol intake/status or on  $\alpha$ -tocopherol kinetics and body pools (Sections 5.1.1.4 and 6.1). The Panel also notes the size of the theoretical  $\alpha$ -tocopherol store in adipose tissue, and that the increase in the percentage of RBC haemolysis up to 'high' values took several months in depleted men receiving a basal diet providing about 3 mg/day of  $\alpha$ -tocopherol (Section 5.2).

The Panel considers that a full compensation of the transitory loss of  $\alpha$ -tocopherol in breast milk is not justified for the derivation of DRVs for  $\alpha$ -tocopherol for lactating women. The Panel therefore proposes that the AI for  $\alpha$ -tocopherol for lactating women is the same as for non-lactating women, i.e. 11 mg/day.

### CONCLUSIONS

The Panel concludes that ARs and PRIs for  $\alpha$ -tocopherol cannot be derived for adults, infants and children, and proposes AIs based on observed intakes. For children and adults, this approach considers the range of average intakes of  $\alpha$ -tocopherol and  $\alpha$ -tocopherol-equivalents estimated from dietary surveys in nine EU countries. For infants aged 7–11 months, the Panel proposes AIs based on estimated intakes in fully breast-fed infants and upwards extrapolation by allometric scaling. The AI set for pregnant or lactating women is the same as for non-pregnant non-lactating women.

**Table 5:** Summary of Dietary Reference Values for  $\alpha$ -tocopherol

Age	AI (mg/day)
7–11 months	5
1–< 3 years	6
3–< 10 years	9
≥ 10 years, males	13
≥ 10 years, females <sup>(a)</sup>	11

(a): Including pregnant and lactating women

## RECOMMENDATIONS FOR RESEARCH

The Panel suggests the development of food composition databases on  $\alpha$ -tocopherol. The Panel also suggests undertaking studies on the suitability of various biomarkers of status as indicators of the requirement, and on the  $\alpha$ -tocopherol requirement of all population groups, especially infants, children and pregnant women.

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## APPENDICES

### Appendix A. Concentrations of $\alpha$ -tocopherol in breast milk of healthy mothers

Reference	n (number of samples)	Country	Maternal dietary intake (mg/day) Mean $\pm$ SD	Stage of lactation	$\alpha$ -Tocopherol concentration in breast milk (mg/L)			Analytical method	Comments
					Mean $\pm$ SD	Median	Range		
Antonakou et al. (2011)	64 (64)	Greece	7.2 $\pm$ 3.7 ('vitamin E')	1 month post partum	<u><math>\alpha</math>-Tocopherol</u> 3.6 $\pm$ 1.5		1.3–9.5	HPLC (with UV and fluorescent detectors)	Three-day food record (1, 3 and 6 months post partum). Full-term infants. Mothers not supplemented with 'vitamin E' during pregnancy or post partum
	39 (39)		6.8 $\pm$ 3.5 ('vitamin E')	3 months post partum	<u><math>\alpha</math>-Tocopherol</u> 3.5 $\pm$ 1.8		1.1–8.2		
	23 (23)		10.9 $\pm$ 5.2 ('vitamin E')	6 months post partum	<u><math>\alpha</math>-Tocopherol</u> 3.7 $\pm$ 2.0		1.0–9.2		
Duda et al. (2009)	30	Poland	7.7 $\pm$ 3.4 ('vitamin E')	Mature milk ( $\approx$ 96 % of the women investigated were breast feeding for 2.5 months (average), during a period ranging from 1 to 12 months)	<u><math>\alpha</math>-Tocopherol</u> 4.11 $\pm$ 3.48	3.48	1.52–9.47	HPLC (fluorescent detection)	24-hour recalls (three consecutive days). No information on whether infants were born at term or not, and on possible maternal supplementation with 'vitamin E'. Exact stage of lactation not reported
Kasparova et al. (2012)	12 (12)	Czech Republic	Not reported	1–2 months post partum	<u><math>\alpha</math>-Tocopherol</u> 3.96 $\pm$ 1.42			HPLC (diode array detector)	27 breastfeeding women were selected for the study. No information about the health of mothers, on whether infants were born at term or not, or on possible maternal supplementation with 'vitamin E'
				3–4 months post partum	<u><math>\alpha</math>-Tocopherol</u> 3.75 $\pm$ 1.68				
				5–6 months post partum	<u><math>\alpha</math>-Tocopherol</u> 3.62 $\pm$ 1.51				
				9–12 months post partum	<u><math>\alpha</math>-Tocopherol</u> 4.01 $\pm$ 1.34				

Reference	n (number of samples)	Country	Maternal dietary intake (mg/day) Mean $\pm$ SD	Stage of lactation	$\alpha$ -Tocopherol concentration in breast milk (mg/L)			Analytical method	Comments
					Mean $\pm$ SD	Median	Range		
Martysiak-Zurowska et al. (2013)	48 (93)	Poland	14.9 $\pm$ 8.3 ( $\alpha$ -TE)					NP-HPLC (UV detector)	Three-day diary. A woman could provide more than one milk sample at different stages of lactation. No information on whether infants were born at term or not
	(17)		Not reported	2 days post partum	<u><math>\alpha</math>-Tocopherol</u> 9.99 $\pm$ 1.51		7.18–12.13		
	(30)		<u>Food</u> 8.20 $\pm$ 3.40 ( $\alpha$ -TE) <u>Supplementation</u> 7.32 $\pm$ 8.34 ( $\alpha$ -TE) (51.7 % women under vitamin supplementation at this stage of lactation)	14 days post partum	<u><math>\alpha</math>-Tocopherol</u> 4.45 $\pm$ 0.95		2.23–6.47		
	(27)		<u>Food</u> 8.41 $\pm$ 3.38 ( $\alpha$ -TE) <u>Supplementation</u> 6.69 $\pm$ 7.19 ( $\alpha$ -TE) (51.9 % women under vitamin supplementation at this stage of lactation)	30 days post partum	<u><math>\alpha</math>-Tocopherol</u> 2.92 $\pm$ 0.84		1.71–4.28		
(19)		<u>Food</u> 9.33 $\pm$ 3.80 ( $\alpha$ -TE) <u>Supplementation</u> 7.62 $\pm$ 3.02 ( $\alpha$ -TE) (38.9 % women under vitamin supplementation at this stage of lactation)	90 days post partum	<u><math>\alpha</math>-Tocopherol</u> 2.07 $\pm$ 0.66		0.94–2.80			

