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VIA ELECTRONIC SUBMISSION

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Re: Draft Codex Nutrient Reference Value – Requirement (NRV-R) for Vitamin E; Codex document CL-2016/19-NFSDU, July 2016

The Council for Responsible Nutrition (CRN) [1] is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements, many of which are multinational and already actively selling ingredients, finished products and services globally.

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

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 labeling, 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.

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.

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."

Bottom line….potencies need to increase not decrease.

Thank you madam Chair.

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

A systematic review published this year (Peter, et al., 2016[2]) considered 179 scientific articles referring to 132 single studies on α-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 µmol/L, primarily observed in children and newborns. Several prospective observational studies recommend that a serum α-tocopherol concentration of ≥30 µmol/L is beneficial, and globally, only 21% of all study populations reached this threshold.

Another analysis by McBurney et al. (2015[3]) discerned a similar pattern of inadequacy. Analyzing the U.S. National Health and Nutrition Examination Survey (NHANES) serum α-tocopherol concentrations, they report that U.S. consumers of food alone (without dietary supplements) and food with dietary supplements, average serum α-tocopherol levels were 2.9 ± 0.2 µmo/L /L and 33.7 0.3 µmo/L, respectively. Using a criterion of 30 µmo/L as nutritionally adequate, they further report that 87% of 20-30 year olds and 43% of 51+year olds had

[2] Peter S, Friedel A, Roos FF, 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.

[3] McBurney MI, Yu EA, Ciappio ED, Bird JK, Eggersdorfer M, Mehta S. (2015) Suboptimal Serum α-Tocopherol Concentrations Observed among Younger Adults and Those Depending Exclusively upon Food Sources, NHANES 2003-20061-3. *PLoS One*.;10(8):e0135510. doi: 10.1371/journal.pone.0135510. eCollection 2015.

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. α- , β- , δ- , and γ-tocopherol intakes and plasma concentrations were analyzed. Twenty three percent of the subjects had plasma α-tocopherol concentrations < 12 µmol/L indicating a biochemical deficiency of Vitamin E, even though the dietary vitamin E intake (from food alone) was 17.68 $\pm$ 14.34 mg α-tocopherol equivalents (α-TE)/day and (food + supplement) was 19.55 $\pm$ 15.78 mg α-TE/day. The authors conclude that the "consumption of vitamin E-rich food sources by some adult South Koreans should be encouraged."[4]

Vitamin E Status – Bangladesh

A case-cohort study of 1605 pregnant Bangladeshi women in a placebo-controlled intervention study demonstrated that a low plasma α-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 α-tocopherol concentration less than 12.0 µmol/L. When stratified by α-tocopherol status, 5.2% of women with adequate α-tocopherol levels miscarried compared to 10.2% of

[4] 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.

women with α-tocopherol levels of <12.0 µmol/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 α-tocopherol nutriture and reduced risk of miscarriage inhuman populations."[5]

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 plasma α-tocopherol and lower estimated radiolabeled α-tocopherol absorption. The authors concluded that "At dietary intakes equivalent to the Recommended Daily Allowance, α-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 α-tocopherol absorption and/or impairs hepatic α-tocopherol trafficking. These findings support higher dietary α-tocopherol requirements for patients with metabolic syndrome."[6]

Conclusion

In response to the Codex CCNFSDU call for data CL 2016/19-NFSDU[7], CRN supports a Nutrient Reference Level-Requirement (NRV-R) of greater than or equal (≥) 12 mg/day for α-

[5] 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.

[6] Mah E, Sapper TN, Chitchumroonchokchai C, Failla ML, Schill KE, Clinton SK, Bobe G, Traber MG, Bruno RS. (2015) α-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.

[7] 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.

tocopherol, on the basis of the IOM[8] recommendations as well as EFSA[9] Scientific Opinion on vitamin E Dietary Reference Values (DRV) taking into account recent scientific studies[10]. A NRV ≥ 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[11] is set for 12 mg α-tocopherol per person per day, the German-speaking countries (D-A-CH, 2013[12]) have recently set the recommendation at 12-15 mg α-tocopherol equivalents/day for men and 11-12 mg α-tocopherol equivalents/day for women according to age. Additionally for pregnant and lactating women 13 and 17 mg/day α-tocopherol equivalents/day are recommended by D-A-C-H (2013).

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[8] U.S. Institute of Medicine (IOM, now identified as the National Academies of Sciences, Engineering, and Medicine).

[9] European Food Safety Authority.

[10] https://www.efsa.europa.eu/en/efsajournal/pub/4149; Scientific Opinion on Dietary Reference Values for vitamin E as α-tocopherol.

