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**Agenda Item 4a**

**CX/NFSDU 16/38/4**

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME  
CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES**

**Thirty-eighth Session**

**Hamburg, Germany**

**5 – 9 December 2016**

**DRAFT NRV-R for Vitamin E**

*Comments of Australia, Canada, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, European Union, Ghana, New Zealand, Paraguay, Philippines, United States, CEFIC, CRN, ELC, IFT, IADSA and ISDI*

**AUSTRALIA**

The CCNFSDU considered several candidate DIRVs and adopted the vitamin E recommendation of 9 mg/day based on an average of four AIs as shown. All candidate DIRVs were based on estimates of dietary intake. All candidate DIRVs were below the UL.

Average of EFSA, NHMRC/MOH, NIHN, WHO/FAO	$(12 + 8.5 + 6.8 + 8.8)/4 = 9.025$ rounded to 9
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Australia notes that a NRV-R based on an Adequate Intake (AI) derived from estimates of dietary intake may reflect the use of dietary equivalent units (and associated conversion factors) in the reported vitamin E content of food consumed.

The vitamin E content of food based on  $\alpha$ -tocopherol only is equal to or less than that calculated as  $\alpha$ -tocopherol equivalents ( $\alpha$ -TE) because  $\alpha$ -TE also weights the known contribution of other tocopherols and [tocotrienols]. The difference in vitamin E units in the supporting composition data may or may not be a significant factor in determining AIs based on dietary intake, depending on the relative contribution of dietary sources of vitamin E. Accurate data on  $\alpha$ -TE values in food depend on having data for all relevant tocopherol [and tocotrienol] isomers. The extent of the isomeric profiles in the supporting nutrient composition data bases is not known for the examined DIRVs.

The IOM DRI report<sup>1</sup> details the US vitamin E intake data expressed in both units and concludes that the impact of choice of unit differs such that  $\alpha$ -toc =  $\alpha$ -TE x 0.8. Soybean and corn oil ( $\gamma$ -tocopherol 10 times  $\alpha$ -tocopherol content) are widely consumed dietary fats and sources of  $\gamma$ -tocopherol in the US diet. The EFSA final opinion<sup>2</sup> also calculated dietary intakes of several European countries as both  $\alpha$ -tocopherol and  $\alpha$ -TE, and noted the methodological limitations of the approach.

Australia has reviewed the available information in RASB reports to identify the units of vitamin E in food used to derive the dietary intakes on which the AIs were based. This information is reproduced from CX/NFSDU 15/37/4 and supplemented by new information in the last column of Table 1 on use of dietary equivalents in the supporting nutrient composition data.

<sup>1</sup> *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. IOM (Institute of Medicine). 2000. Washington DC: National Academy Press. [http://www.nap.edu/catalog.php?record\\_id=9810](http://www.nap.edu/catalog.php?record_id=9810)

<sup>2</sup> EFSA NDA Panel, 2015. Scientific Opinion on Dietary Reference Values for vitamin E as  $\alpha$ -tocopherol. EFSA Journal 2015;13(7):4149, 72 pp. <http://www.efsa.europa.eu/en/efsajournal/pub/4149>

**Table 1** Basis of candidate DIRVs for vitamin E that contributed to NRV-R (2015)

RASB	INL <sub>98</sub> or AI	DIRV (mg)	Basis of AI from Att 2, CX/NFSDU 15/37/4	Dietary intake based on $\alpha$ -toc or $\alpha$ -TE
EFSA (European Union)	AI	12	Observed dietary intakes of healthy populations without apparent $\alpha$ -toc deficiency suggesting that current intakes are adequate. Dietary intakes expressed as $\alpha$ -toc or $\alpha$ -TE based on approximate midpoints of surveys.	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.  Based on the available data, the Panel considers that no conclusions can be drawn on the relationship between PUFA intake and $\alpha$ -tocopherol requirement.
NHMRC/ MOH (Australia & New Zealand)	AI	8.5	Based on median intake from respective 1995 and 1997 national nutrition surveys in Australia and New Zealand – with no apparent vitamin E deficiency.	Australian nutrition survey: vit E units not known; New Zealand survey refers to mg Vit E calculated as $\alpha$ -TE.  DIRV is expressed as $\alpha$ -TE with conversion factors given for several forms of $\alpha$ -tocopherol, plus $\beta$ -tocopherol and $\gamma$ -tocopherol.
NIHN (Japan)	AI	6.8	Based on median dietary intakes reported in 2005 and 2006 NHNS 18–29 years. These intakes are expected to yield blood $\alpha$ -toc level >12 $\mu$ mol/L.	Based on 2005 and 2006 National Health and Nutrition Survey (NHNS) median values for those aged 18 to 29 years stratified by sex and age group ( $\alpha$ -tocoferol).
WHO/FAO	RNI (AI)	8.8	WHO/FAO (2004). Values are taken from an average of 'safe' dietary intakes from UK of M:F 10:7 mg $\alpha$ TE and 'arbitrary but practical' median intakes from US of M:F 10:8 mg $\alpha$ TE that approximate the median intakes in those countries.	Dietary intake data expressed as $\alpha$ -TE in UK and US.

In relation to the basis of the vitamin E conversion factors, Australia observes that conversion factors for tocopherols and tocotrienols, where stated in nutrition publications, are often not referenced.

Bieri and McKenna (1981)<sup>3</sup> explain the background to the first official use of  $\alpha$ -tocopherol equivalents in the 9<sup>th</sup> edition of the US Recommended Dietary Allowances<sup>4</sup>.

*The naturally occurring forms of vitamin E had to be compared against [the vitamin E] standard in a bioassay utilizing the reproductive performance of female rats. No international body has recommended an official table of equivalencies for the different forms of  $\alpha$ -tocopherol or for other tocopherols and tocotrienols. In addition to  $\alpha$ -tocopherol, three other vitamers exist in nature,  $\beta$ -,  $\gamma$ -, and  $\delta$ - tocopherols. Four similar compounds with unsaturated side chains, the tocotrienols, are also found.*

.....

*Only d- $\alpha$ -tocopherol exists naturally ....The other tocopherols and tocotrienols which occur in nature have no officially recognised equivalency, but from studies by many investigators a general consensus has emerged. Compared to d- $\alpha$ -tocopherol the relative potencies are approximately  $\beta$ -tocopherol, 40%;  $\gamma$ -*

<sup>3</sup> Bieri JG, McKenna MC (1981) *Expressing dietary values for fat-soluble vitamins: changes in concepts and terminology.* Am J Clin Nutr 34: 289-95.

<sup>4</sup> *Recommended Dietary Allowances.* Food and Nutrition Board. 1980.9<sup>th</sup> rev. ed. Washington DC: National Academy of Sciences.

*tocopherol, 10%; δ-tocopherol, 1%. Only α-tocotrienol in the trienol series has significant activity about 25% that of α-tocopherol. To complicate matters, different types of bioassays e.g. in vitro hemolysis of red cells, curing of rabbit muscle dystrophy, liver storage, etc. have given relative potencies frequently significantly different from those obtained by the rat fertility test.*

Table 2 contains information on the scientific basis of the vitamin E units, reproduced from CX/NFSDU 15/37/4 and references all original candidate DIRVs.

