CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 4b **CRD 6**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECCIAL DIETARY USES

Thirty-eighth Session

Hamburg, Germany, 5 – 9 December 2016

PROPOSED DRAFT ADDITIONAL OR REVISED NUTRIENT REFERENCE VALUES FOR LABELLING (VITAMIN D AND THE DIETARY EQUIVALENTS AND CONVERSION FACTOR FOR VITAMIN E)

Comments of India, Indonesia, Malaysia, African Union, NHF

INDIA

Specific Comment:

A. India proposes the value of 10 µg and to add a footnote on Vitamin D, under section 3.4.4.1, NRVs-R (CAC/GL 2-1985) to read as follows "Competent National and/or regional authorities should determine an appropriate NRV-R that best accounts for population sunlight exposure and other relevant factors".

B. Conversion Factor of Vitamin E: Dietary Equivalents: India supports the inclusion of α tocopherols as the active form of Vitamin E and its dietary equivalent 1 mg of α-tocopherol = 1 mg of RRR-α-tocopherol.

INDONESIA

Indonesia supports an NRV-R for vitamin D of 15 µg based on the IOM (2011) DIRVs of 15 µg and Dietary Reference Value for Indonesia population.

MALAYSIA

Malaysia would like to reiterate our position at the last CCNFSDU37 that Malaysia strongly objects to recognising α-tocopherol as the only form of vitamin E.

Malaysia also would like to state that based on the EFSA's 2015 report, some of the biological activities outlined as vitamin E activities, are also exhibited by other isomers such as the tocotrienols. For example, the EFSA report had specified that the α-tocopherol deficiency is associated with neurological symptoms, including ataxia. In this context, tocotrienols have also shown remarkable neuroprotective effects as reported by Gopalan et al (2014).

Tocotrienols (T3) possess many health benefits as has been demonstrated in many clinical trials. Supplementation of T3 in various population groups was found to show beneficial effects in cardiovascular health, cancer, immune modulation, neuroprotection and skin protection. While tocopherols have failed to offer protection, Tocotrienols have demonstrated these health promoting properties reinforces the notion that tocotrienols are indeed more than antioxidants (Nesaretnam et al., 2012; Meganathan & Fu et al., 2016).

Malaysia is of the opinion that the activities of other isomers of vitamin E besides α-tocopherol should not be ignored and should be given due recognition. In order for these isomers to be recognised along with α-tocopherol, conversion factors are therefore needed to account for the effects from other tocopherol and tocotrienol isomers. Malaysia strongly recommends that the committee include all the vitamin E isomers and the conversion factors listed by the FAO/WHO (2004) publication due to the growing evidence on the important biological activities of the other forms of vitamin E namely tocotrienols, which are different from that of α-tocopherol. The report from FAO/WHO (2006) although has indicated the use of only α-tocopherol as vitamin E, no explanations were provided on what grounds these changes were made. The document on itself was not dedicated to address the requirements of vitamin and minerals. Malaysia strongly objects to recognising α-tocopherol as the only form vitamin E. The other forms of vitamin E complex namely the tocotrienols do exhibit vitamin E activities that have been implicated to be exhibited only by α-tocopherol.

The justification and evidence that clarifies that the other forms do exhibit vitamin E activities are presented in Annex 1.

Annex 1

Justification for including other isomers of vitamin E besides α-tocopherol in determining NRV-R for vitamin E

The majority of science in the past has looked at vitamin E in the α-tocopherol form in the context of elucidating an effect that relates to certain activities. However, on the basis of more recent evidence, other forms of vitamin E including α-, γ-, and δ-tocotrienols have been shown to be present in the plasma and vital organs. There is growing evidence on the important biological activities of the tocotrienol forms of vitamin E, which are different from that of α-tocopherol, independent of the alpha-tocopherol transfer proteins. It is therefore crucial to assess the current evidence on the role of all forms of vitamin E in human health and to recommend a suitable level of daily intake for all these forms.

The recent scientific opinion on Dietary Reference Values for vitamin E as α-tocopherol by EFSA (2015) discusses in detail the effects of α-tocopherol and the required intake for various age groups in order to address vitamin E deficiencies which were also outlined. It is important to note that the discussions were solely directed to the effects of α-tocopherol alone as only α-tocopherol was considered as vitamin E.