Reference	n (number of samples)	Country	Maternal dietary intake (mg/day) Mean $\pm$ SD	Stage of lactation	$\alpha$ -Tocopherol concentration in breast milk (mg/L)			Analytical method	Comments
					Mean $\pm$ SD	Median	Range		
Molto-Puigmarti et al. (2009)	10 (10)	Spain	Not reported	Colostrum	<u><math>\alpha</math>-Tocopherol</u> 37.84 $\pm$ 24.52			UHPLC (PDA detector)	No information on whether infants were born at term or not, and on possible maternal supplementation with 'vitamin E'. The exact stage of lactation was not reported
	10 (10)			Mature milk	<u><math>\alpha</math>-Tocopherol</u> 3.39 $\pm$ 2.12				
Molto-Puigmarti et al. (2011) <sup>1</sup>	10	Spain	Not reported	Mature milk	<u><math>\alpha</math>-Tocopherol</u> 7.17 $\pm$ 2.60			UHPLC (fluorescent detector)	The aim of the study was to investigate the effect of pasteurisation (heat treatment) on the concentration of vitamins in human milk. The values presented here are for untreated milk. No information on whether infants were born at term or not and on possible maternal supplementation with 'vitamin E'. The exact stage of lactation was not reported
Orhon et al. (2009)	20 non-smoking mothers	Turkey	Not reported	7 days post partum	<u><math>\alpha</math>-Tocopherol</u> 13.3 $\pm$ 0.7 (SEM)			HPLC	Full-term infants (mean gestational age: 38.8 weeks in both groups). No information on possible maternal supplementation with 'vitamin E'. Data on 20 smoking mothers are also reported in the study. Plasma $\alpha$ -tocopherol reported
Quiles et al. (2006)	15	Spain	'Vitamin E' 6.1 $\pm$ 0.9	3 days post partum 8 days post partum 30 days post partum	<u><math>\alpha</math>-Tocopherol</u> $\approx$ 25 <u><math>\alpha</math>-Tocopherol</u> $\approx$ 16 <u><math>\alpha</math>-Tocopherol</u> $\approx$ 9			HPLC-EC	The aim of the study was to determine coenzyme Q10 concentration in breast milk. Four-day dietary records were collected. The article did not provide the exact figures of $\alpha$ -tocopherol concentration in breast milk; thus, the values presented here were determined graphically. Full-term infants. No information on possible maternal supplementation with 'vitamin E'

Reference	n (number of samples)	Country	Maternal dietary intake (mg/day) Mean $\pm$ SD	Stage of lactation	$\alpha$ -Tocopherol concentration in breast milk (mg/L)			Analytical method	Comments
					Mean $\pm$ SD	Median	Range		
Romeu-Nadal et al. (2006)	Not reported	Spain	Not reported	Mature milk	<u><math>\alpha</math>-Tocopherol</u> 4.7 $\pm$ 0.2			HPLC (UV detector)	The aim of the study was to compare the sensibility of methods of detection of $\alpha$ - and $\gamma$ -tocopherols in human milk: UV detection and evaporating light scattering detection. Full-term infants. The exact stage of lactation was not reported. No information on possible maternal supplementation with 'vitamin E'
					<u><math>\alpha</math>-Tocopherol</u> 3.7 $\pm$ 0.2			HPLC (UV detector, with saponification)	
					<u><math>\alpha</math>-Tocopherol</u> 3.7 $\pm$ 0.2			HPLC- evaporative light scattering detection (with saponification)	
Romeu-Nadal et al. (2008a) <sup>1</sup>	10 (20)	Spain	Not reported	Mature milk	<u><math>\alpha</math>-Tocopherol</u> 4.41 $\pm$ 0.16			HPLC (UV-visible detector)	The aim of the study was to investigate the effects of pasteurisation on human milk composition. The values presented here are for unpasteurised milk. Milk samples were pooled, divided into six groups, each containing 10 aliquots. No information on whether infants were born at term or not and on possible maternal supplementation with 'vitamin E'
Romeu-Nadal et al. (2008b)	5 (10)	Not reported	Not reported	Mature milk	<u><math>\alpha</math>-Tocopherol</u> 3.85 $\pm$ 0.16			RP-HPLC (UV detector)	The aim of the study was to investigate the effect of cold storage and time of storage on human milk composition. The values presented here are for fresh milk samples. Milk samples from five mothers were pooled and divided into 10 aliquots. No information on whether infants were born at term or not and on possible maternal supplementation with 'vitamin E'
Schweigert et al. (2004)	21	Germany	Not reported. 'Women on regular diet without supplements'	4 days post partum 19 days post partum	<u><math>\alpha</math>-Tocopherol</u> 22.0 $\pm$ 13.4			HPLC	Plasma $\alpha$ -tocopherol was determined at two days post partum: 42.3 $\pm$ 5.8 $\mu$ mol/L and at 19 days post partum: 36.4 $\pm$ 7.2 $\mu$ mol/L (mean $\pm$ SD). Full-term infants

Reference	n (number of samples)	Country	Maternal dietary intake (mg/day) Mean $\pm$ SD	Stage of lactation	$\alpha$ -Tocopherol concentration in breast milk (mg/L)			Analytical method	Comments
					Mean $\pm$ SD	Median	Range		
Sziklai-Laszlo et al. (2009)	12 (12)	Hungary	Not reported	5–10 days post partum	<u><math>\alpha</math>-Tocopherol</u> 4.1 $\pm$ 2.2	4.3	1.3–6.6	HPLC (UV/visible detector)	30 women participated in the study. Full-term infants.
	18 (18)			14–280 days post partum	<u><math>\alpha</math>-Tocopherol</u> 3.0 $\pm$ 1.2	2.8	1.8–5.0		No information on possible maternal supplementation with ‘vitamin E’
Tokusoglu et al. (2008)	92 (92)	Turkey	Not reported	60–90 days post partum	<u><math>\alpha</math>-Tocopherol</u> 9.8 $\pm$ 2.1			HPLC (UV detector)	Food frequency questionnaire completed by the mothers but $\alpha$ -tocopherol or ‘vitamin E’ intakes were not reported. Full-term infants. No use of $\alpha$ -tocopherol supplements

HPLC–EC, High Performance Liquid Chromatography - electrochemical detection; NP-HPLC, normal-phase HPLC; PDA, photodiode array; RP-HPLC, reversed-phase HPLC; SD: Standard Deviation; SEM: Standard Error of the Mean;  $\alpha$ -TE:  $\alpha$ -tocopherol equivalent; UV, ultraviolet; UHPLC, ultra-high performance liquid chromatography.

Molecular mass of  $\alpha$ -tocopherol = 430.71 Da.

Note: Studies explicitly dealing with only breast milk composition of mothers of preterm infants identified through the comprehensive literature search (LASER Analytica, 2014) are not presented in this appendix table. Studies undertaken in non-European countries are not presented in this appendix table (Barkova et al., 2005; Kodentsova and Vrzhesinskaya, 2006; Tijerina-Saenz et al., 2009; de Lira et al., 2012).