**Table 2 Basis of vitamin E units for all original candidate DIRVs**

	<b>Relevant parameters informing vitamin E units</b>	<b>Vitamin E units</b>
United States & Canada	<p>Vitamin E forms are absorbed by the small intestine in chylomicrons but plasma concentration depends on the affinity for them by α-tocopherol transfer protein in the liver. Only the 2R stereoisomeric forms of α-tocopherol are preferentially secreted in VLDL into plasma; other forms such as a synthetic SRR α-tocopherol, or γ-tocopherol are poorly recognised by the transfer protein for secretion.</p> <p>Of the 8 naturally occurring isomers, only α-tocopherol is maintained in the plasma. Of the synthetic forms, only the 2R stereoisomers (RRR-, RSR-, RRS-, RSS-) are maintained.</p>	α-tocopherol only
European Union	<p>Only the naturally occurring RRR-α-tocopherol is considered to be the physiologically active vitamer, as blood α-tocopherol concentrations are maintained by the preferential binding of α-tocopherol transfer protein (α-TTP) compared to other tocopherols or tocotrienols.</p> <p>Among chemically synthesized α-tocopherol forms, only 2R α-tocopherol stereoisomers were found to meet human nutrient requirements because the 2S stereoisomers present in all-rac α-tocopherol possess low affinity to α-TTP and are rapidly metabolized in the liver.</p>	α-tocopherol only
Nordic Council of Ministers	<p>The naturally occurring form of α-tocopherol is RRR-α-tocopherol. Synthetic α-tocopherol (also known as all-rac-α-tocopherol or dl-α-tocopherol) contain an equal mixture of 8 different stereoisomers with equal antioxidative properties but only those with the 2R-configuration have biologically relevant activities.</p> <p>Due to lower affinity that α-tocopherol transport protein has for 2S-isomers, the relative bioavailability of the synthetic form of all-rac -α-tocopherol is suggested to be only half that of the naturally occurring α-tocopherol. This means that only α-tocopherol in foods and 2R-α-tocopherols in vitamin E preparations contribute to vitamin E activity.</p>	α-tocopherol only
Australia & New Zealand	<p>α-TE should continue to be used for vitamin E, because it is premature to state that gamma (γ)-tocopherol, the other major tocopherol in foods, has no biological activity. Little is known about the exact biological functions of α-tocopherol, γ -tocopherol or other forms of vitamin E. γ-tocopherol is a commonly consumed component of the diet. All forms of naturally occurring vitamin E appear to be equally well absorbed and incorporated into chylomicrons. Plasma γ tocopherol concentrations are influenced by dietary intake and range from 5-20% of α-tocopherol concentrations despite the absence of a specific transport protein for γ-tocopherol. Moreover, there is evidence that γ-tocopherol is not inert, but has biological effects or is associated with reduced disease risk in humans.</p>	<p>1 mg α-tocopherol equivalents (α-TE) = 1 mg RRR-α-tocopherol (d-α-tocopherol)</p> <p>2 mg β-tocopherol</p> <p>10 mg γ-tocopherol</p> <p>3.3 mg α-tocotrienol</p>
Japan	<p>Vitamin E is composed of 8 analogues: α-, β-, γ-, and δ-forms, of tocopherol and tocotrienol. After intestinal absorption, vitamin E is packaged into chylomicrons, transformed into chylomicron</p>	α-tocopherol only

	Relevant parameters informing vitamin E units	Vitamin E units
	remnant by lipoprotein lipase, and transported to the liver. Of the 8 analogues, only $\alpha$ -tocopherol is preferentially bound to $\alpha$ -tocopherol binding protein, whereas the other analogues are metabolized in the liver. Alpha-tocopherol is then formed into VLDL, converting into LDL and distributed to various tissues. Due to these metabolic processes, $\alpha$ -tocopherol constitutes the predominant vitamin E analogue present in the blood and various tissues. Based on these facts, only $\alpha$ -tocopherol was considered when determining the current DRI for vitamin E.	
WHO/FAO	<p>WHO/FAO (2004)</p> <p>From a nutritional perspective, the most important form of vitamin E is <math>\alpha</math>-tocopherol; this is corroborated in animal model tests of biopotency which assess the ability of the various homologues to prevent fetal absorption and muscular dystrophies.</p> <p>WHO/FAO (2006)</p> <p>[Australia's comment] The units were amended from <math>\alpha</math>-TE to <math>\alpha</math>-tocopherol in the tables of RNI and EAR. No explanation given for the change from WHO/FAO (2004).</p>	<p>2004:</p> <p>1 mg <math>\alpha</math>-tocopherol equivalents (<math>\alpha</math>-TE) =</p> <p>1 mg RRR-<math>\alpha</math>-tocopherol (d-<math>\alpha</math>-tocopherol)</p> <p>2 mg <math>\beta</math>-tocopherol</p> <p>10 mg <math>\gamma</math>-tocopherol</p> <p>3.3 mg <math>\alpha</math>-tocotrienol</p> <p>20 mg <math>\beta</math>-tocotrienol</p> <p>Annex 2 gives the units for vitamin as <math>\alpha</math>-TE and Table 5.1 gives approximate biological activity for natural isomers</p> <p>2006:</p> <p><math>\alpha</math>-tocopherol only; no equivalents given in Tables 7.1 and 7.2.</p>

## CANADA

### GENERAL COMMENTS

In response to the Request for Comments at Step 6 on the draft NRV-R for Vitamin E as indicated in CL 2016/19-NFSDU, July 2016, Canada appreciates the opportunity to provide the following input.

### SPECIFIC COMMENTS

Canada reiterates our support for establishing an NRV-R for vitamin E of 9 mg. This value is supported by two different modern scientific approaches.

The Nordic Council's INL<sub>98</sub> is derived based on two criteria used for establishing the average requirements and the recommended vitamin E intakes: 1) plasma concentration of  $\alpha$ -tocopherol and 2) the relationship to PUFA intake, expressed as the ratio of mg  $\alpha$ -tocopherol equivalents ( $\alpha$ -TE) per g of polyunsaturated fatty acids (PUFA). This approach led to the RI of vitamin E being set at 8 mg  $\alpha$ -TE/day for women and 10 mg  $\alpha$ -TE/day for men. Averaging between these two subpopulations leads to an NRV-R of 9 mg  $\alpha$ -TE/day.

The Nordic Council recognized that their recommendation differs from the IOM (2000) INL<sub>98</sub> recommendation of 15 mg. They state that the U.S. Institute of Medicine (recently renamed the Health and Medicine Division [HMD] of the National Academies of Sciences, Engineering, and Medicine) derived an estimated average requirement (EAR) for adults on vitamin E intakes sufficient to prevent hydrogen peroxide-induced haemolysis mainly based on a study on men by Horwitt (1963). However, the study diets contained high amounts of corn oil and estimates indicate that the proportion of linoleic acid was 11–12 E%, which is above the upper recommended range for PUFA in NNR 2012. Also, they questioned the bioavailability evidence. Using an observed absorption of 33%, the amount of dietary  $\alpha$ -tocopherol needed daily to replace irreversible losses would be about 15 mg/d, which seems to support the current recommended daily allowance for vitamin E

adopted by the US Institute of Medicine. However, absorption rates of 55–79% have been reported which, using the same approach, would lead to markedly lower estimates (6–9 mg/day).

Thus, the Nordic Council (2012) has come to a different conclusion from the IOM (2000) based on more recent and different evidence. This approach differs from the AI approach used by other RASBs.

EFSA very recently (2015) issued an opinion on the DRVs for vitamin E. The Panel concluded 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. Therefore, the Panel set Adequate Intakes (AIs) based on observed dietary intakes in healthy populations with no apparent  $\alpha$ -tocopherol deficiency. The Panel considered the approximate mid-points of the range of mean intakes for  $\alpha$ -tocopherol and for  $\alpha$ -TE and, after rounding, set an AI for  $\alpha$ -tocopherol at 13 mg/day for men and 11 mg/day for women.

Japan (NIHN) also rejected the evidence of Horwitt (1960) and instead used studies that simultaneously reported vitamin E intake and average serum  $\alpha$ -tocopherol levels to set AI values of 7.0 mg/day for men and 6.5 mg/day for women that are expected to yield blood  $\alpha$ -tocopherol levels exceeding 12  $\mu$ mol/L.

In 2005, Australia and New Zealand (NHMRC 2006) also provided a critique of the Horwitt evidence as the basis of the IOM RDA. NHMRC also used an AI rather than an EAR for vitamin E based on median population intakes in Australia and New Zealand – both healthy populations with no apparent vitamin E deficiency. The AI for men 19 to >70 y was set at 10 mg/day and for women 7 mg/day. The values set for men and women were the highest median intake for any respective adult age band.

WHO (2004) concluded that at present, data are not sufficient to formulate recommendations for vitamin E intake for different age groups except for infancy. Therefore, they did not set RNIs for vitamin E but their best estimates of requirements were 7.5 mg  $\alpha$ -TE/day for adult women and 10.0 mg  $\alpha$ -TE/day for adult males 19–65 y of age.

