13 Vitamin E

13.1 Introduction

Vitamin E consists of two families of compounds, the tocopherols and tocotrienols, characterised by a 6-chromanol ring and an isoprenoid side chain. The members of each family are designated alpha((α)-, beta(β)-, gamma(γ)-, or delta(δ)- according to the position of methyl groups attached to the chroman nucleus. Therefore, 8 stereoisomers of the large vitamin E family are possible but only the RRR-form occurs naturally. Tocopherols and tocotrienols are differentiated by their phenyl "tails" as these are saturated in the tocopherols but unsaturated in the tocotrienols (Combs, 1992).

Vitamin E was discovered in 1922 but it was not until 40 years later that the vitamin was established as essential to human nutrition. Since vitamin E is synthesised only in plants, the vitamin is an essential nutrient in the diet of animals and man. Appropriately, FAO/WHO (2002) and the Institute of Medicine (IOM, 2000), Food and Nutrition Board, United States, have recommended reference intake values for vitamin E.

Unlike most nutrients, a specific role for vitamin E in a required metabolic function has not been found. Vitamin E's major function appears to be as a non-specific chain-breaking antioxidant that prevents the propagation of free-radical reactions. The vitamin is a peroxyl radical scavenger and especially protects polyunsaturated fatty acids (PUFAs) within membrane phospholipids and in plasma lipoproteins.

The efficiency of vitamin E absorption is low in humans (IOM, 2000). Vitamin E is absorbed with the fat component of food, "piggy-rides" on chylomicrons (formed in intestinal mucosal cells) through the lymphatic system and are finally released into the blood stream. Vitamin E is transported in the blood by the plasma lipoproteins and erythrocytes.

13.2 Deficiency

Vitamin E deficiency occurs only rarely in humans and overt deficiency symptoms in normal individuals consuming diets low in vitamin E have never been described (IOM, 2000). Vitamin E deficiency occurs only as a result of genetic abnormalities in α–tocopherol transfer protein, as a result of various fat malabsorption syndromes, or as a result of protein-energy malnutrition (IOM, 2000).

Deficiency can of course result from insufficient dietary intake of the vitamin. Several other dietary factors affect the need for vitamin E. Two are most important in this regard: selenium (Se) and polyunsaturated fatty acids (PUFAs). Se spares the need for vitamin E and therefore, adequate intake of vitamin E becomes even more important in individuals taking low Se-diets (Combs, 1992).

The primary human vitamin E deficiency symptom is a peripheral neuropathy characterized by the degeneration of the large-caliber axons in the sensory neurons.

Other symptoms observed in humans include spinocerebellar ataxia, skeletal myopathy, and pigmented retinopathy. Other symptoms include increased erythrocyte fragility, and increased ethane and pentane production.

13.3 Food Sources

Vitamin E is synthesised only by plants and, therefore, is found primarily in plant products, the richest sources being vegetable oils and to a lesser extent, seeds, nuts and cereal grains. The vitamer of highest biopotency and nutritional importance, d-α-tocopherol, is widely distributed in foods and is commonly found in leaves and other green parts of higher plants (Combs, 1992).

The dietary sources of tocotrienols are palm oil, rice bran oil, and the bran and germ portions of cereals such as oat, barley and rice. Surprisingly, most other common edible oils contain only very small amounts of tocotrienols.

13.4 Factors affecting requirements

Bioavailability is an important factor affecting requirements. Most dietary vitamin E is found in food that contains fat. Vitamin E absorption requires micelle formation and chylomicron secretion by the intestine, although the optimal amount of fat to enhance vitamin E absorption has not been reported.

Information presently available indicates that vitamin E functions primarily as an antioxidant in biological systems by trapping peroxyl free radicals (Combs, 1992; IOM, 2000). In this regard, vitamin E is found in cellular membranes associated with PUFA in phospholipids. In vitamin E deficiency, the oxidation of PUFA is more readily propagated along the membrane, leading to cell damage and eventually symptoms, mainly neurological.

Vitamin E requirements have thus been reported to increase when intakes of polyunsaturated fatty acids (PUFAs) are increased. It has been suggested that a ratio of at least 0.4 mg (1 μmol) α-tocopherol per gram of PUFA should be consumed by adults. However, the method of determining the vitamin E requirement generated by PUFA intakes is not universally accepted. There are also data to suggest that low-density lipoprotein (LDL) oxidation susceptibility *in vitro* is dependent upon its PUFA content. Although it is clear that the relationship between dietary PUFA and vitamin E needs is not simple, high PUFA intakes should certainly be accompanied by increased vitamin E intakes.