**Appendix B. Dietary surveys in the EFSA Comprehensive European Food Consumption Database included in the nutrient intake calculation for  $\alpha$ -tocopherol and  $\alpha$ -tocopherol equivalents**

Country	Dietary survey (year)	Year	Method	Days	Age (years)	Number of subjects						
						Infants < 1 year	Children 1–3 years	Children 3–10 years	Children 10–18 years	Adults 18–65 years	Adults 65–75 years	Adults ≥ 75 years
Finland/1	DIPP	2000–2010	Dietary record	3	< 1–6	499	500	750				
Finland/2	NWSSP	2007–2008	48-hour dietary recall <sup>(b)</sup>	2 × 2 <sup>(b)</sup>	13–15				306			
Finland/3	FINDIET2012	2012	48-hour dietary recall <sup>(b)</sup>	2 <sup>(b)</sup>	25–74					1 295	413	
France	INCA2	2006–2007	Dietary record	7	3–79			482	973	2 276	264	84
Germany/1	EsKiMo	2006	Dietary record	3	6–11			835	393			
Germany/2	VELS	2001–2002	Dietary record	6	< 1–4	158	347	299				
Ireland	NANS	2008–2010	Dietary record	4	18–90					1 274	149	77
Italy	INRAN-SCAI 2005–06	2005–2006	Dietary record	3	< 1–98	16 <sup>(c)</sup>	36 <sup>(c)</sup>	193	247	2 313	290	228
Latvia	FC_PREGNANT WOMEN 2011	2011	24-hour dietary recall	2	15–45				12 <sup>(c)</sup>	991 <sup>(d)</sup>		
Netherlands	DNFCS	2007–2010	24-hour dietary recall	2	7–69			447	1142	2 057	173	
Sweden	RISKMATEN	2010–2011	Dietary record (Web) <sup>(e)</sup>	4	18–80					1 430	295	72
United Kingdom/1	DNSIYC	2011	Dietary record	4	0.3–1.5	1 369	1 314					
United Kingdom/2	NDNS Rolling Programme (Years 1–3)	2008–2011	Dietary record	4	1–94		185	651	666	1 266	166	139

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FC\_PREGNANTWOMEN, food consumption of pregnant women in Latvia; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione – Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELS, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): Infants 1–11 months of age.

(b): A 48-hour dietary recall comprising two consecutive days.

(c): 5<sup>th</sup> or 95<sup>th</sup> percentile intakes calculated from fewer than 60 subjects require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5<sup>th</sup> and 95<sup>th</sup> percentile estimates are not presented in the intake results.

(d): One subject was excluded from the dataset due to the fact that only one 24-hour dietary recall day was available, i.e. the final n = 990.

(e): The Swedish dietary records were introduced through the internet.

**Appendix C. Intakes of  $\alpha$ -tocopherol (mg/day and mg/MJ) in males in different surveys, according to age class and country, based on Finnish and Swedish  $\alpha$ -tocopherol composition data**

Age class	Country	Survey	Intakes expressed in mg/day					Intakes expressed in mg/MJ				
			n <sup>(a)</sup>	Average	Median	P5	P95	n <sup>(a)</sup>	Average	Median	P5	P95
< 1 year <sup>(b)</sup>	Finland	DIPP_2001_2009	247	3.2	3.1	0.4	6.4	245	1.5	1.5	0.8	2.1
	Germany	VELS	84	4.5	4.3	2.2	7.2	84	1.4	1.3	0.7	2.5
	Italy	INRAN_SCAI_2005_06	9	4.9	5.3	(c)	(c)	9	1.7	1.7	(c)	(c)
	United Kingdom	DNSIYC_2011	699	5.4	5.3	3.4	7.8	699	1.6	1.6	1.1	2.1
1 to < 3 years	Finland	DIPP_2001_2009	245	4.4	4.2	2.1	7.1	245	1.2	1.2	0.7	1.8
	Germany	VELS	174	4.9	4.5	2.3	8.8	174	1.0	1.0	0.6	1.7
	Italy	INRAN_SCAI_2005_06	20	5.7	5.0	(c)	(c)	20	1.1	1.1	(c)	(c)
	United Kingdom	DNSIYC_2011	663	4.4	4.2	2.2	7.3	663	1.1	1.0	0.6	1.7
	United Kingdom	NDNS Rolling Programme Years 1–3	107	5.4	4.9	2.7	9.4	107	1.1	1.1	0.6	1.7
3 to < 10 years	Finland	DIPP_2001_2009	381	7.3	7.0	4.4	11.7	381	1.2	1.2	0.8	1.7
	France	INCA2	239	8.7	8.0	4.2	15.7	239	1.4	1.3	0.8	2.3
	Germany	EsKiMo	426	8.1	7.6	4.5	13.7	426	1.1	1.0	0.6	1.8
	Germany	VELS	146	5.8	5.2	3.1	9.7	146	1.0	0.9	0.6	1.9
	Italy	INRAN_SCAI_2005_06	94	9.6	9.0	5.0	15.3	94	1.3	1.2	0.9	1.8
	Netherlands	DNFCS 2007–2010	231	10.9	10.0	5.3	19.2	231	1.2	1.2	0.7	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	326	7.2	7.0	4.0	11.7	326	1.1	1.1	0.7	1.8
	United Kingdom	NDNS Rolling Programme Years 1–3	326	7.2	7.0	4.0	11.7	326	1.1	1.1	0.7	1.8
10 to < 18 years	Finland	NWSSP07_08	136	10.5	10.5	4.7	16.6	136	1.3	1.3	0.8	1.7
	France	INCA2	449	10.0	9.1	4.9	18.2	449	1.3	1.2	0.7	2.1
	Germany	EsKiMo	197	9.2	8.1	4.8	15.7	197	1.1	1.0	0.6	1.9
	Italy	INRAN_SCAI_2005_06	108	12.4	11.8	7.5	18.7	108	1.3	1.2	0.9	1.8
	Netherlands	DNFCS 2007–2010	566	14.3	12.7	6.1	29.0	566	1.3	1.3	0.8	2.0
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.1	8.8	4.7	14.7	340	1.1	1.1	0.7	1.7
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.1	8.8	4.7	14.7	340	1.1	1.1	0.7	1.7
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.1	8.8	4.7	14.7	340	1.1	1.1	0.7	1.7
18 to < 65 years	Finland	FINDIET2012	585	12.4	11.5	5.0	22.9	585	1.3	1.3	0.7	2.1
	France	INCA2	936	10.5	9.6	4.8	19.8	936	1.2	1.1	0.7	2.0
	Ireland	NANS_2012	634	12.5	11.9	5.6	21.7	634	1.2	1.2	0.7	1.9
	Italy	INRAN_SCAI_2005_06	1 068	11.8	11.1	6.7	18.6	1 068	1.3	1.2	0.9	2.0
	Netherlands	DNFCS 2007–2010	1 023	16.0	15.0	6.9	28.5	1 023	1.4	1.4	0.8	2.1
	Sweden	Riksmaten 2010	623	11.6	11.0	4.8	20.3	623	1.2	1.1	0.6	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	560	10.6	9.9	4.7	18.3	560	1.2	1.1	0.7	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	560	10.6	9.9	4.7	18.3	560	1.2	1.1	0.7	1.9