Thus, the AIs (or best estimates) for vitamin E in adult women and men from EFSA (11 and 13 mg  $\alpha$ -TE/day), Japan (6.5 and 7.0 mg  $\alpha$ -TE/day), Australia-New Zealand (7 and 10 mg  $\alpha$ -TE/day) and WHO (7.5 and 10 mg  $\alpha$ -TE/day), when averaged between males and females (12.0, 6.75, 8.5, and 8.75 mg  $\alpha$ -TE/day respectively) and then averaged across agencies, gives a value of 9 mg  $\alpha$ -TE/day. This is the same value as the Nordic INL<sub>98</sub> average between males and females, even though the two sets of values have very different derivations.

#### CHILE

For vitamin E, Chile supports 9 mg (pdd) AI with the following conversion factors:

- 1.10 mg RRR-  $\alpha$ -tocopheryl acetate
- 1.23 mg RRR-  $\alpha$ -tocopheryl succinate
- 2 mg all-rac-  $\alpha$ -tocopheryl acetate
- 2.46 mg-all-rac-  $\alpha$ -tocopheryl succinate

#### COLOMBIA

- A. Insert an entry for vitamin E in the second table of paragraph 3.4.4.1 of the Guidelines on Nutrition Labelling.
- B. Include  $\alpha$ -tocopherol as the active form of vitamin E occurring naturally in food, as indicated in section 4.3.
- C. Include the three common forms of vitamin E that are added to food, as shown in section 4.4.

#### COSTA RICA

Costa Rica supports the value proposed for vitamin E of 9 mg, which is based on INL<sub>98</sub> according to the Council of Ministers of Nordic countries.

With respect to the value proposed by IOM of 15 mg, this amount exceeds the vitamin E requirements set out in CX/NFSDU 15/37/4 of September 2015, and therefore Costa Rica does not support it, even though it is based on INL<sub>98</sub>.

Vitamin E dietary equivalents and conversion factors:

Costa Rica supports the proposal in CX/NFSDU 15/37/4.

Insert an entry for vitamin E in the second table of paragraph 3.4.4.1 of the Guidelines on Nutrition Labelling.

Include  $\alpha$ -tocopherol as the active form of vitamin E occurring naturally in food. Include the three common forms of vitamin E that are added to food, as supported by the majority of members of the 2015 eWG:

“Vitamin dietary equivalents, niacin etc. ... Vitamin E is present in natural forms in food 1 mg of  $\alpha$ -tocopherol = 1 mg of RRR- $\alpha$ -tocopherol (d- $\alpha$ -tocopherol) = Vitamin E added to food 1 mg of RRR- $\alpha$ -tocopherol = 1.10 mg of acetate of RRR- $\alpha$ -tocopheryl \*\* 1.23 mg of succinate of RRR- $\alpha$ -tocopheryl \*\* 2 mg of all-rac- $\alpha$ -tocopherol (dl- $\alpha$ -tocopherol)\*\*\*

\*\* Calculated using stoichiometry based on RRR- $\alpha$ -tocopherol \*\*\* Conversion factor for all of the all-rac- $\alpha$ -tocopherols based on the reduced activity in the RRR- $\alpha$ -tocopherol. It is therefore recommended that these forms all be added to the second chart in para. 3.4.4.1 of the Guidelines on Nutritional Labelling.”

### CUBA

Cuba agrees and does not have any further comments.

### DOMINICAN REPUBLIC

#### General comment on vitamin E

The term vitamin E includes a number of natural compounds with a similar biological activity. Of these, the most nutritionally important is  $\alpha$ -tocopherol because of its wide distribution and high activity. However, the content of gamma-tocopherol, another member of this group, in mixed diets is close to three times greater than alpha-tocopherol, as a result of which and even though it is less potent (1/10 the potency of alpha-tocopherol) it is considered to be an important dietary source of vitamin E.

In relation to the requirements and recommendations, we can say the following: The vitamin E requirement is determined primarily on the basis of the level of polyunsaturated fatty acids (PUFA)<sup>11</sup> of the tissues; as a result, it varies depending on the dietary content of these. For infants aged 6 to 12 months, the recommendation is 5 mg/day, which is increased as infants age until it reaches 10 mg and 8 mg for adult men and adult women, respectively. Daily amounts of this magnitude maintain blood plasma levels within the normal limits. Infants who are breastfed by a well-nourished mother receive optimal amounts of vitamin E, with colostrum providing three times more than mature breast milk.

Physiological requirements increase during pregnancy and breastfeeding, so an additional 2 mg and 3 mg/day, respectively, is recommended.

Vitamin E is highly compromised when it is absorbed because it is more hydrophobic. A vitamin E deficit causes sequential degenerative neuropathy, characterized by sinewy hyperreflexia, truncal ataxia, decreased proprioception and vibratory sensation, which can even be observed in infants under the age of 18 months. Values of less than 0.4 UI cause lipid peroxidation, which, if it is serious or prolonged, can affect vitamin A levels. In addition, such values are also related to abnormally weak red blood cells and muscle wasting as well as very low vitamin plasma levels.

Liver patients (who require special diets) with a confirmed deficit should be given 50-200 mg/day of tocopherol (liposoluble) and 15-25 mg/kg/day of succinate d-alpha tocopheryl polyethylene glycol (STPG hydrosoluble).

Following is a general chart of the requirements of the two liposoluble vitamins based on age and sex:

#### DAILY DIETARY RECOMMENDATIONS FOR LIPOSOLUBLE VITAMINS: D Y E<sup>a</sup>

AGE	D mcg	E Mg ET
<b>CHILDREN</b>		
<b>Months:</b>		
0-2.9	8	3
3-5.9	8	3
6-11.9	7	4
<b>Years:</b>		
1-2.9	7	5
3-6.9	<sup>b</sup>	6
7-9.9	--	7
<b>MEN</b>		
10-11.9	--	9
12-13.9	--	10
14-17.9	--	10
18-64.9	--	10
65+	10	8

WOMEN			
10-11.9		b	8
12-13.9		--	8
14-17.9		--	8
18-64.9		--	8
65+		10	6
ADDITIONAL QUANTITIES DURING:			
PREGNANCY		b	2
BREASTFEEDING		5	3

b) From 4 to 64 years: 5 mg of vitamin D/day solely from the sun is not sufficient for individuals and groups at risk of vitamin D deficiency.

PUFA: Polyunsaturated fatty acids (internationally recognised English acronym).

## Conclusion

The Dominican Republic supports the VRN-N for vitamin E proposed in procedure 6.

### EUROPEAN UNION

The European Union (EU) maintains its position expressed in 2015 that the EU would opt for the NRV that has been most recently suggested by the RASBs and would therefore support a value of 12 mg for Vitamin E.

### GHANA

Ghana supports the establishment of NRV-R for Vitamin E at 9mg.

### NEW ZEALAND

New Zealand appreciates the opportunity to contribute to the work on the nutrient reference values (NRV-R) for labelling purposes in the Guidelines on Nutrition Labelling. New Zealand notes that the discussion on the draft NRV-R for vitamin E was retained at Step 5/8 by CAC39 while the conversion factors and dietary equivalents were returned to Step 3 for comments; and that these issues should be considered together prior to adopting the NRV-R for vitamin E. As such New Zealand has provided comment on both the NRV-R and associated dietary equivalents and conversion factors for vitamin E.

## NRV-R Vitamin E

New Zealand continues to support the recommendation to retain an NRV-R of 9 mg for vitamin E. This approach was agreed to by the Committee at CCFSDU37 (REP16/NFSDU, Para 22) and the subsequent decisions regarding dietary equivalents and conversion factors do not alter this recommendation.

As evidenced in the documentation of physiological endpoints provided by the Chair of the eWG there is considerable uncertainty in the establishment of a DIRV for vitamin E from almost all RASBs. Due to the level of uncertainty in establishing a DIRV for vitamin E, New Zealand is supportive of maintaining the WHO/FAO<sup>1</sup> as a primary source to establish an NRV-R for vitamin E in line with the General Principles. The WHO/FAO value is based on the average dietary intakes of population median intakes in countries where vitamin E deficiency is not apparent and could be rounded to 9 mg  $\alpha$ -tocopherol for labelling purposes<sup>1</sup>.