It is also recognised that the requirements for vitamin E increase with increasing body weight until adulthood.

Biological activity and units of expression

Biopotencies of tocopherols and tocotrienols are traditionally determined by different assays, namely foetal resorption (rat), haemolysis (rat), myopathy prevention (chick) and myopathy cure (rat). Based on these assays, the different stereoisomers of vitamin E have widely varying biological activities which are expressed in international units (IU) or in terms of milligram tocopherol equivalents (mg TE) of the most biopotent natural vitamer, d-α-tocopherol (also called RRR-α-tocopherol).

Besides d-α-tocopherol, other forms of vitamin E are also found in a mixed diet and their biopotencies, although weaker by comparison, should also be taken into consideration in the calculation of total vitamin E activity. Thus, total vitamin E activity can be calculated as follows (FNB, 1989):

mg TE = mg d-α-tocopherol + (mg β-tocopherol x 0.5) +
(mg γ-tocopherol x 0.1) + (mg α-tocotrienol x 0.3)

With advances in the scientific knowledge on the role of vitamin E in human health, new indices on vitamin E biopotency (eg. antioxidative properties), apart from the traditional assays mentioned earlier, may warrant serious consideration in the future.

13.5 Setting requirements and recommended intakes for vitamin E

In the FAO/WHO (2002) consultation report, a separate chapter discussed the potential role of several vitamins (especially vitamin E and C) and several minerals as antioxidants in the human body. The consultation discussed whether antioxidant properties of these nutrients *per se* should be and can be considered in setting a requirement. It was decided that there was insufficient evidence to enable as recommended nutrient intake to be based on the additional health benefits obtainable from nutrient intakes above those usually found in the diet. Even for vitamin E with its important biologic antioxidant properties, there was no consistent evidence for protection against chronic disease from dietary supplements. Nevertheless, the main function of vitamin E appears to be that of preventing oxidation of PUFAs, and this has been used by those bodies proposing RNIs for vitamin E because there is considerable evidence in different animal species that low vitamin E and PUFAs excess gives rise to a wide variety of clinical signs.

The main references used by the Technical Sub-Committee (TSC) on Vitamins were the 2002 FAO/WHO report of the Technical Consultation and the IOM report of 2000. The rationale and approaches taken by these consultations were considered. The dietary pattern of the community is also taken into consideration. The FAO/WHO consultation felt that data available then were not sufficient to formulate recommendations for vitamin E intake for different age groups except for infancy. The Consultation had therefore used the term “accepted intakes” which represents the best

estimates of requirements, based on the currently acceptable intakes that support the known function of this vitamin. The TSC is in general agreement with the approaches of the FAO/WHO report. The proposed values for the revised RNI for Malaysia are given in bold in the following paragraphs according to age groups and summarised in Appendix 13.1.

Infants

No functional criteria of vitamin E status have been demonstrated which reflect response to dietary intake in infants. Thus IOM (2000) had recommended intakes for vitamin E based on Adequate Intake, calculated based on vitamin E intake of infants fed principally with human milk.

A similar approach was taken by FAO/WHO (2002). The concentration of vitamin E in early human milk remains fairly constant at 0.32 mg TE/100 ml of milk after 12 days. Therefore, an infant consuming 850 ml human milk a day would have an intake of 2.7 mg TE of vitamin E. Recommended intake for infants is thus rounded off to 3 mg in the present report.

RNI for infants

0 - 5 months	**3 mg/day**
6 - 11 months	**3 mg/day**

Children and adolescents

As there were no data to guide in the estimation of average requirements for children and adolescents, IOM (2000) had recommended vitamin E intakes for these groups based on extrapolation from adult values based on lean body mass and need for growth.

The TSC on vitamins proposed that vitamin E requirements for Malaysians follow closely that presently recommended by FAO/WHO (2002) for the various age groups.

RNI for children

1 - 3 years	**5 mg/day**
4 - 6 years	**5 mg/day**
7 - 9 years	**7 mg /day**

RNI for adolescents

Boys 10 - 18 years	**10 mg/day**
Girls 10 - 18 years	**7.5 mg/day**

Adults and elderly

Although it is known that humans require vitamin E, overt vitamin E deficiency is rare in the developed countries. Thus, current dietary patterns appear to provide sufficient vitamin E to prevent deficiency symptoms such as peripheral neuropathy. However, since vitamin E intakes are underestimated, particularly with respect to estimates of intake associated with fats, IOM (2000) felt that an AI could not be reliably determined from the available data on intakes.