Age class	Country	Survey	n <sup>(a)</sup>	Intakes expressed in mg/day				n <sup>(a)</sup>	Intakes expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	210	11.3	10.4	4.4	20.8	210	1.4	1.3	0.7	2.1
	France	INCA2	111	11.6	10.8	5.2	21.5	111	1.4	1.2	0.7	2.7
	Ireland	NANS_2012	72	11.7	10.8	4.3	21.8	72	1.3	1.3	0.7	2.0
	Italy	INRAN_SCAI_2005_06	133	11.6	11.2	5.8	16.9	133	1.3	1.3	0.8	2.0
	Netherlands	DNFCS 2007–2010	91	12.7	11.7	5.3	24.0	91	1.3	1.3	0.8	2.0
	Sweden	Riksmaten 2010	127	10.9	10.6	4.4	19.0	127	1.2	1.2	0.7	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	75	10.8	9.8	5.2	17.6	75	1.3	1.2	0.7	2.3
≥ 75 years	France	INCA2	40	10.6	9.8	(c)	(c)	40	1.4	1.3	(c)	(c)
	Ireland	NANS_2012	34	9.8	8.6	(c)	(c)	34	1.3	1.0	(c)	(c)
	Italy	INRAN_SCAI_2005_06	69	10.8	10.6	6.0	17.1	69	1.3	1.2	0.8	2.0
	Sweden	Riksmaten 2010	42	11.4	10.5	(c)	(c)	42	1.3	1.3	(c)	(c)
	United Kingdom	NDNS Rolling Programme Years 1–3	56	8.2	7.8	(c)	(c)	56	1.1	1.1	(c)	(c)

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FC\_PREGNANTWOMEN, food consumption of pregnant women in Latvia; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): n, number of subjects.

(b): Infants between 1 and 11 months. The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5<sup>th</sup> or 95<sup>th</sup> percentile intakes calculated from fewer than 60 subjects require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5<sup>th</sup> and 95<sup>th</sup> percentile estimates are not presented in the intake results.

Note: The composition data was submitted to EFSA as 'vitamin E' data. The national database compilers of Finland and Sweden confirmed that their food composition database contains information for vitamin E as  $\alpha$ -tocopherol.

**Appendix D. Intakes of  $\alpha$ -tocopherol (mg/day and mg/MJ) in females in different surveys, according to age class and country, based on Finnish and Swedish  $\alpha$ -tocopherol composition data**

Age class	Country	Survey	Intakes expressed in mg/day					Intakes expressed in mg/MJ				
			n <sup>(a)</sup>	Average	Median	P5	P95	n <sup>(a)</sup>	Average	Median	P5	P95
< 1 year <sup>(b)</sup>	Finland	DIPP_2001_2009	252	2.9	2.7	0.3	5.8	251	1.5	1.5	0.8	2.1
	Germany	VELS	75	4.7	4.1	2.5	8.9	75	1.6	1.5	0.9	2.8
	Italy	INRAN_SCAI_2005_06	7	4.4	3.9	(c)	(c)	7	1.6	1.7	(c)	(c)
	United Kingdom	DNSIYC_2011	670	4.9	4.8	2.7	7.1	670	1.6	1.6	1.0	2.1
1 to < 3 years	Finland	DIPP_2001_2009	255	4.0	3.7	1.9	6.6	255	1.2	1.1	0.7	1.7
	Germany	VELS	174	4.7	4.1	2.3	9.6	174	1.1	0.9	0.6	2.3
	Italy	INRAN_SCAI_2005_06	16	5.0	4.1	(c)	(c)	16	1.0	1.0	(c)	(c)
	United Kingdom	DNSIYC_2011	651	4.4	4.2	2.2	7.3	651	1.1	1.1	0.6	1.8
3 to < 10 years	United Kingdom	NDNS Rolling Programme Years 1–3	78	4.5	4.2	2.1	8.1	78	1.0	0.9	0.6	1.5
	Finland	DIPP_2001_2009	369	6.6	6.5	3.7	10.0	369	1.2	1.2	0.8	1.7
	France	INCA2	243	8.0	7.3	4.1	14.4	243	1.4	1.3	0.9	2.4
	Germany	EsKiMo	409	7.4	6.9	3.8	13.7	409	1.1	1.0	0.6	1.8
	Germany	VELS	147	5.4	5.0	3.0	9.8	147	1.0	0.9	0.6	1.7
	Italy	INRAN_SCAI_2005_06	99	9.3	8.9	5.0	14.5	99	1.3	1.2	0.9	1.8
	Netherlands	DNFCS 2007–2010	216	10.3	9.4	5.0	19.6	216	1.2	1.2	0.7	1.8
10 to < 18 years	United Kingdom	NDNS Rolling Programme Years 1–3	325	7.1	6.9	3.7	11.1	325	1.2	1.1	0.7	1.7
	Finland	NWSSP07_08	170	9.0	8.4	5.2	14.2	170	1.4	1.3	0.9	1.8
	France	INCA2	524	8.9	8.2	4.3	16.1	524	1.4	1.3	0.8	2.5
	Germany	EsKiMo	196	8.8	7.8	4.1	17.4	196	1.2	1.0	0.6	2.5
	Italy	INRAN_SCAI_2005_06	139	10.8	10.4	5.9	18.3	139	1.4	1.3	0.9	2.0
	Latvia <sup>(d)</sup>	FC_PREGNANTWOMEN_2011	12	13.2	13.4	(c)	(c)	12	1.4	1.3	(c)	(c)
	Netherlands	DNFCS 2007–2010	576	11.5	10.9	5.5	20.2	576	1.3	1.3	0.7	1.9
18 to < 65 years	United Kingdom	NDNS Rolling Programme Years 1–3	326	8.2	7.9	4.2	14.1	326	1.2	1.2	0.7	1.9
	Finland	FINDIET2012	710	10.4	9.8	4.7	17.8	710	1.4	1.4	0.8	2.2
	France	INCA2	1 340	9.7	9.1	4.1	17.4	1 340	1.5	1.4	0.8	2.5
	Ireland	NANS_2012	640	10.2	9.8	4.9	17.8	640	1.4	1.3	0.8	2.1
	Italy	INRAN_SCAI_2005_06	1 245	10.1	10.0	5.5	15.3	1 245	1.4	1.4	0.9	2.0
	Latvia <sup>(d)</sup>	FC_PREGNANTWOMEN_2011	990	12.4	11.6	6.2	21.2	990	1.5	1.4	0.8	2.4
	Netherlands	DNFCS 2007–2010	1 034	12.5	11.5	5.6	22.1	1 034	1.5	1.4	0.8	2.3
	Sweden	Riksmaten 2010	807	10.5	9.5	4.5	18.9	807	1.5	1.3	0.8	2.2
	United Kingdom	NDNS Rolling Programme Years 1–3	706	8.8	8.2	3.9	15.9	706	1.3	1.2	0.7	2.2