The most recent review of evidence on establishing an NRV-R for vitamin E was conducted by EFSA in 2015<sup>2</sup>. The conclusions of this review were that there was insufficient evidence to derive an individual nutrient level (INL98) for vitamin E based on currently available evidence. As such, EFSA recommended an adequate intake was determined based on the observed average intakes of healthy populations with no apparent  $\alpha$ -tocopherol deficiency in the European Union<sup>2</sup>.

It is also recognised that averaging the DIRVs based on dietary intakes WHO/FAO<sup>1</sup>, EFSA<sup>2</sup>, NHMRC/MOH<sup>3</sup>, NIH<sup>4</sup> would result in a NRV-R of 9 mg. New Zealand notes as there is no new evidence to deviate from the WHO/FAO<sup>1</sup> value this should be referred to in the Source of NRVs table in line with GP 3.1.1

## Vitamin E Dietary Equivalents and Conversion Factors

New Zealand supports the recommendations of the 2015 electronic working group (14 A and B) – to include an entry for vitamin E in the second table to paragraph 3.4.4.1 and to list this as  $\alpha$ -tocopherol only.

As discussed at the Committee, and explained in the 2015 Agenda paper (CX/NFSDU 15/37/4), the results of the review of both IOM<sup>4</sup> and EFSA<sup>2</sup> concluded that vitamin E consists of only  $\alpha$ -tocopherol. Based on evidence that only the naturally occurring RRR- $\alpha$ -tocopherol is the physiologically active vitamer, and of the chemically synthesised only the 2RR forms have been shown to meet human nutrient requirements. Blood  $\alpha$ -tocopherol concentrations are maintained by the preferential binding of  $\alpha$ -tocopherol, other forms (i.e.  $\gamma$ - tocopherols or

tocotrienols) are poorly recognised and as such only  $\alpha$ -tocopherol is considered to contribute to the dietary essentiality of vitamin E. It is also noteworthy that the Representative of WHO explained that the 2006 FAO/WHO<sup>5</sup> publication identified  $\alpha$ -tocopherol as the only isomer with vitamin E activity (REP16/NFSDU, para 42).

New Zealand supports the recommendations of the 2015 eWG based on the most recent reviews of recognised authoritative scientific bodies (FAO/WHO<sup>5</sup>; EFSA<sup>2</sup>; IOM<sup>4</sup>) that vitamin E is listed as  $\alpha$ -tocopherol only, with no units of equivalence provided.

### Specification of Different Forms of Vitamin E

As agreed by the Committee, it was agreed to delete reference to different forms of vitamin E (REP16/NFSDU, para 43). Inclusion of molar weight conversion factors of individual fortificants is not considered necessary and is inconsistent with the listing of other nutrients. This approach is consistent with the conclusions of the Committee regarding vitamin A: *the Committee was agreed to delete reference to chemical forms of Vitamin A added to food as it was not necessary to include molecular calculations* (REP16/NFSDU, Para 39).

### References

1. WHO/FAO. Vitamin and mineral requirements in human nutrition: Report of a joint FAO/WHO expert consultation, Bangkok, Thailand, 21-30 September 1998. . 2004; World Health Organisation and Food and Agriculture Organization of the United Nations.
2. EFSA (European Food Safety Authority). Scientific opinion on dietary reference values for vitamin E as  $\alpha$ -tocopherol. *EFSA Journal*. 2015;13(7):4149.
3. National Health and Medical Research Council (AU). Nutrient reference values for Australia and New Zealand including recommended dietary intakes. 2006. <http://www.nhmrc.gov.au/publications/synopses/n35syn.htm>.
4. IOM (Institute of Medicine). *Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids*. Washington DC, USA: National Academies Press; 2000.
5. World Health Organization, Food and Agriculture Organization. *Guidelines on food fortification with micronutrients*. First ed. Geneva, Switzerland: World Health Organization; 2006.

### PARAGUAY

We propose a value of 10 for vitamin E (mg), as this is the value used in the country in line with regional standards, which has been applied without any adverse effects to date. Likewise, we agree with the statement by the WHO based on the information published by the FAO/WHO in 2006 that identified  $\alpha$ -tocopherol as the sole isomer that demonstrated the activity of vitamin E.

### PHILIPPINES

The Philippines supports the proposed Nutrient Reference Value for Vitamin E (9 mg). This recommendation was also based on the average Acceptable Intakes from a number of Recognized Authoritative Scientific Bodies (RASBs).

Though we are in agreement with the conversion factors on Vitamin Dietary equivalents for Vitamin E 1 mg  $\alpha$ -tocopherol = 1 mg RRR- $\alpha$ -tocopherol (d- $\alpha$ -tocopherol), we are of the opinion that all forms of Vitamin E isomers as listed by the FAO/WHO(2004) publication should be considered as active forms of Vitamin E.

### RATIONALE

The argument of global harmonization of nutrient-based dietary guidelines is based on the premise that the physiologic requirements are expected to be similar across healthy population groups. However, nutrient requirements are known to be affected by other factors such as genetic heterogeneity, usual diet composition, lifestyle, etc. (WHO/FAO 2004). Our support for the proposed value of Vitamin Estems from the fact that this value is similar if not closely similar with the Philippine recommended nutrient intakes for these nutrients. This recommendation was also based on the average Acceptable Intakes from a number of Recognized Authoritative Scientific Bodies (RASBs).

However, we support inclusion of all forms of Vitamin E isomers as listed by the FAO/WHO (2004) publication, as the active forms of Vitamin E since these isomers also exhibited Vitamin E activity in addition to other important biological activities. These isomers are present in a number of foods making them available in the daily diet. The eight forms of Vitamin E are all absorbed by humans but their degradation and retention time in the body varies which impact on their relative biopotency. Though alpha tocopherol is preferentially accumulated in the cellular membranes of tissues, other Vitamin E isomers are rapidly metabolized. (Raedrostoff et al, 2015)



The major role of vitamin E is to protect polyunsaturated fatty acids (PUFA) from oxidation (NHMRC, 2014). The embryogenesis problems have been related to the protective effects of vitamin E against damage to polyunsaturated fatty acids (PUFA) in cell membranes thereby confirming its role as an essential nutrient. The presence of vitamin E is of key importance in cellular membranes rich in highly unsaturated fatty acids such as DHA & arachidonic acid (AA), which are found in high concentrations in the brain, and the retina (Raederstorff et al, 2015). Thus, it becomes imperative to consider the association of vitamin E and PUFA, in the establishment of NRV. Otherwise, if we just focus on individual nutrient without taking into consideration the nutrient interplay, this could result to the brokenness of intervention approaches used in human nutrition science.

### UNITED STATES OF AMERICA

#### General Comments

The United States supports the Committee's recommendation of 9 mg as the NRV-R for Vitamin E. The United States suggests that the NRV-R be based on Adequate Intakes (AIs) of Vitamin E that have been associated with no apparent Vitamin E deficiency. AIs are preferred in this case as the INL98s may overestimate Vitamin E requirements (IOM) or its derivation is unclear (Nordic Council).

The majority of AIs from RASBs (EFSA 2015, NIH 2013, WHO/FAO 2006) report estimated dietary intake of Vitamin E as mg  $\alpha$ -tocopherol. As the amount of  $\alpha$ -tocopherol may differ when calculated by  $\alpha$ -tocopherol equivalents, the United States prefers that AIs that use  $\alpha$ -tocopherol be used as the basis for the NRV-R; however, we would not object to the inclusion of AIs that use  $\alpha$ -tocopherol equivalents.

#### Proposed NRV-R

Average of AIs from EFSA, NIH, WHO/FAO  $(12 + 6.8 + 8.8)/3 = 9.2$  rounded to 9.

### CEFIC - European Chemical Industry Council

In response to the CODEX CNSFDU call for data 2016/19, Cefic supports a Nutrient Reference Level (NRV)  $\geq 12$  mg/day for  $\alpha$  tocopherol, on the basis of the EFSA Scientific Opinion on vitamin E Dietary Reference Values (DRV) taking into account recent scientific studies.

The Cefic appreciates the work carried out by the Codex in reviewing the Nutrient Reference Values (NRV) for vitamin E. When defining the value, it is important to consider all scientific evidence: this should include recent research already accepted by well recognised agencies, such as the Institute of Medicine in the US and the D-A-CH report for Germany, Austria and Switzerland.