[11] 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.

[12] 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.

For all the above reasons, CRN believes that currently available scientific evidence supports a NRV-R ≥ 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.

Respectfully submitted,

James C Griffiths, Ph.D., DABT, FSB, CFS

Appendix 1

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

Q1	**Candidate DIRVs for NRVs-R** 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? a) one or more candidate DIRV(s) including from WHO/FAO; b) the current NRV-R; c) no NRV-R to be established.	CRN and CRN Members support Option a). Regarding the vitamins under consideration we support the following candidate DIRVs: *Vitamin A:* IOM value of 800 (RAE) as suitable basis for the NRV-R as it represents of a more heterogeneous population. *Vitamin D:* IOM value of 15 µg as said above, because IOM represents a more heterogeneous population. *Vitamin E:* IOM value of 15 mg α-toc as said above, because IOM represents a more heterogeneous population. However the suggested values from WHO/FAO which use α-tocopherol equivalents (α-TE) should be used for clarity.
Q2	**Vitamin A, D, E, Magnesium, Phosphorus, Copper** Which unit (µg 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.
Q4	**Vitamin units of equivalents** Should the selection of candidate DIRV(s) for vitamin A (and vitamin E if expressed as α-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.
Q7	**Vitamin E isomers naturally occurring in food** 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.
Q8A	**Vitamin E isomers added to food and used in supplements** 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-α-tocopheryl acetate 1.23 mg RRR-α-tocopheryl succinate 1.35 OR 2.00 mg all-rac-α-tocopherol (dl-α-tocopherol)

		1.49 OR 2.22 mg all-rac-α-tocopheryl acetate 2.44 mg all-rac-α-tocopheryl succinate
Q8B	**Vitamin E isomers added to food and used in supplements** 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-α-tocopheryl acetate 1.23 mg RRR-α-tocopheryl succinate 1.35 OR 2.00 mg all-rac-α-tocopherol (dl-α-tocopherol) 1.49 OR 2.22 mg all-rac-α-tocopheryl acetate 2.44 mg all-rac-α-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

Conclusion

38. The Commission adopted the Annex I noting the concerns of Colombia, Costa Rica and the European Union and its Member States.

Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU)

Additional or Revised Nutrient Reference Values for Labelling Purposes in the Guidelines on Nutrition Labelling (CAC/GL 2-1985)[17]

Vitamin E

39. Malaysia, supported by Indonesia proposed to return the NRV for Vitamin E to Step 3 until the work on the related conversion factor was finalised. These delegations pointed out that there were divergent views and lack of consensus in CCNFSDU on whether to identify all forms of Vitamin E isomers or only alpha-tocopherols as exhibiting Vitamin E activity. They noted that work should proceed in a logical order and that the first part of the task should be to adopt the conversion factor for the vitamin before proceeding to adopt the NRV for Vitamin E. Returning the NRV to Step 3 would allow discussion on the NRV to be carried out in parallel with the discussion on the conversion factor. These delegations further proposed that JEMNU should be requested to look at the NRV for Vitamin E and its conversion factor.

40. Two observers also noted that the proposed NRV for Vitamin E was not based on the latest science; that vitamin E was made up of eight isomers not only alpha tocopherol, and that the NRV should be higher than the proposed 9 mg level.

41. The Representative of FAO clarified that FAO would welcome requests for scientific advice, but that requests to JEMNU should come from the relevant technical committee.

42. The CCNFSDU Chairperson clarified that at the last session of CCNFSDU, the NRV had been extensively discussed and that CCNFSDU had agreed to submit the NRV for adoption while noting reservations from three countries. The Committee had also agreed to postpone discussion on the conversion factor and dietary equivalents. However, noting the concerns expressed and that the conversion factor should be agreed first before finalising the NRV, the chair proposed that the NRV be adopted at Step 5 as a compromise. The next session of CCNFSDU would then consider Vitamin E dietary equivalents and conversion factor and in this context could consider if there was an effect on the NRV value.

Conclusion

43. The Commission adopted the NRV for Vitamin E at Step 5 noting that any request for scientific advice from JEMNU should be sent through CCNSFDU.

Amendments to the Annex of CAC/GL 2-1985: definition for Recognised Authoritative Scientific Bodies (RASB)[18]

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[13].

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[14].

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[15].

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

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[13] **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/.

[14] 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***).

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

outcomes during pregnancy for both infant and mother, and neurological disorders and muscle deterioration in children with an overt deficiency[4].

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[4].

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.[16]"

Bottom line….potencies need to increase not decrease.

[16] http://umm.edu/health/medical/altmed/supplement/vitamin-e