Age class	Country	Survey	Intakes expressed in mg/day					Intakes expressed in mg/MJ				
			n <sup>(a)</sup>	Average	Median	P5	P95	n <sup>(a)</sup>	Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	203	9.0	8.1	4.1	15.6	203	1.4	1.3	0.8	2.1
	France	INCA2	153	9.9	9.1	4.3	18.1	153	1.6	1.5	1.0	2.8
	Ireland	NANS_2012	77	9.3	8.7	5.4	15.2	77	1.4	1.3	0.8	2.1
	Italy	INRAN_SCAI_2005_06	157	9.7	9.7	4.9	15.5	157	1.4	1.3	0.9	2.1
	Netherlands	DNFCS 2007–2010	82	10.9	10.1	5.2	17.7	82	1.5	1.5	0.9	2.4
	Sweden	Riksmaten 2010	168	9.3	8.6	4.4	16.8	168	1.3	1.3	0.8	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	91	8.6	8.4	4.6	15.4	91	1.4	1.4	0.8	2.3
≥ 75 years	France	INCA2	44	10.1	9.4	(c)	(c)	44	1.7	1.5	(c)	(c)
	Ireland	NANS_2012	43	8.9	8.5	(c)	(c)	43	1.4	1.3	(c)	(c)
	Italy	INRAN_SCAI_2005_06	159	8.8	8.5	4.7	13.7	159	1.3	1.3	0.9	2.0
	Sweden	Riksmaten 2010	30	9.3	9.4	(c)	(c)	30	1.3	1.3	(c)	(c)
	United Kingdom	NDNS Rolling Programme Years 1–3	83	7.8	7.9	4.2	11.5	83	1.3	1.2	0.7	1.9

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FC\_PREGNANTWOMEN, food consumption of pregnant women in Latvia; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): n, number of subjects.

(b): Infants between 1 and 11 months. The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5<sup>th</sup> or 95<sup>th</sup> percentile intakes calculated from fewer than 60 subjects require cautious interpretation as the results may not be statistically robust (EFSA, 2011a) and, therefore, for these dietary surveys/age classes, the 5<sup>th</sup> and 95<sup>th</sup> percentile estimates are not presented in the intake results.

(d): Pregnant women only.

Note: The composition data was submitted to EFSA as 'vitamin E' data. The national database compilers of Finland and Sweden confirmed that their food composition database contains information for vitamin E as  $\alpha$ -tocopherol.

**Appendix E. Intakes of  $\alpha$ -tocopherol equivalents (mg  $\alpha$ -TE/day and mg  $\alpha$ -TE/MJ) in males in different surveys, according to age class and country, based on  $\alpha$ -TE composition data of five countries (France, Germany, Italy, the Netherlands and the UK)**

Age class	Country	Survey	n <sup>(a)</sup>	Intakes expressed in mg/day				n <sup>(a)</sup>	Intakes expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
< 1 year <sup>(b)</sup>	Finland	DIPP_2001_2009	247	3.4	3.4	0.4	7.0	245	1.6	1.7	0.9	2.2
	Germany	VELS	84	4.6	4.3	2.3	7.7	84	1.4	1.4	0.7	2.6
	Italy	INRAN_SCAI_2005_06	9	5.4	3.5	<sup>(c)</sup>	<sup>(c)</sup>	9	1.8	1.3	<sup>(c)</sup>	<sup>(c)</sup>
	United Kingdom	DNSIYC_2011	699	5.9	5.7	3.5	8.5	699	1.7	1.8	1.1	2.3
1 to < 3 years	Finland	DIPP_2001_2009	245	4.7	4.4	2.0	7.9	245	1.3	1.2	0.7	2.0
	Germany	VELS	174	5.7	5.2	2.8	10.0	174	1.2	1.1	0.7	2.0
	Italy	INRAN_SCAI_2005_06	20	7.3	6.8	<sup>(c)</sup>	<sup>(c)</sup>	20	1.4	1.5	<sup>(c)</sup>	<sup>(c)</sup>
	United Kingdom	DNSIYC_2011	663	5.1	5.0	2.5	8.2	663	1.2	1.2	0.7	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	107	6.0	5.5	3.2	9.9	107	1.2	1.1	0.7	1.9
3 to < 10 years	Finland	DIPP_2001_2009	381	7.4	7.1	4.4	11.8	381	1.3	1.2	0.8	1.7
	France	INCA2	239	9.4	8.6	4.5	16.6	239	1.5	1.4	0.8	2.3
	Germany	EsKiMo	426	9.4	8.8	4.9	15.7	426	1.2	1.2	0.7	2.0
	Germany	VELS	146	7.1	6.6	3.8	12.4	146	1.3	1.2	0.7	2.2
	Italy	INRAN_SCAI_2005_06	94	12.4	12.3	5.8	19.2	94	1.7	1.6	1.1	2.3
	Netherlands	DNFCS 2007–2010	231	11.7	10.7	5.3	20.7	231	1.3	1.3	0.7	2.0
	United Kingdom	NDNS Rolling Programme Years 1–3	326	8.0	7.7	4.0	12.7	326	1.3	1.2	0.8	1.8
	United Kingdom	NDNS Rolling Programme Years 1–3	326	8.0	7.7	4.0	12.7	326	1.3	1.2	0.8	1.8
10 to < 18 years	Finland	NWSSP07_08	136	10.5	10.3	4.5	16.9	136	1.3	1.3	0.8	1.7
	France	INCA2	449	10.8	10.2	5.1	18.8	449	1.4	1.3	0.8	2.1
	Germany	EsKiMo	197	10.8	9.7	5.7	19.1	197	1.3	1.2	0.8	2.2
	Italy	INRAN_SCAI_2005_06	108	15.9	14.8	9.0	24.4	108	1.6	1.6	1.1	2.3
	Netherlands	DNFCS 2007–2010	566	14.3	12.8	6.1	27.6	566	1.3	1.2	0.7	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.6	8.9	4.8	16.8	340	1.2	1.1	0.6	1.8
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.6	8.9	4.8	16.8	340	1.2	1.1	0.6	1.8
	United Kingdom	NDNS Rolling Programme Years 1–3	340	9.6	8.9	4.8	16.8	340	1.2	1.1	0.6	1.8
18 to < 65 years	Finland	FINDIET2012	585	13.7	12.6	5.5	25.5	585	1.5	1.4	0.8	2.4
	France	INCA2	936	10.9	10.0	4.5	20.2	936	1.2	1.2	0.7	2.1
	Ireland	NANS_2012	634	11.6	10.9	4.6	21.1	634	1.1	1.1	0.6	1.9
	Italy	INRAN_SCAI_2005_06	1 068	15.4	14.7	8.7	24.5	1 068	1.7	1.6	1.1	2.5
	Netherlands	DNFCS 2007–2010	1 023	16.0	15.1	6.8	28.9	1 023	1.4	1.4	0.7	2.2
	Sweden	Riksmaten 2010	623	13.3	12.5	5.4	23.3	623	1.3	1.3	0.7	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	560	10.9	10.3	4.7	18.8	560	1.2	1.2	0.7	2.0
	United Kingdom	NDNS Rolling Programme Years 1–3	560	10.9	10.3	4.7	18.8	560	1.2	1.2	0.7	2.0