However, outlined below are some crucial points to indicate that the effects discussed in the paper may not be limited to, the effects from α-tocopherol alone, but other isoforms including tocotrienols which have been shown to exhibit similar effects. In addition, the report also indicates that in many instances, the data currently available are not conclusive to establish a recommended intake for vitamin E.

The EFSA report had specified that α-tocopherol deficiency is associated with neurological symptoms, including ataxia. We would like to highlight that, tocotrienols have also shown remarkable neuroprotective effects as reported by Gopalan et al (2014) and hence their effects should be taken into consideration when recommending intake of vitamin E.

The report also agreed on the limited data on other functions of α-tocopherol such as inhibition of platelet aggregation and considers that markers of these functions are not specific to effects of α-tocopherol. Besides the report notes the lack of information on the effect of genotypes on α-tocopherol absorption and distribution are insufficient to be used for deriving the requirement for α-tocopherol according to genotype variants.

It agrees that there is a lack of convergence of the values that would be derived from the use of data on markers of α-tocopherol intake/status or on α-tocopherol kinetics and body pools. Similarly, it was noted that the inconsistence and limitations in the available α-tocopherol/'vitamin E' intakes and health consequences.

Hence, the EFSA panel has decided that neither on their own, nor in combination, the aforementioned criteria cannot be used in deriving the DRV for α-tocopherol. Hence, there is no concrete evidence to support the decision to adopt 9 mg as DIRV of α-tocopherol.

Tocotrienols (T3) possess many health benefits as has been demonstrated in many clinical trials. Supplementation of T3 in various population groups was found to show beneficial effects in cardiovascular health, cancer, immune modulation, neuroprotection and skin protection. While tocopherols have failed to offer protection, Tocotrienols have demonstrated these health promoting properties reinforces the notion that tocotrienols are indeed more than antioxidants (Nesaretnam et al., 2012; Meganathan & Fu et al., 2016). The beneficial role of Tocotrienols as well as its bioavailability and safety is discussed in the following clinical / physiological settings:

1. Neuroprotection

Neuroprotective ability conferred by T3 in pre-clinical research has gained momentum and was further explored as a novel approach in humans. Beyond their antioxidative nature, T3, particularly α-T3, were found to induce neuroprotection at nanomolar concentrations. In fact, the circulating plasma T3 were found to be 20 times more than the required dose for neuroprotection (Patel et al., 2012). TRF supplementation showed significant reduction in mean White Matter Lesion volume change as compared to the placebo group. This attenuation of WML and the safety of TRF as a supplement strengthened the neuroprotective ability of T3 (Gopalan et al., 2014).

2. Cardiovascular Health

Association of reduced cardiovascular disease risk with long term vitamin E supplementation was well established among health practitioners despite contradictory findings on high dose α-TP supplementation (Meganathan & Fu et al., 2016). In trials involving hypercholesterolemic subjects, supplementation of tocotrienol-rich fractions (TRF) ranging from 200 to 300 mg per day resulted in significant decrease in Total Cholesterol (TC) and Low Density Lipoprotein (LDL) (Qureshi et al 1991; 1997; 2001; 2002; Yuen et al., 2011).

In patients with type 2 diabetes mellitus, TRF supplementation reduced TC, LDL, and Triglyceride (TG) in addition to plasma glucose and glycated hemoglobin (HbA1c) levels after 60 days (Baliarsingh et al., 2005).

3. Cancer

Tocotrienols have gained the attention of clinicians by demonstrating compelling anti-cancer activities in pre-clinical research. The underlying mechanism facilitating this effect has been attributed to the anti-proliferative, anti-angiogenic, pro-apoptotic and immune enhancing nature of T3 (Nesaretnam et al., 2008; Nesaretnam et al., 2012).

a) Results from the clinical trial involving breast cancer patients treated with Tamoxifen and TRF showed that upon completion of the study, there were six deaths and 20 local or systemic recurrence reported in the placebo arm while the TRF arm had only two deaths and 16 incidence of recurrence. All the women well-tolerated the TRF supplementation without any deviation reflected in their liver and blood parameters. The numbers needed to treat (NNT) showed that one out of 30 women with breast cancer can be saved with T3 supplementation (Nesaretnam et al., 2010; Nesaretnam et al., 2012)

b) In pre-operative pancreatic cancer patients supplemented with Vitamin E δ-Tocotrienol (VEDT), increased caspase-3 positive cells in the surgically removed tumor cells denote enhanced apoptotic activity and were associated with good biological effect response (Springett et al., 2015).