Vitamin E is a powerful antioxidant and carries an approved EFSA health claim for 'contributing to the protection of cells from oxidative stress (1). Emerging data also suggest that vitamin E in higher doses holds promise beyond these recognized benefits of vitamin E as an essential nutrient. For selected individuals and population groups, vitamin E is understood to reduce the risk of Alzheimer's disease (2) and to limit the negative health implications of fatty liver (3) and air pollution (4,5).

Several scientific studies suggest that an optimal blood concentration of vitamin E (plasma concentration of at least 30  $\mu\text{mol/L}$ ) is associated with several benefits in healthy populations:

- Outcomes from the main epidemiological studies show a risk reduction of 24% for cardiovascular events, when comparing high versus low vitamin E concentrations.
- Other studies highlight beneficial effect on cancer prevention (6)

A NRV  $\geq 12$  mg/day (based on an average of EFSA average intake of 13 mg/day for men and 11 mg/day for women) would secure an optimal blood concentration of vitamin E for the general population. (7)

Low intake of vitamin E is linked to negative health effects such as higher rate of miscarriage (8) as well as asthma and allergies in children.

The recommended daily intake of vitamin E varies according to the age, gender and criteria applied in individual countries. For example, the German-speaking countries (D-A-CH, 2013) have recently set the recommendation at 12-15mg  $\alpha$ -TE/day for men and 11-12 mg  $\alpha$ -TE/day for women according to age. Additionally for pregnant and lactating women 13 and 17 mg/day  $\alpha$ -TE/day are recommended by D-A-C-H (2013).

For all the above reasons, Cefic believes that currently available scientific evidence strongly supports a NRV  $\geq 12$ mg/day, whilst being aware of the need for more scientific studies to fully uncover positive human health effects of vitamin E.

(1) <http://www.efsa.europa.eu/en/efsajournal/pub/1816.htm>

- (2) M. Dyksen et al, 'Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease,' *Journal of the American Medical Association*, Vol 311, No 1 (2014)
- (3) Sanyal A. J. et al. 'Pioglitazone, vitamin E, or placebo for non-alcoholic steatohepatitis.' *N Engl J Med*. 2010; 362(18):1675–1685
- (4) Hueylen Sue et al, 'Effect of Vitamin C and E intake on peak respiratory flow rate of asthmatic children exposed to atmospheric particulate matter,' *Arch Environ Occup H* 2013;68:80
- (5) Zhang, W. et al. Nutrition solutions to counter health impact of air pollution: scientific evidence of marine omega-3 fatty acids and vitamins minimizing some harms of PM2.5. (2015) *J Food Nutr Sci* 2(2): 1-6
- (6) For all the studies, see Zhang, W. et al. Nutrition solutions to counter health impact of air pollution: scientific evidence of marine omega-3 fatty acids and vitamins minimizing some harms of PM2.5. (2015) *J Food Nutr Sci* 2(2): 1-6; Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. *Am J Clin Nutr*. 1991;53:326s-34s; Gey KF. Prospects for the prevention of free radical disease, regarding cancer and cardiovascular disease. *Br Med Bull*. 1993;49:679-99; Knekt P, Ritz J, Pereira MA, O'Reilly EJ, Augustsson K, Fraser GE, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr*. 2004;80:1508-20; Biesalski HK, Bohles H, Esterbauer H, Furst P, Gey F, Hundsdorfer G, et al. Antioxidant vitamins in prevention. *Clin Nutr*. 1997;16:151-5 ; Gey KF. Cardiovascular disease and vitamins. Concurrent correction of 'suboptimal' plasma antioxidant levels may, as important part of 'optimal' nutrition, help to prevent early stages of cardiovascular disease and cancer, respectively. *Bibl Nutr Dieta*. 1995:75-91
- (7) Szabolcs Péter, Ulrich Moser, Stefan Pilz, Manfred Eggersdorfer and Peter Weber. The Challenge of setting appropriate intake recommendations for vitamin E: Considerations on status and functionality to define nutrient requirements. (2013), *International Journal for Vitamin and Nutrition Research*. 83 (2), pp. 129-136.
- (8) Shamim AA, Schulze K, Merrill RD, Kabir A, Christian P, Shaikh S, et al. First-trimester plasma tocopherols are associated with risk of miscarriage in rural Bangladesh. *Am J Clin Nutr*. 2015;101:294-301

### **CRN – Council for Responsible Nutrition**

#### **Previous CRN Comments – Written, March, 2015**

CRN respectfully submitted comments to the chair of the electronic Working Group (eWG) regarding a series of questions, several of which related specifically to an appropriate NRV-R value for Vitamin E, the units for labelling, isomers and conversion factors (See Appendix 1, Questions 1, 2, 4, 7, 8A, and 8B and CRN Responses). Our recommendation was to use the U.S. Institute of Medicine (IOM, now identified as the National Academies of Sciences, Engineering, and Medicine) value of 15 mg/day.

#### **Previous CRN Comments – Oral, June, 2016**

At the Codex Alimentarius Commission (CAC) meeting in Rome during the week of June 27-July 1, 2016, CRN and another NGO and two Countries (Malaysia, Indonesia, National Health Federation (NHF) and Council for Responsible Nutrition (CRN) See Appendix 2, paragraph 39 and 40) argued for higher levels of Vitamin E, at a minimum of 12 – 15 mg/day, and recommended that this NRV-R proposal be returned to the CCNFSDU at Step 3 (in need of further discussion at the Committee level), instead of the CCNFSDU Chair request for the CAC to adopt this at Step 5/8 (final). The NGOs, NHF and CRN stressed the fact that the proposed level of 9 mg/day is too low for the general population. As a compromise, the CAC chair recommended and it was approved by the delegations to return this NRV-R to Step 5, which does revert this issue back to CCNFSDU for further discussion. CRNs oral comments to the Codex CAC assembly are below and in Appendix 3 with references.

The Council for Responsible Nutrition (CRN) representing US and multinational dietary supplement and nutritional products manufacturers offers the following science-based comments:

We are concerned that Vitamin E values are not where they need to be. The 2015 Dietary Guidelines for Americans report established vitamin E as a shortfall nutrient.

According to the National Health and Nutrition Examination Survey data, as many as 93% of Americans fall short on this essential nutrient when it comes to intake from diet alone.

Using multivitamins has helped decrease that figure, “but it’s definitely a nutrient the American population is not getting enough of.”

Research out of Oregon State University’s Linus Pauling Institute outlined some recent findings—most notably, vitamin E’s significance during fetal development and throughout the first years of life, the correlation between adequate intake and dementia later in life, and the difficulty of evaluating vitamin E adequacy through blood level measurements alone.

The review of multiple studies, published in *Advances in Nutrition* revealed that inadequate vitamin E is associated with increased infection, anemia, stunting of growth, and poor outcomes during pregnancy for both infant and mother, and neurological disorders and muscle deterioration in children with an overt deficiency.

On the other hand, increased vitamin E concentrations at birth were associated with improved cognitive function by age two. The nutrient was also found to possibly slow Alzheimer's progression, increase cognitive function, and even reduce risk of dementia

The University of Maryland Medical Center states that "Many population studies have found that people with higher levels of Vitamin E in their bodies have a lower risk of heart disease."

### **A Systematic Review of Global Alpha-Tocopherol Status – United States**

A systematic review published this year (Peter, et al., 2016<sup>5</sup>) considered 179 scientific articles referring to 132 single studies on  $\alpha$ -tocopherol status. When they applied the current U.S. Recommended Daily Allowance (RDA) of 15 mg/day and an Estimated Average Requirement (EAR) of 12 mg/day to all populations with a minimum age of 14 years, they reported that 82% of the population was below the RDA and 61% of the population was below the EAR. When examining serum concentrations, they reported that 13% of the data points were below the functional deficiency threshold concentration of 12  $\mu\text{mol/L}$ , primarily observed in children and newborns. Several prospective observational studies recommend that a serum  $\alpha$ -tocopherol concentration of  $\geq 30 \mu\text{mol/L}$  is beneficial, and globally, only 21% of all study populations reached this threshold.