Age class	Country	Survey	n <sup>(a)</sup>	Intakes expressed in mg/day				n <sup>(a)</sup>	Intakes expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	210	12.8	11.5	4.9	24.3	210	1.5	1.5	0.8	2.5
	France	INCA2	111	11.6	11.0	4.6	22.2	111	1.4	1.2	0.6	2.8
	Ireland	NANS_2012	72	12.0	11.3	3.2	23.4	72	1.3	1.2	0.7	2.3
	Italy	INRAN_SCAI_2005_06	133	15.4	15.2	7.9	23.0	133	1.8	1.7	1.1	2.6
	Netherlands	DNFCS 2007–2010	91	12.9	12.9	6.0	22.8	91	1.4	1.3	0.9	1.9
	Sweden	Riksmaten 2010	127	12.5	12.3	5.8	21.6	127	1.4	1.4	0.9	2.2
	United Kingdom	NDNS Rolling Programme Years 1–3	75	12.5	11.0	5.0	22.0	75	1.5	1.5	0.6	2.2
≥ 75 years	France	INCA2	40	11.6	11.5	(c)	(c)	40	1.5	1.4	(c)	(c)
	Ireland	NANS_2012	34	10.4	8.6	(c)	(c)	34	1.3	1.1	(c)	(c)
	Italy	INRAN_SCAI_2005_06	69	14.2	13.8	8.8	22.1	69	1.7	1.6	1.1	2.6
	Sweden	Riksmaten 2010	42	13.0	13.0	(c)	(c)	42	1.5	1.5	(c)	(c)
	United Kingdom	NDNS Rolling Programme Years 1–3	56	10.1	9.1	(c)	(c)	56	1.4	1.3	(c)	(c)

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FC\_PREGNANTWOMEN, food consumption of pregnant women in Latvia; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): n, number of subjects.

(b): Infants between 1 and 11 months. The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5<sup>th</sup> or 95<sup>th</sup> percentile intakes calculated from fewer than 60 subjects require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5<sup>th</sup> and 95<sup>th</sup> percentile estimates are not presented in the intake results.

Note: The composition data was submitted to EFSA as ‘vitamin E’ data. The national database compilers of Finland and Sweden confirmed that their food composition database contains information for vitamin E as  $\alpha$ -tocopherol.

**Appendix F. Intakes of  $\alpha$ -tocopherol equivalents (mg  $\alpha$ -TE/day and mg  $\alpha$ -TE/MJ) in females in different surveys, according to age class and country, based on  $\alpha$ -TE composition data of five countries (France, Germany, Italy, the Netherlands and the UK)**