4. Immune modulation

Modulation of the immune system has become an emerging field of interest in recent years due to its multi-targeted effect. Marked increment in anti-tetanus toxoid IgG was noted in the subjects that were supplemented with TRF and received an intramuscular injection of tetanus toxoid vaccine. When challenged by tetanus toxoid, blood leukocytes from the TRF group showed significant higher production of interferon-gamma and interleukin-4 compared to placebo group (Mahalingam et al., 2011).

5. Skin Protection

Ultraviolet radiation is a common cause for oxidative damage of the skin by increasing the production of ROS which initializes a series of signaling cascade that aggravates the condition. Upon a single application prior to the provocative test, the topical formulation containing T3 was able to confer effective protection as compared to the vehicle and Vitamin A products (Pedrelli et al., 2012).

6. Other Clinical Effects

In addition to the above functionalities, several exploratory studies found various response of TRF supplementation in different individuals. Increasing prevalence of Non Alcoholic Fatty Liver Disease (NAFLD) in both Asian and western nations led to initiation of a study to investigate the hepatoprotectivity of T3 in 64 individuals with NAFLD. Patients in the tocotrienol arm showed significant improvement in normalization of hepatic echogenic response in addition to absence of worsening of NAFLD grade. On the other hand, two patients in the placebo arm were reported to show disease progression with worsening grade. Moreover, significant reduction of TC, LDL and TG levels was observed in the TRF arm compared to the baseline. All the patients tolerated the supplementation well without any adverse event (Magosso et al., 2013). Similar findings were reported in another study aimed at assessing the safety and tolerability of TRF in subjects with metabolic syndrome. Two weeks supplementation of 400 mg TRF daily did not cause any implication to hematological markers, serum liver function markers and liver enzymes (Gan et al., 2016). This implies that TRF supplementation does not cause hematoxicity and hepatotoxicity in metabolic syndrome subjects (Fu & Meganathan., 2016).

In a study that assessed the association between early supplementation of TRF and the incidence of pregnancy induced hypertension (PIH) in healthy primigravidae recruited in their early second trimester and followed till delivery, remarkably, women in TRF arm were reported to have reduced blood loss in comparison with women on placebo. This finding dismisses the conventional concern that tocotrienols increases risk of bleeding and further asserts its safety (Mahdy et al., 2013).

7. Pharmacokinetics / Bioavailability

Despite promising findings on the health protective properties of T3, their bioavailability has been debated among health authorities. The concentration of α-, γ- and δ-tocotrienols in plasma elevated significantly when taken with food in healthy individuals (Yap et al., 2001). Twice daily dosing was justified from the findings of this study as the half-life of tocotrienols was relatively much shorter than TP. Therefore, double dosing will ensure the presence of T3 in the circulating plasma for longer duration (Yap et al., 2001).

Tocotrienol isoforms were found to be concentrated in circulating blood, skin, liver, cardiac muscle, brain and adipose tissue following TRF supplementation. This study asserted that circulating levels of T3 were adequate and was higher than the therapeutic dose required to exert certain biological effects, such as neuroprotection (Patel et al., 2012).

Conclusion

Tocotrienols being a well-tolerable natural compound with many distinct therapeutic properties may provide a possibility for better health care that may not only be used to treat but may also play a major role in prevention various disease conditions. Despite the variations in the findings, these studies have facilitated the understanding on the potential physiological effect of T3. One of the major limitations of T3 debated in human trials was the lower bioavailability in plasma. Key findings from several studies have reported substantial concentration of T3 in plasma and vital organs which are sufficient to exert health protective role in humans. Bleeding was a major concern with tocotrienols being labelled as anti-coagulant. Consistently, almost all the trials discussed have reported that T3 supplementation at different doses was safe and well-tolerated in the population studied. From healthy subjects to pre-surgical cancer patients and even pregnant women have tolerated the supplementation for short and long duration without any serious adverse event.

Based the evidence presented above, it is unjustifiable to ignore the effects of some of the isomers of vitamin E and to only accept α-tocopherol especially in determining the NRV-R for vitamin E. Malaysia seeks the action of the Committee to recognize these isomers as contributors to vitamin E activity.