Another analysis by McBurney et al. (2015<sup>6</sup>) discerned a similar pattern of inadequacy. Analyzing the U.S. National Health and Nutrition Examination Survey (NHANES) serum  $\alpha$ -tocopherol concentrations, they report that U.S. consumers of food alone (without dietary supplements) and food with dietary supplements, average serum  $\alpha$ -tocopherol levels were  $2.9 \pm 0.2 \mu\text{mol/L}$  and  $33.7 \pm 0.3 \mu\text{mol/L}$ , respectively. Using a criterion of 30  $\mu\text{mol/L}$  as nutritionally adequate, they further report that 87% of 20-30 year olds and 43% of 51+year olds had inadequate vitamin E status ( $p < 0.1$ ). The prevalence of inadequate vitamin E levels is significantly higher among food only (i.e., non-dietary supplement users).

### **Vitamin E Status – South Korea**

South Korean adults living in Seoul, self-reporting as being in "good health", with "no known diseases" and having a "good diet" participated in a study consisting of three consecutive 24 hour diet recalls and fasting blood samples.  $\alpha$ -,  $\beta$ -,  $\delta$ -, and  $\gamma$ -tocopherol intakes and plasma concentrations were analyzed. Twenty three percent of the subjects had plasma  $\alpha$ -tocopherol concentrations  $< 12 \mu\text{mol/L}$  indicating a biochemical deficiency of Vitamin E, even though the dietary vitamin E intake (from food alone) was  $17.68 \pm 14.34 \text{ mg } \alpha\text{-TE/day}$  and (food + supplement) was  $19.55 \pm 15.78 \text{ mg } \alpha\text{-TE/day}$ . The authors conclude that the "consumption of vitamin E-rich food sources by some adult South Koreans should be encouraged."<sup>7</sup>

### **Vitamin E Status – Bangladesh**

A case-cohort study of 1605 pregnant Bangladeshi women in a placebo-controlled intervention study demonstrated that a low plasma  $\alpha$ -tocopherol concentration was associated with an odds ratio (OR) of 1.83 (95% CI: 1.04, 3.20) for miscarriage, confirming the hypothesis that maternal vitamin E status in the first trimester may influence the risk of early pregnancy loss. Further 72.3% of the women (1161 of 1605) had vitamin E deficiency as evidenced by a plasma  $\alpha$ -tocopherol concentration less than 12.0  $\mu\text{mol/L}$ . When stratified by  $\alpha$ -tocopherol status, 5.2% of women with adequate  $\alpha$ -tocopherol levels miscarried compared to 10.2% of women with  $\alpha$ -tocopherol levels of  $< 12.0 \mu\text{mol/L}$  (unadjusted OR (95% CI) of 2.07 (1.31, 3.28;  $P = 0.002$ ). The authors conclude that their "findings showed an association between adequate  $\alpha$ -tocopherol nutrition and reduced risk of miscarriage in human populations."<sup>8</sup>

### **Vitamin E Status – Metabolic Syndrome**

A randomized cross-over double-blind study was conducted on health and individuals with metabolic syndrome. Compared to healthy participants, those with metabolic syndrome had lower ( $P < 0.05$ ) baseline

<sup>5</sup> Peter S, Friedel A, Roos FE, Wyss A, Eggersdorfer M, Hoffmann K, Weber P. (2016). A Systematic Review of Global Alpha-Tocopherol Status as Assessed by Nutritional Intake Levels and Blood Serum Concentrations. *Int J Vitam Nutr Res*:1-21.

<sup>6</sup> McBurney MI, Yu EA, Ciappio ED, Bird JK, Eggersdorfer M, Mehta S. (2015) Suboptimal Serum  $\alpha$ -Tocopherol Concentrations Observed among Younger Adults and Those Depending Exclusively upon Food Sources, NHANES 2003-2006. *PLoS One*;10(8):e0135510. doi: 10.1371/journal.pone.0135510. eCollection 2015.

<sup>7</sup> Kim, Y-N and Cho, Y-O (2015). Vitamin E status of 20- to 59-year-old adults living in the Seoul metropolitan area of South Korea. *Nutrition Research and Practice*; 9(2):192-198.

<sup>8</sup> Shamim, AA, Schulze, K, Merrill, RD, et al. (2014). First trimester plasma tocopherols are associated with risk of miscarriage in rural Bangladesh. *Am J Clin Nutr* doi: 10.3945/ajcn.114.094920.

plasma  $\alpha$ -tocopherol and lower estimated radiolabeled  $\alpha$ -tocopherol absorption. The authors concluded that “At dietary intakes equivalent to the Recommended Daily Allowance,  $\alpha$ -tocopherol bioavailability is unaffected by dairy fat, but is lower in metabolic syndrome afflicted adults, likely due to greater inflammation and oxidative stress that limits small intestinal  $\alpha$ -tocopherol absorption and/or impairs hepatic  $\alpha$ -tocopherol trafficking. These findings support higher dietary  $\alpha$ -tocopherol requirements for patients with metabolic syndrome.”<sup>9</sup>

## Conclusion

In response to the Codex CCNFSDU call for data CL 2016/19-NFSDU<sup>10</sup>, CRN supports a Nutrient Reference Level-Requirement (NRV-R) of greater than or equal ( $\geq$ ) 12 mg/day for  $\alpha$ -tocopherol, on the basis of the IOM<sup>11</sup> recommendations as well as EFSA<sup>12</sup> Scientific Opinion on vitamin E Dietary Reference Values (DRV) taking into account recent scientific studies<sup>13</sup>. A NRV  $\geq$  12 mg/day (based on an average of the EFSA average intakes of 13 mg/day for men and 11 mg/day for women) would secure an adequate blood concentration of vitamin E for the general population.

Low intake of vitamin E is linked to negative health effects such as higher risks for non-communicable diseases (NCDs), a risk for higher rate of miscarriage as well as asthma and allergies in the offspring.

The recommended daily intake of vitamin E varies according to the age, gender and criteria applied in individual countries. For example, in the U.S. the EAR<sup>14</sup> is set for 12 mg  $\alpha$ -tocopherol per person per day, the German-speaking countries (D-A-CH, 2013<sup>15</sup>) have recently set the recommendation at 12-15 mg  $\alpha$ -tocopherol equivalents/day for men and 11-12 mg  $\alpha$ -tocopherol equivalents/day for women according to age. Additionally for pregnant and lactating women 13 and 17 mg/day  $\alpha$ -tocopherol equivalents/day are recommended by D-A-C-H (2013).

For all the above reasons, CRN believes that currently available scientific evidence supports a NRV-R  $\geq$  12mg vitamin E/day, whilst being aware of the need for more scientific studies to fully uncover positive human health effects of vitamin E.

Should the eWG have further questions that CRN and CRN Members could address, please do not hesitate contacting me at your earliest convenience.

## Appendix 1

In response to fourteen questions posed by the eWG; CRN and CRN Members have the following comments.

<p><b>Q1</b></p>	<p><b>Candidate DIRVs for NRVs-R</b></p> <p>For each vitamin and mineral under consideration (subsections B3.1–3.8), which of these options do you prefer as the most suitable basis for the NRVs-R and why?</p> <p>a) one or more candidate DIRV(s) including from WHO/FAO;</p> <p>b) the current NRV-R;</p>	<p>CRN and CRN Members support Option a).</p> <p>Regarding the vitamins under consideration we support the following candidate DIRVs:</p> <p><i>Vitamin A:</i> IOM value of 800 (RAE) as suitable basis for the NRV-R as it represents of a more heterogeneous population.</p> <p><i>Vitamin D:</i> IOM value of 15 <math>\mu</math>g as said above, because IOM represents a more heterogeneous population.</p> <p><i>Vitamin E:</i> IOM value of 15 mg <math>\alpha</math>-toc as said above, because IOM represents a more heterogeneous population. However</p>
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<sup>9</sup> Mah E, Sapper TN, Chitchumroonchokchai C, Failla ML, Schill KE, Clinton SK, Bobe G, Traber MG, Bruno RS. (2015)  $\alpha$ -Tocopherol bioavailability is lower in adults with metabolic syndrome regardless of dairy fat co-ingestion: a randomized, double-blind, crossover trial. *Am J Clin Nutr.*; 102(5):1070-80. doi: 10.3945/ajcn.115.118570.

<sup>10</sup> [http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202016-19%252Fcl16\\_19e.pdf](http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202016-19%252Fcl16_19e.pdf). Request for Comments at Step 6 on the Draft NRV-R for Vitamin E.