Age class	Country	Survey	n <sup>(a)</sup>	Intakes expressed in mg/day				n <sup>(a)</sup>	Intakes expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
< 1 year <sup>(b)</sup>	Finland	DIPP_2001_2009	252	3.2	3.0	0.3	6.4	251	1.7	1.7	0.9	2.3
	Germany	VELS	75	4.8	4.2	2.6	10.0	75	1.7	1.5	0.9	3.1
	Italy	INRAN_SCAI_2005_06	7	5.3	4.5	<sup>(c)</sup>	<sup>(c)</sup>	7	1.9	1.3	<sup>(c)</sup>	<sup>(c)</sup>
	United Kingdom	DNSIYC_2011	670	5.2	5.2	2.9	7.9	670	1.7	1.7	1.0	2.3
1 to < 3 years	Finland	DIPP_2001_2009	255	4.4	4.1	1.9	7.5	255	1.3	1.2	0.7	1.9
	Germany	VELS	174	5.6	5.0	2.6	10.7	174	1.3	1.2	0.7	2.4
	Italy	INRAN_SCAI_2005_06	16	6.8	6.0	<sup>(c)</sup>	<sup>(c)</sup>	16	1.4	1.4	<sup>(c)</sup>	<sup>(c)</sup>
	United Kingdom	DNSIYC_2011	651	5.0	4.8	2.6	8.2	651	1.3	1.2	0.7	2.0
	United Kingdom	NDNS Rolling Programme Years 1–3	78	5.5	5.1	2.5	9.6	78	1.2	1.2	0.7	1.9
3 to < 10 years	Finland	DIPP_2001_2009	369	6.7	6.5	3.7	10.1	369	1.3	1.2	0.8	1.8
	France	INCA2	243	8.9	8.3	4.4	15.6	243	1.6	1.5	1.0	2.4
	Germany	EsKiMo	409	8.8	8.2	4.2	15.7	409	1.3	1.2	0.7	2.1
	Germany	VELS	147	6.5	6.2	3.4	11.5	147	1.3	1.2	0.7	1.9
	Italy	INRAN_SCAI_2005_06	99	11.8	11.2	6.9	19.0	99	1.6	1.6	1.1	2.4
	Netherlands	DNFCS 2007–2010	216	10.7	9.8	5.6	20.0	216	1.3	1.2	0.8	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	325	7.9	7.7	3.8	12.4	325	1.3	1.3	0.8	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	78	5.5	5.1	2.5	9.6	78	1.2	1.2	0.7	1.9
10 to < 18 years	Finland	DIPP_2001_2009	369	6.7	6.5	3.7	10.1	369	1.3	1.2	0.8	1.8
	France	INCA2	243	8.9	8.3	4.4	15.6	243	1.6	1.5	1.0	2.4
	Germany	EsKiMo	409	8.8	8.2	4.2	15.7	409	1.3	1.2	0.7	2.1
	Germany	VELS	147	6.5	6.2	3.4	11.5	147	1.3	1.2	0.7	1.9
	Italy	INRAN_SCAI_2005_06	99	11.8	11.2	6.9	19.0	99	1.6	1.6	1.1	2.4
	Netherlands	DNFCS 2007–2010	216	10.7	9.8	5.6	20.0	216	1.3	1.2	0.8	2.1
	United Kingdom	NDNS Rolling Programme Years 1–3	325	7.9	7.7	3.8	12.4	325	1.3	1.3	0.8	1.9
	United Kingdom	NDNS Rolling Programme Years 1–3	78	5.5	5.1	2.5	9.6	78	1.2	1.2	0.7	1.9
	Finland	NWSSP07_08	170	9.1	8.7	5.2	14.9	170	1.4	1.4	0.9	1.9
	France	INCA2	524	9.5	8.8	4.3	17.0	524	1.5	1.4	0.9	2.4
18 to < 65 years	Germany	EsKiMo	196	9.8	8.9	4.7	17.9	196	1.3	1.2	0.7	2.5
	Italy	INRAN_SCAI_2005_06	139	13.8	13.3	7.7	22.2	139	1.7	1.6	1.0	2.6
	Latvia <sup>(d)</sup>	FC_PREGNANTWOMEN_2011	12	12.8	12.1	<sup>(c)</sup>	<sup>(c)</sup>	12	1.3	1.3	<sup>(c)</sup>	<sup>(c)</sup>
	Netherlands	DNFCS 2007–2010	576	11.7	11.1	5.4	20.0	576	1.3	1.3	0.7	2.0
	United Kingdom	NDNS Rolling Programme Years 1–3	326	8.8	8.2	4.1	14.7	326	1.3	1.2	0.8	2.0
	Finland	FINDIET2012	710	11.6	10.7	4.9	22.1	710	1.6	1.5	0.9	2.5
	France	INCA2	1 340	10.3	9.5	4.4	18.7	1340	1.6	1.5	0.9	2.6
	Ireland	NANS_2012	640	9.8	9.1	4.2	16.9	640	1.3	1.3	0.7	2.0
	Italy	INRAN_SCAI_2005_06	1 245	13.5	13.2	7.2	20.9	1 245	1.9	1.8	1.1	2.7
	Latvia <sup>(d)</sup>	FC_PREGNANTWOMEN_2011	990	12.5	11.8	6.2	21.7	990	1.5	1.4	0.8	2.4
18 to < 65 years	Netherlands	DNFCS 2007–2010	1 034	12.3	11.4	5.3	21.8	1 034	1.5	1.4	0.8	2.4
	Sweden	Riksmaten 2010	807	12.3	11.3	5.4	23.7	807	1.8	1.5	0.9	2.7
	United Kingdom	NDNS Rolling Programme Years 1–3	706	9.4	8.9	4.0	16.1	706	1.4	1.3	0.8	2.2

Age class	Country	Survey	n <sup>(a)</sup>	Intakes expressed in mg/day				n <sup>(a)</sup>	Intakes expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	203	10.2	9.1	4.3	20.0	203	1.6	1.5	0.9	2.5
	France	INCA2	153	10.3	9.0	4.5	20.2	153	1.6	1.5	0.9	2.8
	Ireland	NANS_2012	77	9.4	8.7	4.7	20.7	77	1.4	1.3	0.8	2.3
	Italy	INRAN_SCAI_2005_06	157	13.1	12.9	6.5	21.5	157	1.9	1.8	1.2	2.9
	Netherlands	DNFCS 2007–2010	82	11.2	10.7	4.9	19.7	82	1.6	1.6	0.8	2.5
	Sweden	Riksmaten 2010	168	11.1	10.4	5.1	19.6	168	1.6	1.5	0.9	2.5
	United Kingdom	NDNS Rolling Programme Years 1–3	91	9.1	9.1	4.6	14.4	91	1.5	1.5	0.9	2.3
≥ 75 years	France	INCA2	44	10.7	9.6	<sup>(c)</sup>	<sup>(c)</sup>	44	1.8	1.6	<sup>(c)</sup>	<sup>(c)</sup>
	Ireland	NANS_2012	43	10.3	9.4	<sup>(c)</sup>	<sup>(c)</sup>	43	1.6	1.5	<sup>(c)</sup>	<sup>(c)</sup>
	Italy	INRAN_SCAI_2005_06	159	11.8	11.4	5.9	18.1	159	1.8	1.7	1.1	2.5
	Sweden	Riksmaten 2010	30	11.3	11.2	<sup>(c)</sup>	<sup>(c)</sup>	30	1.6	1.6	<sup>(c)</sup>	<sup>(c)</sup>
	United Kingdom	NDNS Rolling Programme Years 1–3	83	8.9	8.6	4.9	13.2	83	1.5	1.4	0.9	2.1

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FC\_PREGNANTWOMEN, food consumption of pregnant women in Latvia; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): n, number of subjects.

(b): Infants between 1 and 11 months. The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5<sup>th</sup> or 95<sup>th</sup> percentile intakes calculated from fewer than 60 subjects require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates are not presented in the intake results.

(d): Pregnant women only.

Note: The composition data was submitted to EFSA as 'vitamin E' data. The national database compilers of Finland and Sweden confirmed that their food composition database contains information for vitamin E as  $\alpha$ -tocopherol.

**Appendix G. Minimum and maximum percentage contribution of different food groups (FoodEx2 level 1) to  $\alpha$ -TE intakes in males, based on  $\alpha$ -TE composition data of five countries (France, Germany, Italy, Netherlands, UK)**