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AFRICAN UNION

Issue: The draft NRV for Vitamin D was circulated for comments at step 6 of the procedure

Comment: The AU proposes to maintain NRV for vitamin D of 5 µg. In addition; a footnote should be introduced to allow national authorities to adjust the levels up to 15 µg.

Rationale: Vitamin D deficiency is mainly related to the exposure to sunlight. Countries within the tropics ideally have a reliable exposure that would enable the people in those region syntheses enough Vitamin D. However, other countries which do not have such exposure may need to have vitamin D supplied through diet and hence the need to allow national authorities the latitude to make a decision on the same.

NHF – National Health Federation

VITAMIN D

Unfortunately, none of the DIRVs proposed by the RASBs are adequate as they are all too low. Even the highest NRV figure given (15 micrograms, by IOM) is predicated upon a statistical mistake that grossly ***underestimates*** the human intake need for Vitamin D. The other figures are so absurdly low as to actually be embarrassing for Codex and its insistence on science-based decisions. They should be dismissed out of hand and not given any consideration whatsoever. **The correct NRV-R for Vitamin D should be 100-224 micrograms.** Here is why, and it is worth repeating the Report in its entirety:

"**The IOM Miscalculated Its RDA For Vitamin D**

Posted on February 13, 2015 by Robert P. Heaney, M.D.

Last year (2014) saw an unusual event. Two statisticians at the University of Edmonton in Canada (Paul Veugelers and JP Ekwaru) published a paper in the online journal Nutrients (6(10):4472-5) showing that the Institute of Medicine (IOM) had made a serious calculation error in its recommended dietary allowance (RDA) for vitamin D. Immediately, other statisticians checked the Canadians' analyses and found that, indeed, they were right. Together with my colleagues at Grassroots Health, I went back to square one, starting with a different population entirely, and came to exactly the same conclusion. The true RDA for vitamin D was about 10 times higher than the IOM had said. Not a small error. To understand how this might have happened and why this is important, some background may be helpful.

Background

An RDA is technically the amount of a nutrient every member of a population should ingest to ensure that 97.5% of its members would meet a specified criterion of nutritional adequacy. For vitamin D, the IOM panel determined that the criterion for adequacy was a serum concentration of a particular vitamin D derivative (25-hydroxyvitamin D) of 20 ng/mL or higher, and that for adults up to age 70, 600 IU of vitamin D per day was the RDA.

Both of those figures provoked immediate and unprecedented dissent from a diverse group of nutritional scientists, but the disagreement centered mostly around the IOM panel's reading and interpretation of the evidence, rather than its calculation of the RDA. The Edmonton statisticians took the dissent a step further, showing that the actual calculation was itself wrong. Here's what seems to have happened.

What Happened

Not everyone gets the same response to a given intake of any particular nutrient, i.e., some require more than others to reach the specified target, and while the average response to a certain dose of vitamin D may be above the target level, a substantial fraction of a population can still be below it. Thus, the RDA will always be higher than the average requirement, and for some nutrients, substantially so. As a consequence, ensuring that every member of a population receives the RDA guarantees that 97.5% of that population will be getting at least enough, while many will be getting more than they actually need.

The IOM panel identified a number of published studies showing the 25-hydroxyvitamin D response to various vitamin D doses. They plotted the average response in each of those studies against dose, thereby generating what is termed a "dose response curve", i.e., a way to estimate how much of a response would be predicted for any given vitamin D intake. But, to make a long story short, because it used average responses, that curve tells us nothing about the intake requirement for the individual members of a population, and particularly those whose response to a given dose falls in the bottom 2.5 percentiles. The IOM panel surely knew that the average intake required to meet or exceed 20 ng/mL was not the same as the RDA, as it would be inadequate for all those with below average responses (about half the population). So, to catch the "weak" responders, they calculated the 95% probability range around their dose response curve, designating as the RDA the point where the bottom end of that probability range exceeded 20 ng/mL. While this might seem to have been the right approach, it was not. The panel appears to have overlooked the fact that the 95% probability range for their curve is for the average values that would be expected from similar studies at any particular dose. The dispersion of averages of several studies is, as every beginning student of statistics knows, much more narrow than dispersion of individual values within a study around its own average. And it's the 2.5th percentile individual values from those studies, not the study averages, that should have been used to create the relevant dose response curve.