<sup>11</sup> U.S. Institute of Medicine (IOM, now identified as the National Academies of Sciences, Engineering, and Medicine).

<sup>12</sup> European Food Safety Authority.

<sup>13</sup> [HTTPS://WWW.EFSA.EUROPA.EU/EN/EFSAJOURNAL/PUB/4149](https://www.efsa.europa.eu/en/efsa-journal/pub/4149); SCIENTIFIC OPINION ON DIETARY REFERENCE VALUES FOR VITAMIN E AS A-TOCOPHEROL.

<sup>14</sup> Estimated Average Requirement (EAR): The average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group. <https://fnic.nal.usda.gov/interactive-dri-glossary>.

<sup>15</sup> <http://www.sge-ssn.ch/grundlagen/lebensmittel-und-naehrstoffe/naehrstoffempfehlungen/dachreferenzwerte/>; the DACH reference values for nutrient intake are published jointly by the German, Austrian and Swiss societies for nutrition. The abbreviation DACH is derived from the usual country code for Germany (d), Austria (a) and Switzerland (ch). The overarching term "reference values for nutrient intake" has been chosen to use the name recommendation unequivocally for the recommended intake of a particular nutrient can. Reference values include recommendations accordingly, estimates and indicative.

	c) no NRV-R to be established.	the suggested values from WHO/FAO which use $\alpha$ -tocopherol equivalents ( $\alpha$ -TE) should be used for clarity.
<b>Q2</b>	<b>Vitamin A, D, E, Magnesium, Phosphorus, Copper</b> Which unit ( $\mu$ g or mg) do you consider to be more appropriate for labelling purposes?	CRN and CRN Members support the use of mg or mcg as appropriate, such as mg for Vitamin E and mcg for Vitamin A and D.
<b>Q4</b>	<b>Vitamin units of equivalents</b> Should the selection of candidate DIRV(s) for vitamin A (and vitamin E if expressed as $\alpha$ -TE) also determine the details of the respective vitamin equivalents – name, natural vitamin isomers, conversion factors – or should such details be determined independently? Please give your reasons.”	CRN and CRN Members support that the details of vitamin equivalents (isomers and conversion factors) should be clarified independently from the candidate DIRV; it should be pointed out that the clarification of these values is also important for consumers understanding and would further facilitate international trade.
<b>Q7</b>	<b>Vitamin E isomers naturally occurring in food</b> If your answer to Q4 supported independent selection of vitamin E units, which set of details for vitamin E units in Table 5 or 6 do you support and why?	CRN and CRN Members support the vitamin E conversion factors from natural occurring forms stated by the WHO/FAO 2004 document (Table 5). Since different forms of vitamin E occur naturally in food, the use of the mentioned conversion factors is important in correct assessment of Vitamin E intake as alpha-tocopherol equivalents.
<b>Q8A</b>	<b>Vitamin E isomers added to food and used in supplements</b> a) Which, if any, of these isomers and conversion factors for vitamin E do you support and why?	CRN and CRN Members support the use of alpha tocopherol equivalents as stated in WHO/FAO 2004 (Table 5). The following conversion factors submitted by various members of the working group shall also be considered: 1.10 mg RRR- $\alpha$ -tocopheryl acetate 1.23 mg RRR- $\alpha$ -tocopheryl succinate 1.35 OR 2.00 mg all-rac- $\alpha$ -tocopherol (dl- $\alpha$ -tocopherol) 1.49 OR 2.22 mg all-rac- $\alpha$ -tocopheryl acetate 2.44 mg all-rac- $\alpha$ -tocopheryl succinate
<b>Q8B</b>	<b>Vitamin E isomers added to food and used in supplements</b> b) Do you wish to nominate other isomers and their similarly derived conversion factors?	CRN and CRN Members support the use of alpha tocopherol equivalents as stated in WHO/FAO 2004 (Table 5). The following conversion factors submitted by various members of the working group shall also be considered: 1.10 mg RRR- $\alpha$ -tocopheryl acetate 1.23 mg RRR- $\alpha$ -tocopheryl succinate 1.35 OR 2.00 mg all-rac- $\alpha$ -tocopherol (dl- $\alpha$ -tocopherol) 1.49 OR 2.22 mg all-rac- $\alpha$ -tocopheryl acetate 2.44 mg all-rac- $\alpha$ -tocopheryl succinate

## Appendix 2

[http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-701-39%252FREPORT%252FREP16\\_CACe.pdf](http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-701-39%252FREPORT%252FREP16_CACe.pdf)

## Appendix 3

### Previous CRN Comments – Oral, June, 2016

Thank you madam Chair. The Council for Responsible Nutrition (CRN) representing US and multinational dietary supplement and nutritional products manufacturers offers the following science-based comments:

We are concerned that Vitamin E values are not where they need to be. The 2015 Dietary Guidelines for Americans report established vitamin E as a shortfall nutrient<sup>16</sup>.

According to the National Health and Nutrition Examination Survey data, as many as 93% of Americans fall short on this essential nutrient when it comes to intake from diet alone<sup>17</sup>.

Using multivitamins has helped decrease that figure, “but it’s definitely a nutrient the American population is not getting enough of.”

Research out of Oregon State University’s Linus Pauling Institute outlined some recent findings—most notably, vitamin E’s significance during fetal development and throughout the first years of life, the correlation between adequate intake and dementia later in life, and the difficulty of evaluating vitamin E adequacy through blood level measurements alone<sup>18</sup>.

The review of multiple studies, published in *Advances in Nutrition* revealed that inadequate vitamin E is associated with increased infection, anemia, stunting of growth, and poor outcomes during pregnancy for both infant and mother, and neurological disorders and muscle deterioration in children with an overt deficiency<sup>4</sup>.

On the other hand, increased vitamin E concentrations at birth were associated with improved cognitive function by age two. The nutrient was also found to possibly slow Alzheimer’s progression, increase cognitive function, and even reduce risk of dementia<sup>4</sup>.

The University of Maryland Medical Center states that “Many population studies have found that people with higher levels of Vitamin E in their bodies have a lower risk of heart disease.<sup>19</sup>”

### ELC - Federation of European Specialty Food Ingredients Industries

During the last CCNSFDU session, the Committee agreed to postpone the discussion on the conversion factors and dietary equivalents for vitamin E isomers. While noting the proposals by some delegates to increase the draft NRV-R value to either 12 mg or 15 mg, the final decision was to adopt an NRV-R value of 9 mg.

ELC is of the view that a value of 9 mg/day is too low and we support a value of 12 mg/day based on the current state of scientific evidence, which is consistent with the conclusions of the final EFSA opinion<sup>20</sup> from 2015 (!)

<sup>16</sup> **What are current consumption patterns of nutrients from foods and beverages by the U.S. population? Source of evidence:** Data analysis. **Conclusion:** Nutrient intake data from a representative sample of the U.S. population ages 2 years and older indicate that: vitamin A, vitamin D, **vitamin E**, folate, vitamin C, calcium, and magnesium are **underconsumed** relative to the EAR. **Implications:** A dietary pattern emphasizing a variety of nutrient-dense foods will help shift individual and population consumption toward recommended intake levels for nutrients of public health concern. The U.S. population should increase consumption of foods rich in vitamin A, vitamin D, **vitamin E**, folate, vitamin C, calcium, and magnesium (**Emphasis added**). <https://health.gov/dietaryguidelines/2015-scientific-report/06-chapter-1/d1-2.asp> ; <https://health.gov/dietaryguidelines/2015-scientific-report/>.

<sup>17</sup> Maras JE, Bermudez OI, Qiao N, Bakun PJ, Boody-Alter EL, Tucker KL. (2004) Intake of alpha-tocopherol is limited among US adults. *J Am Diet Assoc.* 104(4):567-75. RESULTS: Only 8.0% of men and 2.4% of women in the United States met the new EARs for vitamin E intake from foods alone. Regionally, only 5.8% of men and 2.1% of women in the South met these EARs, relative to 9.0% and 2.6%, respectively, in the Northeast. Top contributors of alpha-tocopherol for men and women included ready-to-eat cereal, sweet baked products, white bread, beef, oils, and salad dressing. APPLICATIONS/CONCLUSIONS: **The majority of men and women in the United States fail to meet the current recommendations for vitamin E intake.** Many of the top contributors are not particularly high sources of alpha-tocopherol but are consumed frequently. Greater inclusion of sources such as nuts, seeds, and vitamin E-rich oils, could improve intake of alpha-tocopherol. (**Emphasis added**).

