Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2017: 4

# Assessment of vitamin E intake in relation to tolerable upper intake levels

**Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety**

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2017: 4
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# Assessment of vitamin E intake in relation to tolerable upper intake levels

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## Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM). Per Ole Iversen (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Kristin Holvik, Martinus Løvik, Bjørn Steen Skålhegg, Tonje Holte Stea and Tor A. Strand.

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## Acknowledgment

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## Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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# Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the intake of vitamin E (alpha-tocopherol) in the Norwegian population in relation to tolerable upper intake levels (ULs). The existing maximum limit for vitamin E in food supplements is 30 mg/day. VKM was also requested to conduct scenario calculations to illustrate the consequences of amending the maximum limit for alpha-tocopherol to 15, 50, 100, 150, 200 and 300 mg/day.

Naturally vitamin E is a fat soluble compound synthesised by plants and consists of eight different tocopherols (α-, β-, γ- and δ- tocopherols and α-, β-, γ- and δ- tocotrienols) with varying vitamin E antioxidant activity. α-Tocopherol is recognised to meet human vitamin E requirements and accounts for 90% of the activity in human tissue. Vitamin E activity in food is expressed as α-tocopherol equivalents (α-TE) and 1 α-TE is defined as 1 mg d-α-tocopherol.

The physiological role of vitamin E is to react with free radicals in cell membranes and other lipid milieu, thereby preventing polyunsaturated fatty acids (PUFA) from being damaged by lipid peroxidation. This antioxidant activity is important to maintain membrane integrity and takes place in all cells in the body.

Vitamin E deficiency symptoms include peripheral neuropathy, ataxia, myopathy and retinopathy. Vitamin E is dependent on lipid and lipoprotein metabolism and it takes decades for body depletion. The Norwegian recommended intakes for vitamin E for adults are 10 α-TE/day for men and 8 α-TE/day for women.

There is no evidence of adverse effects from the consumption of vitamin E naturally occurring in foods. Animal studies have shown that α-tocopherol is not mutagenic, carcinogenic or teratogenic. However, high doses of α-tocopherol supplements can cause haemorrhage and interrupt blood coagulation.

VKM propose to adopt the tolerable upper intake level set by the Scientific Committee for Food Safety (SCF) which is based on one human dose-response study. Hence, the upper level for supplemental vitamin E is suggested to 300 mg/day for adults. The upper level for children and adolescents is derived from scaling the adult upper level based on body surface area (body weight$^{0.75}$).

The tolerable upper intake levels set for vitamin E concern only intake from supplements, since intake of vitamin E from the diet is considered safe. VKM has therefore not conducted or evaluated scenarios with intake from both diet and supplements.

Dietary calculations have, however, been performed for intake in various percentiles (P) P5, P25, mean, P50, P75 and P95 in children (2- 4- and 9-year-olds), adolescents (13-year-olds) and in adult men and women as background information.

Mean and median intakes of vitamin E are above the recommended intakes for all age groups. No age group reaches the recommended intake at P5, and 9- and 13-year-old boys and 9-year-old girls do not reach the recommended intake at P25 from diet alone.

Because the tolerable upper intake level for supplemental vitamin E for adults is 300 mg/day, none of the suggested amendments of the maximum limit in food supplements (to 15, 50, 100, 150, 200 and 300 mg/day) will lead to exceedance of this upper level in adults. In 13-year-olds supplements with 300 mg/day vitamin E will lead to exceedance of the upper level. In 9-year-olds supplements with 200 mg/day vitamin E will lead to exceedance of the upper level. In 4- and 2-year-olds supplements with 150 mg/day vitamin E will lead to exceedance of the upper level. Vitamin E intake from fortified products is not included in the calculations, but are however, evaluated to be very low.

**Key words**: VKM, risk assessment, Norwegian Scientific Committee for Food Safety, alpha-tocopherol, vitamin E, food supplement, upper level, exposure.

# Sammendrag på norsk

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet vurdert inntaket av vitamin E (alfatokoferol) i den norske befolkningen i relasjon til øvre tolerable inntaksnivåer (UL). Den eksisterende maksimumsgrensen for vitamin E i kosttilskudd er 30 mg/dag. VKM ble også bedt om å gjøre scenarioberegninger for å illustrere konsekvensene av å endre maksimumsgrensene for vitamin E til 15, 50, 100, 150, 200 and 300 mg/dag i kosttilskudd.