It's this latter approach that the Canadian statisticians used. They took precisely the same studies as the IOM had used and demonstrated that the requirement to ensure that 97.5% of the population would have a value of at least 20 ng/mL, was 8,895 IU per day. Recall that the IOM figure was less than 1/10 that, i.e. 600 IU per day up to age 70 (and 800 IU per day thereafter). When my colleagues and I analyzed the large GrassrootsHealth dataset, we calculated a value closer to 7,000 IU per day, still a full order of magnitude higher than the estimate of the IOM, and not substantially different from the estimate of Veugelers and Ekwaru.

Why This Is A Problem

This is an important mistake, not simply because it shouldn't have been allowed in a major policy document, but because IOM recommendations have important effects on a wide array of government programs. These include nutritional standards for US military, for school lunch programs, for WIC and many others, both in the United States and in Canada.

Canada, which paid one third the cost of generating the IOM report, is in a particularly difficult situation. Its First Nations peoples, living near the Arctic Circle, do not get any vitamin D from the sun, as do those of us living at more temperate latitudes. They are totally dependent upon food and supplement sources. Their ancestral diets, based largely on seals and whales, constituted a rich source of vitamin D. They are much less commonly consumed today, in part because of the ready availability of low nutrient density foods flown in from the south, and in part because environmental pollution has made seal and whale products a source of dangerous toxins (as well as necessary nutrients). The Canadian government, responsible for the health of all of its citizens, can turn only to the existing IOM recommendation (600 IU per day) to set standards for the people living in its northern territories. But, as the Edmonton statisticians noted, that number is woefully inadequate.

There is almost no public awareness of this error or its implications in the United States, but that is not true for Canada. A large nutritional health foundation located in Calgary (Pure North S'Energy Foundation) has taken out a series of half page advertisements in Canada's national newspaper (*Globe and Mail*), alerting

Canadians to the fact that the error was made and that they need more vitamin D than current policy indicates (http://www.purenorth.ca/?page_id=1356). The IOM, Health Canada, and the Canadian Ministry of Health have all been formally alerted to this problem. The Health Ministry has agreed to undertake an independent reanalysis of the calculation of the RDA, but the results are not yet available and the shape of the ministry's action is still uncertain.

How It May Have Happened

It's one thing to know how the mistake was made, and quite another to know how it could have happened. Here, one can only speculate, as the IOM processes are shrouded in secrecy. The IOM report was a massive document and it is likely that much of the background work, such as the literature search, the drafting of the report, and the statistical calculations, were done by IOM staff members who may not, themselves, have been sufficiently expert in the vitamin D field to recognize discrepancies that might have popped up. (It is noteworthy that several of the dissenting letters submitted to scientific publications following release of the IOM report had specifically cited the fact that 600 IU per day was not sufficient to guarantee a level of 20 ng/mL.) It would then have been up to the expert panel to review and adjust this staff work. To be fair to the panel, it is important to understand that the scientific members of IOM panels are not compensated for their time and effort. They do it as a public service, and they are all busy scientists with work of their own. Still, it was their job, and one must wonder how they failed to see an error that was apparent to other equally knowledgeable, but outside, scientists.

Comment

There may be a moral here. It is widely recognized that many of the panel members, before coming together to review the evidence, had already staked out a position to the effect that, while the previous (1997) recommendation for vitamin D (200 IU per day) was probably inadequate, the actual RDA was almost certainly below 1000 IU per day. Accordingly, when the statistical calculations produced a number that matched their own expectations, they may not have been inclined to question its derivation.

There is a generally held belief that science is objective, data-driven. And to a substantial extent that is so. But science and scientists are not identical. Scientists often have strongly held opinions and, like people in general, find ways to construe the evidence to support their beliefs. When those beliefs are wrong, science, as a field, ultimately abandons them. I am confident that this IOM error will be corrected sooner or later. This is partly because it is demonstrably erroneous, and partly because the related set of IOM recommendations for vitamin D has not elicited a consensus in the field of vitamin D research. If the Dietary Reference Intakes produced by the IOM are important, then it is important that they be right. I can only hope that not too much human damage will occur as we wait for the needed correction to happen."[i]

Summary: The analyses in this paper shows that rather than 600 IU/d, it would take 8,895 IU/d to achieve 25(OH)D above 50 nmol/L in 97.5% of the population using data from 8/10 studies that the IOM considered (the other 2 studies did not report all necessary information). In other words, the RDA should be 8,895 IU/d (or 222.37 micrograms).