Upon reviewing the literature, IOM (2000) reported only one study has been carried out in apparently healthy human adults who were depleted of vitamin E over 6 years and then repleted (Horwitt, 1960, 1962; Horwitt *et al.,* 1956). In response to vitamin E deficiency, increased erythrocyte fragility (as assessed by an *in vitro* test of hydrogen peroxide-induced hemolysis) was observed, which was reversed by vitamin E supplementation.

Data on human experimental vitamin E deficiency are very limited but do provide some guidance in estimating a requirement. The values recommended by IOM (2000) were based largely on studies of induced vitamin E deficiency in humans and the correlation with hydrogen peroxide-induced erythrocyte lysis and plasma α-tocopherol concentrations. In the absence of other scientifically sound data, hydrogen peroxide-induced hemolysis, although recognized as having specific drawbacks, was accepted as the best marker at the present time and used by IOM (2000) to estimate intakes for a-tocopherol requirements.

The TSC took note of a recent Malaysian report (Ng, 2003) recommended 10 mg TE/day for adults, an estimate using the "Horwitt's equation" (Horwitt, 1974) which was based on dietary PUFA and some allowance for cellular synthesis and retention of PUFA in adipose tissues. In the report, the palm oil-based diets contained 66g total fat (26% energy) and 3.3% energy PUFA (12.7% of total fatty acids or 8.4g PUFA) provided mainly by linoleic acid.

The TSC decided to adopt this value as the recommended intake for adults. This is also the RNI for vitamin E in the FAO/WHO Consultation report (2002).

IOM (2000) felt that there is no scientific basis for assuming different requirements for men and women, and although body weights may be greater in men, women have larger fat masses as a percent of body weight, and thus may have similar requirements. The FAO/WHO consultation report however had provided for a lower recommended intake for women. The TSC decided to follow this approach of FAO/WHO (2002).

RNI for adults

Men	**19 - 65 years**	**10 mg/day**
Women	**19 - 65 years**	**7.5 mg/day**

IOM (2000) was of the opinion that there is no evidence that the aging process impairs vitamin E absorption or utilization. On the other hand, the limited clinical trial evidence does not justify providing for higher recommendations for higher vitamin E intakes at this time. Therefore, the same intake was recommended for the elderly adults. Similarly, the FAO/WHO (2002) had also provided for the same RNI for elderly subjects.

RNI for elderly

Men	**> 65 years**	**10 mg/day**
Women	**> 65 years**	**7.5 mg/day**

Pregnancy and lactation

IOM (2000) felt that there is no evidence at the present time that the requirement for women during pregnancy should be increased above the level recommended for women in the nonpregnant state. For lactating women, an additional amount equal to the total quantity of a-tocopherol secreted in human milk (4 mg) was added to the recommended intake for non-pregnant women.

FAO/WHO (2002) consultation report, however, did not provide for increased requirements for vitamin E in pregnancy and lactation as it was felt that there is no evidence of vitamin E requirements different from those of other adults and presumably also as the increased energy intake would compensate for the increased needs for infant growth and milk synthesis. The TSC on vitamins decided to follow the same approach.

RNI for

Pregnancy	**10 mg/day**
Lactation	**7.5 mg/day**

Discussions on revised RNI for Malaysia

There were no recommendations for vitamin E in the previous version of the Malaysian RDI (Teoh, 1975). The proposed recommended intakes for the revised recommended intakes for Malaysia are basically similar to those of FAO/WHO (2002). Appendix 13.1 provides a summary of these revised RNI, compared with the FAO/WHO (2002) recommendations and the values recommended by IOM (2000).

Recommended intakes by IOM (2000) are on the average, significantly higher than the corresponding values cited by FAO/WHO (2002). This was particularly evident in the adults where FAO/WHO (2002) recommended a RNI of 10 mg TE/day for adult males, compared with 15 mg TE by IOM (2000).

As mentioned earlier the main factor used to assess the adequacy of vitamin E intakes in the United States and United Kingdom advisory bodies was the dietary intake

of PUFAs (FAO/WHO, 2002). PUFA intakes in the United States are estimated at slightly above 6% energy which is much higher than the 3.3% energy reported for palm oil-based diets (Ng, 1995). As such, it is not surprising that the IOM (2000) has recommended a RNI of 15 mg TE/day for adults.