Naturlig vitamin E er et fettløselig vitamin som syntetiseres fra planter, og består av åtte ulike tokoferoler (α-, β-, γ- og δ- tokoferoler og α-, β-, γ- og δ- tokotrienoler) med varierende antioksidantaktivitet. Alfatokoferol utgjør 90 prosent av vitamin E-aktiviteten hos oss mennesker. Innholdet av vitamin E i mat uttrykkes som α-tokoferolekvivalenter (α-TE), og 1 α-TE er definert som 1 mg d-α-tokoferol.

I cellemembraner og andre fettvev reagerer vitamin E med frie radikaler og hemmer derfor lipidperoksidering av flerumettede fettsyrer (PUFA). Denne antioksidantaktiviteten er viktig for å unngå skader på cellemembranen. Den foregår i alle celler i kroppen.

Symptomer på vitamin E-mangel inkluderer perifer nevropati, ataksi, myopati og retinopati. Vitamin E er avhengig av lipid- og lipoproteinmetabolismen, og det tar flere tiår for kroppen å utvikle vitamin E mangel. Norske anbefalinger for inntak av vitamin E er 10 α-TE/dag for menn og 8 α-TE/dag for kvinner.

Det er ikke vist at inntak av vitamin E fra mat og drikke kan gi negative helseeffekter. Dyrestudier har vist at α-tokoferol ikke er mutagent, kreftfremkallende eller teratogent. Imidlertid kan store doser av α-tokoferol i kosttilskudd forårsake blødninger og hindre blodkoagulasjon. Blødninger er den vanligste negative helseeffekten av kosttilskudd med vitamin E.

I denne vurderingen har VKM benyttet de øvre tolerable inntaksnivåene som er fastsatt av EUs tidligere vitenskapskomite for mat (Scientific Committee for Food). Disse er basert på en dose-respons-studie i mennesker. VKM har derfor foreslått at det øvre tolerable inntaksnivået for tilskudd av vitamin E er 300 mg/dag for voksne. Øvre inntaksnivå for barn og unge er ekstrapolert fra øvre inntaksnivå for voksne på grunnlag av kroppsoverflaten (body weight$^{0.75}$).

Ettersom inntak av vitamin E fra kosten regnes som trygt, gjelder disse øvre tolerable inntaksnivåene kun inntak av vitamin E i kosttilskudd. VKM har derfor ikke laget noen scenarier med inntak fra både kosthold og kosttilskudd som beskrevet i oppdraget fra Mattilsynet.

VKM har imidlertid gjort inntaksberegninger av vitamin E for ulike persentiler (P) for inntak (P5, P25, P50, P75 og P95), samt gjennomsnittlig inntak hos barn (2-, 4- og 9-åringer), ungdom (13-åringer) og hos voksne menn og kvinner som bakgrunnsinformasjon.

Gjennomsnittlig og mediant inntak av α-tokoferol overstiger anbefalt inntak i alle aldersgruppene. Ingen aldersgruppe når det anbefalte inntaket i 5-persentilen, og 25-persentilen blant 9- og 13-årigene oppnår heller ikke anbefalte inntak for vitamin E fra kosten alene.

Ettersom øvre tolerabelt inntaksnivå for vitamin E i tilskudd for voksne er 300 mg/dag, vil ingen av de foreslåtte endringene av maksimumsgrensene i kosttilskudd (til 15, 50, 100, 150, 200 og 300 mg/dag) føre til overskridelse av dette øvre inntaksnivået hos voksne. For 13-åringer vil kosttilskudd med 300 mg vitamin E per dag føre til overskridelse av det øvre inntaksnivået. For 9-åringer vil kosttilskudd med 200 mg vitamin E per dag føre til overskridelse av det øvre inntaksnivået, og for 2- og 4-åringer vil kosttilskudd med 150 mg vitamin E per dag føre til overskridelse av det øvre inntaksnivået. Data om inntak av vitamin E fra beriket mat er ikke tilgjengelig og er derfor ikke inkludert i VKMs beregninger. Inntak av vitamin E fra beriket mat antas imidlertid å være svært lavt.