The science supporting the human need for ***significantly*** higher levels of Vitamin D is increasing by leaps and bounds. In particular, the old and outdated concept that humans can get by on a daily intake of just 5 micrograms of Vitamin D is dead. As the United States noted in its recent comments, "the 2004 FAO/WHO RNI of 5 mcg was based on the 1997 IOM AI which has since been updated by the IOM in 2011 to 15 mcg." And recently, EFSA came out with its opinion that 15 mcg was the appropriate daily intake level for Vitamin D. So, there is no justification for leaving the Vitamin-D NRV at an unhealthy 5 mcg.

Instead, **adequate** levels of Vitamin D (i.e., from 25 micrograms up) are recognized as being necessary by such agencies as Health Canada and others. The scientific evidence supporting this position is extremely well-documented, but NHF will only footnote a small portion of such research here.[1] To ignore this current

[1] Mezquita Raya P, Munoz Torres M, Lopez Rodriguez F, Martinez Martin N, Conde Valero A, Ortego Centeno N, Gonzalez Calvin J, Raya Alvarez E, Luna Jd Jde D, Escobar Jimenez F, "Prevalence of vitamin D deficiency in populations at risk for osteoporosis: impact on bone integrity," *Med Clin (Barc)*, 2002 Jun 22;119(3):85-9; Rodriguez-Martinez MA, Garcia-Cohen EC, "Role of Ca(2+) and vitamin D in the prevention and treatment of osteoporosis," *Pharmacol Ther*. 2002 Jan;93(1):37-49; Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ, "Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention," *Maturitas*, 2003 Apr 25;44(4):299-305; Pfeiffer, *J Bone Min Res*. 2000, 15:1113-6; Trivedi DP, Doll R, Khaw KT, "Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial," *BMJ* 2003;326:469-72; Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ, "Vitamin D3 and calcium to prevent hip fractures in the elderly women," *N Engl J Med*, 1992; 327:1637-1642; Dawson-Hughes B., Harris S. S., Krall E. A., Dallal G. E, "Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 Years of Age or Older," *N Engl J Med*, 1997; 337:670-676; Fardellone P, Sebert JL, Garabedian M, Bellony R, Maamer M, Agbomson F, Brazie rM, "Prevalence and biological consequences of vitamin D deficiency in elderly institutionalized subjects," *Rev Rhum Engl Ed*. 1995 Oct;62(9):576-81; Markestad T, "Effect of

science by establishing below-minimum nutritional requirements for Vitamin D (such as an NRV of only 5 micrograms) is racially discriminatory, scientifically negligent, and completely unnecessary.

NHF does not expect this Committee to break with a traditional and long-accepted view held on Vitamin-D NRVs and accept values of 100-224 mcg, no matter how demonstrably wrong the suggested values of 5 mcg, 10 mcg, and even 15 mcg might be. However, the above scientific discussions and new evidence do reveal how dangerously off-target the values suggested at this Committee are. Not only do these low values ***racially discriminate*** against various First Nations and other such darker-skinned groups living above the 33rd-degree Latitude, but they also adversely affect the health of ***all*** races, age groups, and gender.

Because Committee members will most probably not accept at this time the greater daily values of 100-125 micrograms necessary to ensure optimal health, the NHF proposes and advocates for setting the NRV for Vitamin D ***at 20 micrograms***, which is in alignment with the DACH values recommended in 2012 and accepted by Germany, Switzerland, and Austria. Although an NRV of 20 mcg is still low, it is probably the highest value that this Committee could accept at this time and will provide some nutritional hope for racial groups previously unrepresented and discriminated against.

VITAMIN E

None of the DIRVs proposed by the RASBs, particularly that of 9 mg/day, are adequate as they are all too low. An adequate level would deliver no less than 400 IUs of natural Vitamin E (preferably in the multi-tocopherol form and not simply alpha-tocopherol form) per day.[ii] This equates to 268 milligrams per day.