13.6 Toxicity and tolerable upper intake levels

There is no evidence of adverse effects from the consumption of vitamin E naturally occurring in foods. Therefore, hazard identification by IOM (2000) was focused on evidence concerning intake of α-tocopherol as a supplement, food fortificant, or pharmacological agent. *RRR*-α-tocopheryl acetate (historically and incorrectly labeled *d*-α-tocopheryl acetate) and *all rac*-α-tocopheryl acetate (historically and incorrectly labeled *dl*-α-tocopheryl acetate) are the forms of synthetic vitamin E used almost exclusively in supplements, food fortification, and pharmacologic agents.

Upon reviewing available data, FAO/WHO (2002) consultation reported that vitamin E appears to have very low toxicity, and amounts of 100–200 mg of the synthetic *all-rac*-α-tocopherol are consumed widely as supplements. Evidence of pro-oxidant damage has been associated with the feeding of supplements but usually only at very high doses (e.g., >1000 mg/day).

Based on considerations of causality, relevance, and the quality and completeness of the database, hemorrhagic effects were selected by IOM (2000) as the critical endpoint on which to base the Tolerable Upper Intake Level (UL) for vitamin E for adults. There is some evidence of an increased incidence of hemorrhagic effects in premature infants receiving supplemental α-tocopherol. The Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study in Finnish smokers consuming 50 mg of *all rac*-α-tocopherol for 6 years, reported a significant 50% increase in mortality from hemorrhagic stroke. However, the human data fail to demonstrate consistently a causal association between excess α-tocopherol intake in normal, apparently healthy individuals and any adverse health outcome. The UL for the vitamin, for the various age groups, are tabulated in Table 13.1.

Table 13.1 Tolerable Upper Intake (UL) levels of vitamin E for various age groups

Age groups	mg/day of any form of supplementary α-tocopherol
Infants	Not possible to establish; source of intake should be formula and food only
Children	
1-3 years	200
4-8 years	300
9-13 years	600
Adolescents	
14-18 years	800
Adults	
≥ 19 years	1,000
Pregnancy	
14-18 years	800
≥ 19 years	1,000
Lactating women	
14-18 years	800
≥ 19 years	1,000

Source: IOM (2000)

13.7 Research Recommendations

The following priority areas of research are recommended:

- Determination of vitamin E content in local foods, focused primarily on vitamin E rich foods, eg fats and oils, and nuts
- Effect of vitamin E on the occurrence of chronic diseases and its influence on ageing.
- Studies on health benefits of tocotrienols
- Assessing vitamin E intakes by different age groups of the local population.

13.8 References

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Appendix 13.1 Comparison of recommended intake for vitamin E: RNI Malaysia (2005), Acceptable Intakes of FAO/WHO (2002) and RDA of IOM (2000)

Malaysia (2005)		FAO/WHO (2002)		IOM (2000)	
Age groups	**RNI (mg/day)**	**Age groups**	**Acceptable intakes (mg/day)**	**Age groups**	**AI (mg/day)**
Infants		Infants		Infants	
0 – 5 months	3	0 – 6 months	2.7	0 – 6 months	4
6 – 11 months	3	7 – 11 months	2.7	7 – 12 months	5
					RDA (mg/d)
Children		Children		Children	
1 – 3 years	5	1 – 3 years	5	1 – 3 years	6
4 – 6 years	5	4 – 6 years	5	4 – 8 years	7
7 – 9 years	7	7 – 9 years	7		
Boys		Boys		Boys	
10 – 18 years	10	10 – 18 years	10	9 – 13 years	11
				14 – 18 years	15
Girls		Girls		Girls	
10 – 18 years	7.5	10 – 18 years	7.5	9 – 13 years	11
				14 – 18 years	15
Men		Men		Men	
19 – 65 years	10	19 – 65 years	10	19 – 30 years	15
> 65 years	10	> 65 years	10	31 – 50 years	15
				51 – 70 years	15
				> 70 years	15
Women		Women		Women	
19 – 65 years	7.5	19 – 65 years	7.5	19 – 30 years	15
> 65 years	7.5	> 65 years	7.5	31 – 50 years	15
				51 – 70 years	15
				> 70 years	15
Pregnancy	7.5	Pregnancy	7.5	Pregnancy	
				< 18 years	15
				19 – 30 years	15
				31 – 50 years	15
Lactation	7.5	Lactation	7.5	Lactation	
				< 18 years	19
				19 – 30 years	19
				31 – 50 years	19