# Abbreviations and/or glossary

## Abbreviations

AI – adequate intake
APTT – activated partial thromboplastin time
AR – average requirement
ATBC Study – Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study
bw – body weight
CHAOS – Cambridge Heart Antioxidant Study
CI – confidence interval
DRI – dietary reference intake
DRV – dietary reference value
EAR – estimated average requirement (IOM).
ECG – electrocardiogram
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
IOM – Institute of Medicine, USA
IU – international unit
LOAEL – lowest observed adverse effect level
MI – myocardial infarction
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PRI – population reference intakes
PUFA – polyunsaturated fatty acids
RDA – recommended dietary allowances
RI – recommended intake
RR – relative risk
SCF – Scientific Committee for Food
SD – standard deviation
SUL – safe upper intake level
TE – tocopherol equivalent
UF – uncertainty factor
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]

## Glossary

**P5, P25, P50, P75 or P95-exposure** is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

**Percentile** is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value below which 95 percent of the observations are found.

### *EFSA - Dietary Reference Values (DRVs)(EFSA, 2010)*

**Average Requirement (AR)** is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by a the specific criterion for adequacy for the nutrient, in half of the heathy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined than an Adequate Intake is used.

**Adequate Intake (AI)** is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

**Population Reference Intake (PRI)** is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals. PRI is defined as AR+2xSD where SD is the standard deviation of the AR.

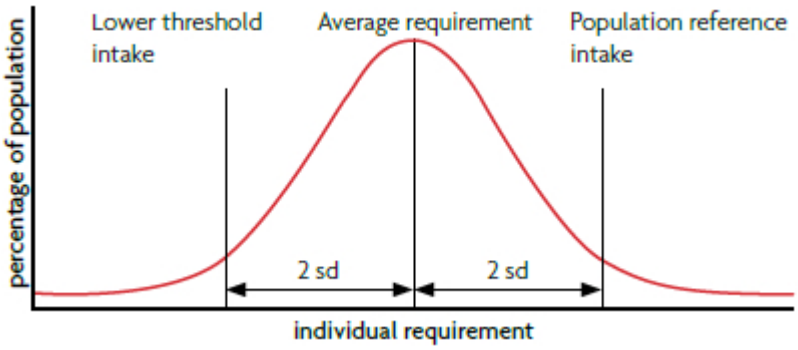


**Figure 1:** Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

**Lower Threshold Intake (LTI)** is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its standard deviation (SD). This will meet the requirement of only 2.5% of the individuals in the population.

**Tolerable Upper intake Level (UL)** is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

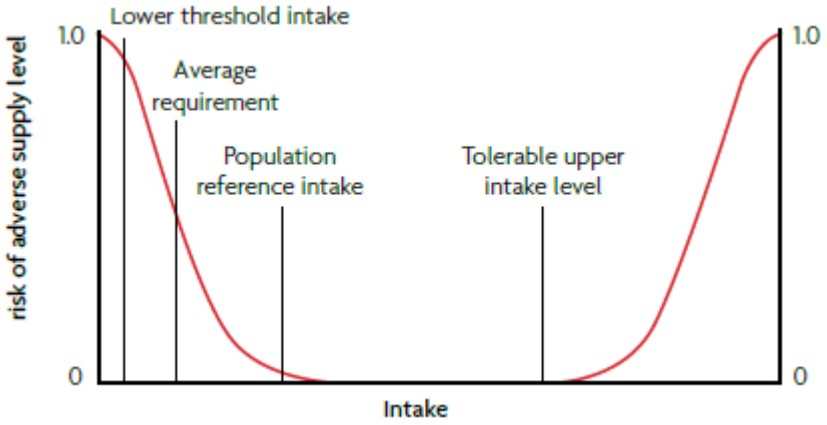


**Figure 2:** Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake using EFSA terminology.

### *IOM - Dietary Reference Intakes (DRIs)(IOM, 2000b)*

**Estimated Average Requirement (EAR)** is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

**Recommended Dietary Allowances (RDA)** is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. RDA = EAR + 2 $SD_{EAR}$ or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; RDA = 1.2*EAR