Optimal Vitamin-E Levels Preserve Health

The World Health Organization currently attributes one-third of all global deaths annually (15.3 million) to cardiovascular disease,[iii] and patients with coronary artery disease have been shown to have significantly lower blood levels of Vitamin E than normal healthy people.[iv]

Studies have demonstrated that Vitamin-E supplements are effective in the treatment of cardiovascular disease,[v] and that the combination of Vitamin E and Vitamin C can slow the advancement of atherosclerosis.[vi] Furthermore, a review of studies of Vitamins A, C, and E and cardiovascular disease found significant evidence to support the supplementation of these vitamins to lower the risk of death from this illness.[vii] As such, it is now clear that the progression of early stages of coronary calcifications can be stopped or limited by the synergistic effect of vitamins and essential nutrients,[viii] and that supplementing the diet with nutrients including Vitamins E, C, B6, and folate is conducive to the prevention of cardiovascular disease.[ix] In this respect it is also interesting to note that some researchers particularly recommend dietary supplementation of Vitamin E and C in Northern Europe, where cardiovascular disease is most prevalent.[x]

Several observational studies have associated lower rates of heart disease with higher Vitamin-E intakes. One study of approximately 90,000 nurses found that the incidence of heart disease was 30% to 40% lower in those with the highest intakes of Vitamin E, primarily from supplements.[xi] Among a group of 5,133 Finnish men and women followed for a mean of 14 years, higher vitamin E intakes from food were associated with decreased mortality from CHD.[xii]

Vitamin-E therapy has also been shown to reduce arterial blockage in patients suffering from intermittent claudication,[xiii] and recent research has indicated that it normalizes high blood pressure.[xiv] Vitamin E also promotes collateral circulation; consequently offering great benefits to diabetes patients.[xv]

A recent study looked at patients with colon cancer who received a daily dose of 750 mg of Vitamin E during a period of two weeks. The researchers found that supplementation with high doses of dietary Vitamin E produced a significant improvement in the immune functions of these patients, all of whom had advanced cancer. It is especially notable that this improvement was achieved in only two weeks.[xvi]

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season and vitamin D supplementation on plasma concentrations of 25-hydroxyvitamin D in Norwegian infants," *Acta Paediatr Scand*, 1983 Nov;72(6):817-21; Zamora SA, Rizzoli R, Belli DC, Slosman DO, Bonjour JP, "Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls," *J Clin Endocrinol Metab*. 1999 Dec; 84(12):4541-4; Garland CF, Garland FC, Gorham ED, "Calcium and vitamin D. Their potential roles in colon and breast cancer prevention," *Ann N Y Acad Sci*. 1999;889:107-19; Peehl DM, "Vitamin D and prostate cancer risk," *Eur Urol*. 1999;35(5-6):392-4; Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM, "Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study," *Lancet*, 2001 Nov 3;358(9292):1500-3; Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willet WC, Ascherio A, "Vitamin D intake and incidence of multiple sclerosis," *Neurology*, 2004 Jan 13;62(1):60-65; Goldberg P, Fleming MC, Picard EH, "Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D," *Med Hypotheses*, 1986 Oct;21(2):193-200; Sasidharan PK, Rajeev E, Vijayakumari V, "Tuberculosis and vitamin D deficiency," *J Assoc Physicians India*, 2002 Apr;50:554-8; Bicknel F, Prescott F, The Vitamins in Medicine, third edition. Milwaukee, WI: Lee Foundation. 1953, p.544, 584-591; Vieth, R. (1999), "Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety," *American Journal of Clinical Nutrition*, Vol. 69, No. 5, 842-856, May 1999; Marya RK, Rathee S, Lata V, Mudgil S, "Effects of vitamin D supplementation in pregnancy," *Gynecol Obstet Invest*. 1981;12(3):155-61.

Other research suggests that Vitamin-E supplementation also improves immune function in healthy elderly people.[xvii]

A high dietary intake of Vitamin E and Vitamin C may lower the risk of Alzheimer disease.[xviii] Other researchers have confirmed this, and have demonstrated that long-term supplement users of Vitamin E with Vitamin C have significantly better mental performance than do people who have never used Vitamin E or Vitamin C supplements,[xix] and that Vitamins E and C may prevent dementia and improve cognitive functioning in later life.[xx] Similarly, a Columbia University study reported that the progression of Alzheimer's disease was significantly slowed in patients taking high daily doses (2,000 IU) of Vitamin E for two years.[xxi]