Food groups	Age						
	< 1 year	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	< 1	< 1	0	0	0	0	0
Alcoholic beverages	0	0	0	0	0	0	0
Animal and vegetable fats and oils	4–21	10–44	14–55	14–56	14–59	14–60	16–59
Coffee, cocoa, tea and infusions	< 1	0–1	< 1–2	< 1–1	< 1–2	< 1–1	< 1–2
Composite dishes	< 1–2	< 1–14	< 1–12	< 1–13	1–23	< 1–21	1–19
Eggs and egg products	< 1	1–3	1–5	1–4	1–2	1–3	1–2
Fish, seafood, amphibians, reptiles and invertebrates	< 1–1	1–2	1–3	1–3	1–8	3–11	3–11
Food products for young population	44–62	4–30	< 1–1	< 1	< 1	– <sup>(a)</sup>	– <sup>(a)</sup>
Fruit and fruit products	2–12	7–10	3–6	2–5	2–6	4–8	3–9
Fruit and vegetable juices and nectars	< 1–6	1–17	2–18	2–17	1–5	< 1–5	< 1–4
Grains and grain-based products	< 1–11	10–29	8–33	8–25	10–25	9–31	10–31
Human milk	< 1 <sup>(b)</sup> –24	< 1–2	– <sup>(a)</sup>				
Legumes, nuts, oilseeds and spices	< 1–4	< 1–2	1–6	1–5	1–6	1–5	< 1–3
Meat and meat products	< 1–1	1–3	2–4	2–4	2–4	1–4	2–3
Milk and dairy products	1–3	5–7	3–9	3–7	2–5	2–5	3
Products for non-standard diets, food imitates and food supplements or fortifying agents	< 1–1	0	< 1–2	< 1–1	< 1–4	< 1	< 1–2
Seasoning, sauces and condiments	< 1–3	< 1–8	1–10	1–13	2–14	1–11	1–12
Starchy roots or tubers and products thereof, sugar plants	< 1–3	1–5	1–12	1–12	< 1–10	< 1–8	< 1–14
Sugar, confectionery and water-based sweet desserts	0	< 1–1	1–2	1–2	< 1–2	< 1–1	< 1–1
Vegetables and vegetable products	1–5	5–8	3–8	3–9	3–11	3–11	4–11
Water and water-based beverages	0	0–1	< 1–1	< 1–1	< 1	< 1	< 1

(a): ‘–’ means that there was no consumption event of the food group for the age and sex group considered, while ‘0’ means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

(b): The lower bound of this range corresponds to the data from the Finnish survey, which did not assess the amount of breast milk consumed.

**Appendix H. Minimum and maximum percentage contribution of different food groups (FoodEx2 level 1) to  $\alpha$ -TE intakes in females, based on  $\alpha$ -TE composition data of five countries (France, Germany, Italy, Netherlands, UK)**

Food groups	Age						
	< 1 year	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	0	0	0	0	0	0	0
Alcoholic beverages	0	0	0	0	0	0	0
Animal and vegetable fats and oils	4–24	11–49	13–55	13–54	11–57	10–57	10–53
Coffee, cocoa, tea and infusions	< 1	< 1–1	< 1–2	< 1–1	< 1–2	< 1–2	< 1–1
Composite dishes	< 1–3	< 1–12	< 1–12	1–13	1–25	< 1–21	< 1–24
Eggs and egg products	< 1–1	< 1–3	1–5	1–4	1–2	1–4	1–2
Fish, seafood, amphibians, reptiles and invertebrates	< 1–2	1–3	< 1–3	1–4	2–7	2–10	2–10
Food products for young population	46–61	6–25	< 1–1	< 1	< 1	– <sup>(a)</sup>	< 1
Fruit and fruit products	4–12	6–10	3–7	3–8	4–7	7–11	5–11
Fruit and vegetable juices and nectars	< 1–5	1–16	2–17	3–15	1–4	< 1–5	< 1–7
Grains and grain-based products	1–7	9–30	8–31	9–30	11–30	10–28	10–27
Human milk	< 1 <sup>(b)</sup> –12	< 1–2	– <sup>(a)</sup>				
Legumes, nuts, oilseeds and spices	< 1–1	< 1–2	1–4	< 1–7	1–8	1–6	1–5
Meat and meat products	< 1–1	1–3	2–4	2–4	2–4	2–3	1–2
Milk and dairy products	1–3	5–7	3–9	3–6	3–5	2–5	3–4
Products for non-standard diets, food imitates and food supplements or fortifying agents	< 1	< 1–1	0–2	< 1–1	< 1–3	0–1	< 1–1
Seasoning, sauces and condiments	< 1–2	< 1–8	1–11	1–17	1–16	1–14	1–13
Starchy roots or tubers and products thereof, sugar plants	< 1–3	< 1–6	1–12	1–12	< 1–8	< 1–8	< 1–6
Sugar, confectionery and water-based sweet desserts	0	< 1–2	1–2	1–3	< 1–2	< 1–1	< 1–1
Vegetables and vegetable products	3–5	5–8	3–8	3–9	4–11	5–12	6–12
Water and water-based beverages	0	0	< 1–1	0–1	< 1	< 1	< 1

(a): ‘–’ means that there was no consumption event of the food group for the age and sex group considered, while ‘0’ means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

(b): The lower bound of this range corresponds to the data from the Finnish survey, which did not assess the amount of breast milk consumed.

## ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BMI	Body mass index
$\alpha$ -CEHC	2,5,7,8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman
CI	Confidence interval
COMA	Committee on Medical Aspects of Food Policy
CV	Coefficient of variation
CYP	Cytochrome P
Da	Dalton
D-A-CH	Deutschland–Austria–Confoederatio Helvetica
DH	UK Department of Health
DIPP	Type 1 Diabetes Prediction and Prevention survey
DNA	Deoxyribonucleic acid
DNFCS	Dutch National Food Consumption Survey
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DRV	Dietary Reference Value
EAR	Estimated average requirement
EsKiMo	Ernährungsstudie als KIGGS-Modul
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FFQ	Food frequency questionnaire
HDL	High-density lipoproteins
HPLC	High performance liquid chromatography
HPLC–EC	High performance liquid chromatography–electrochemical detection
INCA	Etude Individuelle Nationale des Consommations Alimentaires
INRAN-SCAI	Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione—Studio sui Consumi Alimentari in Italia
IOM	US Institute of Medicine of the National Academy of Sciences
IU	international unit
LDL	Low-density lipoproteins
LPL	Lipoprotein lipase
NANS	National Adult Nutrition Survey
NCM	Nordic Council of Ministers

NHANES	National Health and Nutrition Examination Survey
NDNS	National Diet and Nutrition Survey
NP-HPLC	Normal-phase HPLC
NWSSP	Nutrition and Wellbeing of Secondary School Pupils
OR	Odds ratio
PDA	Photodiode array
PRI	Population Reference Intake
PUFA	poly-unsaturated fatty acids
RBC	Red blood cell
r	Correlation coefficient
RCT	Randomised controlled trial
RDA	Recommended Dietary Allowance
RI	Recommended Intake
RP-HPLC	Reversed-phase HPLC
RR	Relative risk
SCF	Scientific Committee on Food
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SU.VI.MAX	Supplémentation en vitamines et minéraux antioxydants
$\alpha$ -TE	Alpha-tocopherol equivalent
$\alpha$ -TTP	Alpha-tocopherol transfer protein
UHPLC	Ultra-high performance liquid chromatography
UK	United Kingdom
UL	Tolerable Upper Intake Level
UV	Ultraviolet
VELS	Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln
VLDL	Very low-density lipoproteins
WCRF	World Cancer Research Fund
WHO	World Health Organization