<sup>18</sup> Traber MG. Vitamin E. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. (2014) *Modern Nutrition in Health and Disease*. 11<sup>th</sup> ed. Philadelphia: Lippincott Williams & Wilkins; 293-304. Traber MG. (2014). Vitamin E inadequacy in humans: causes and consequences. *Adv Nutr.*; 5(5):503-14.

<sup>19</sup> <http://umm.edu/health/medical/altmed/supplement/vitamin-e>

<sup>20</sup> 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

(Adequate intake of 13 mg/d for men and 11 mg/d for women) and with the value defined in the EU Regulation 1169/2011 on food information to consumers. The role of Vitamin E is key to protect cells from oxidative stress and in particular to protect the long-chain poly-unsaturated fatty acids.

With regards to conversion factors and dietary equivalence, there is growing evidence of the biological role and importance of the different isomers of vitamin E. Thus, it is important to take them duly into consideration. ELC therefore supports conversion factors based on stoichiometry as showed below:

1 mg RRR- $\alpha$  tocopherol activity is equivalent to (or provided by):

- 1.10 mg RRR- $\alpha$  tocopherol acetate
- 1.23 mg RRR- $\alpha$  tocopherol succinate
- 2 mg all-rac- $\alpha$  tocopherol
- 2.2 mg all-rac- $\alpha$  tocopherol acetate
- 2.46 mg all-rac- $\alpha$  tocopherol succinate

**In conclusion, ELC supports a value of 12 mg/d with the conversion factors for the different isomers based on stoichiometry.**

#### IFT - Institute of Food Technologists

##### (ii) Specific comments:

IFT supports the amount of 9 mg of RRR-alpha tocopherol for the NRV-R.

IFT believes that because the value relates to requirements, considerations should be given to those isomers that meet *essential* nutrient needs, where essential means preventing mortality. The term “tocopherol,” which was coined by Dr. Herbert Evans, one of the vitamin’s discoverers, is derived from the Greek *tokos*= childbirth and *pherein*= to bear, as this nutrient prevented the embryonic death and degeneration of rat pups in pregnant dams<sup>1</sup>. Early studies with the rat-pup reabsorption assay found that food extracts containing predominantly other, non-alpha, tocopherol isomers had some activity. However, these extracts were not characterized by modern sensitive analytical techniques, leaving open the very real possibility of trace amounts of alpha-tocopherol in the extracts.

More recent evidence found that only RRR- $\alpha$  tocopherol is selectively retained by the body through the tocopherol transfer protein<sup>2</sup>, with the gene name of TTPA<sup>3</sup>. Humans with defects in this gene are unable to maintain their alpha-tocopherol reserves and progressively lose tendon reflexes and have signs and symptoms of spinocerebellar ataxia when plasma vitamin E level drops below 2  $\mu$ g/ml<sup>4</sup>. This is despite consuming normal diets in which all tocopherol isomers are available. The presence of a selective molecular mechanism to retain one specific isomer of the multiple tocopherol and tocotrienol isomers found in food provides a strong biological rationale to support RRR-alpha-tocopherol as *the* essential isomeric form, based on the current evidence. Conversion factors for synthetic alpha-tocopherol contain both R and S structural isomers of alpha-tocopherol and are termed “all-rac-alpha-tocopherol.” These preparations provide essential vitamin activity in accordance with the proportion of the RRR-alpha-tocopherol isomer present in them.

Evidence suggests that other isomers such as gamma, beta or delta, as well as the tocotrienol isomers may have biological actions, including antioxidant activity, within the body and its associated microbiota, that benefit human health. The potential beneficial bioactivity of these isomers may be a consideration for future discussion; nevertheless, these biological functions may not equate to the essential role of preventing mortality.

##### References:

1. Evans HM, Bishop KS.1922. On the existence of a hitherto unrecognized dietary factor essential for reproduction.Science 56(1458):650–651.
2. Catignani GL, Bieri JG.1977. Rat liver alpha-tocopherol binding protein. Biochim Biophys Acta 497:349-357.
3. <https://www.ncbi.nlm.nih.gov/homologene/37295>
4. Eggermont E.2006. Recent advances in vitamin E metabolism and deficiency. Eur J Pediatr 165:429–434.DOI 10.1007/s00431-006-0084-5

#### IADSA – International Alliance of Dietary/Food Supplement Associations

In November 2015 the CCNFSDU agreed to postpone discussion on the conversion factors and dietary equivalents for vitamin E isomers and to consider these topics again in December 2016. The CCNFSDU will also consider whether this further discussion is likely to have any effect on the selection of a Nutrient Reference Value for Requirements (NRV-R) of 9 mg for vitamin E.



In its submission to the CCNFSDU in October 2015, IADSA commented that the appropriate candidate Dietary Intake Reference Values (DIRVs) should be in the range 9–15 mg. IADSA provided a rationale to support a single value of 12 mg based on the EFSA Adequate Intakes (AIs) of 13 mg/day for males and 11 mg/day for females, together with the average values of the IOM, Nordic Council of Ministers and EFSA values, as well as the average values of the IOM and WHO/FAO values.

In November 2015 the majority of Codex member countries preferred, and the CCNFSDU Chair then concluded, that the NRV-R should be 9 mg/day based on the Nordic candidate DIRV, a rounded WHO/FAO value and various averages of other candidate AIs. However, three countries and a number of non-governmental organisations including IADSA considered that although a scientific consensus on the level of daily intake of vitamin E needed for optimal health has not been reached, the selection of an NRV-R of 9 mg/day was too low. All the nutritional effects of vitamin E are consistent with its role in the antioxidant defence system. It is of basic and fundamental importance in the maintenance of membrane integrity in every cell in the body. The various signs of vitamin E deficiency are believed to be manifestations of membrane dysfunction, the result of oxidative damage of polyunsaturated membrane phospholipids, and/or the disruption of other critical cellular processes. The targets of deficiency are the neuromuscular, vascular and reproductive systems.

IADSA therefore reiterates its support for an NRV-R of a single value of 12 mg/day based on its assessment of the science and of the values of the candidate DIRVs, and in particular, the conclusions of the final EFSA scientific opinion on Dietary Reference Values for vitamin E as  $\alpha$ -tocopherol (*EFSA J* 2015; 13(7): 4149). The conclusions of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) were to define AIs based on estimates of observed intakes of vitamin E from several comprehensive dietary surveys in healthy populations with no apparent vitamin E deficiencies.

Moreover, from a labelling perspective, IADSA notes that the selection of a value of 12 mg/day for vitamin E would be consistent with the EU Regulation 1169/2011 on the provision of food information to consumers.

Regarding conversion factors and dietary equivalents, IADSA recommends that, because there is growing evidence that different forms of vitamin E may confer biologically beneficial effects that are different from that of  $\alpha$ -tocopherol, as much detail as possible should be included with respect to the names of the different forms and the appropriate conversion factors. IADSA continues to support the inclusion of all the forms of vitamin E found in foods and food supplements.

Based on stoichiometry, IADSA supports the inclusion of the following vitamin E isomers:

1 mg RRR- $\alpha$  tocopherol activity is equivalent to (or provided by):

- 1.10 mg RRR- $\alpha$  tocopherol acetate
- 1.23 mg RRR- $\alpha$  tocopherol succinate
- 2 mg all-rac- $\alpha$  tocopherol
- 2.2 mg all-rac- $\alpha$  tocopherol acetate
- 2.46 mg all-rac- $\alpha$  tocopherol succinate

#### **ISDI – International Special Dietary Food Industries**

ISDI appreciates the on-going work of CCNFSDU to establish a NRV-R for Vitamin E.

ISDI supports the proposal to adopt a NRV-R for Vitamin E of 9 mg for labelling purposes in the Guidelines on Nutrition Labelling (CAC/GL 2-1985)

However, noting the concerns expressed at the 39th session of CAC and the 37th session of CCNFSDU that the conversion factors should be agreed first before finalising the NRV, ISDI would welcome a final review of this NRV when the conversion factors have been finalised.