In another study, 400 IU of Vitamin E per day given to epileptic children for several months reduced the frequency of seizures in most of them by over 60 percent, while half of them had a 90 to 100 percent reduction in seizures. This study is also notable for the fact that the researchers specifically stated that the children suffered no adverse side effects from the Vitamin-E treatment.[xxii] Similarly, preterm infants given 100 mg of Vitamin E per kilogram body weight (as a preventative treatment for incubator oxygen retina damage – a major cause of retrolental fibroplasia and subsequent blindness in premature infants) suffer no detrimental side effects from such therapy.[xxiii] It is also notable that a statistical analysis of published clinical results showed as early as 1940 that Vitamin E supplements reduce the rate of recurrent miscarriage.[xxiv]

An increased intake of Vitamins E and C has been found to reduce the risk of hip fractures,[xxv] and researchers have also demonstrated that a mixture of Vitamins E, C, and A dramatically reduces the postoperative complication rate.[xxvi] Similarly, critically ill surgery patients have been shown to be significantly less likely to experience organ failure, spend less time using mechanical ventilation, and have shorter times in intensive care units when they are given supplements of Vitamin E and Vitamin C.[xxvii]

Research has shown that healthy centenarians have high levels of both Vitamin E and Vitamin A, and that this seems to be important in guaranteeing their extreme longevity.[xxviii]

Finally, we also note that the 2000 report by the Institute of Medicine of the National Academy of Sciences acknowledges that 1,000 mg (1,500 IU) Vitamin E is a "tolerable upper intake level . . . that is likely to pose no risk of adverse health effects for almost all individuals in the general population."

All of the above studies were conducted using daily intake levels for Vitamin E higher than those proposed by any of the RASBs, indicating that the RASBs are once again incorrectly fixated upon suboptimal levels of nutrient intake exacerbated by the error of employing only one fraction of Vitamin E when it possesses eight functioning as a complex.

Current Vitamin-E Intake Levels are Too Low

Very importantly, a recent study (2015) showed that “Using a criterion of adequacy of 30 μmol/L, **87% of persons 20-30 y and 43% of those 51+y had inadequate vitamin E status (p<0.01)**.”[xxix] This is a significant level of Vitamin-E deficiency within a population that is supposedly well nourished. It demonstrates that current NRV levels are woefully inadequate at addressing this deficiency and must be raised.

Another recent study (2016) systematically reviewed the published literature on Vitamin-E intake levels and serum concentrations in order to obtain a global overview of α-tocopherol status. Articles published between 2000 and 2012 were considered; 176 articles referring to 132 single studies were included. In applying an RDA of 15 mg/day and EAR (estimated average requirement) of 12 mg/day to all populations with a minimum age of 14 years, **82% and 61% of mean and median data points were below the RDA and the EAR, respectively**. Regarding serum concentrations, globally 13% of the included data points were below the functional deficiency threshold concentration of 12 μmol/L, mostly for newborns and children. Several prospective observational studies suggest that a serum α-tocopherol concentration of ≥30 μmol/L has beneficial effects on human health. **Of the reported study populations and subpopulations, only 21% reached this threshold globally.** This systematic review suggests that the α-tocopherol status is inadequate in a substantial part of the studied populations.[xxx]

Conclusion

The current proposal to establish an NRV for Vitamin E of 9 mg/day is not supported by the science. Such a daily level would condemn the vast majority of the human population to inadequate levels of this key nutrient with all the attendant health consequences. The absolute minimum NRV that should be established is 15 mg a day; but even this level, as demonstrated above, is not adequate to avoid widespread Vitamin-E deficiencies. A truly optimal nutrient intake would dictate daily levels of 200 mg and more, but NHF acknowledges that this Committee may not yet be prepared to stretch that far.

[i] *See* Robert P. Heaney, M.D., Professor of Medicine and John A. Creighton Professor Emeritus, at http://blogs.creighton.edu/heaney/2015/02/13/the-iom-miscalculated-its-rda-for-vitamin-d/

[ii] Because Vitamin E is a complex and not simply a single vitamin, all of its components must be considered: alpha tocopherol, beta tocopherol, delta tocopherol, gamma tocopherol, and the tocotrienol components. To only consider alpha tocopherol and to ignore all of the other Vitamin-E components would be like considering only the tires on an automobile and ignoring the engine, transmission, and other components that make a car a car.
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