**Adequate Intake (AI)** is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined

**Tolerable Upper Intake Level (UL)** is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

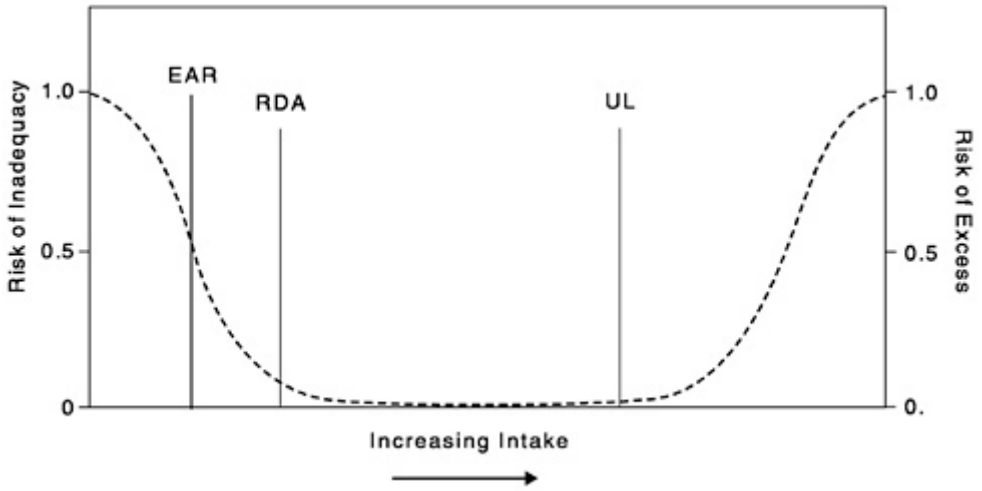


**Figure 3:** Dietary reference intakes using IOM terminology.

### *NNR -Recommended Intake (NNR Project Group, 2012)*

**Average Requirement (AR)** is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$

**Recommended Intake (RI)** is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR.}$

$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$

**Upper Intake Level (UL)** is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$

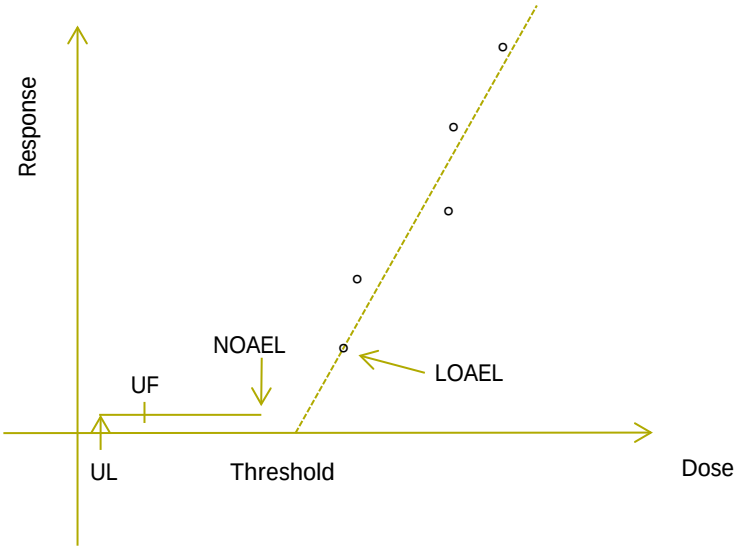


**Figure 4:** Derivation of Upper Intake Level (UL) UF: Uncertainty factor

### *Expert group on vitamins and minerals (EVM), UK (EVM, 2003)*

**Safe Upper Intake Level (SUL):** EVM used SUL instead of UL and defined SUL as the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

# Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented in Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The European Commission started establishing common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on the basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:

- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

**Assessment of vitamin E**

The Norwegian Food Safety Authority will evaluate the national maximum limits for vitamin E in the food supplement regulation. The minimum and maximum limits for the content of vitamins and minerals in food supplements are listed in Annex 1 to the food supplement regulation:

**Background Table:** Minimum and maximum limits for vitamin E in the food supplement regulation (May 2016).

| | Minimum amount per recommended daily dose | Maximum amount per recommended daily dose |
|---|---|---|
| **Vitamin E (mg α-TE)** | 3 | 30 |

Permitted vitamin E substances which may be used in the manufacture of food supplements are listed in "Forskrift om kosttilskudd 2012", http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-20040520-0755.html.

# Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of vitamin E from the diet, including fortified products, in all age groups in the population above 1 year (mean intakes, median, P5, P95).

VKM is also requested to conduct scenario estimations to illustrate the consequences of amending maximum limits for vitamin E to 15, 50, 100, 150, 200 and 300 mg/day in food supplements, and to evaluate these scenarios against already established tolerable upper intake levels.

# Assessment vitamin E

# 1 Introduction

Naturally vitamin E is a fat soluble compound synthesised by plants and consists of eight different tocopherols (α-, β-, γ- and δ- tocopherols and α-, β-, γ- and δ- tocotrienols) with varying vitamin E antioxidant activity. α-Tocopherol is recognised to meet human vitamin E requirements and accounts for 90% of the activity in human tissue. There are eight stereometric forms of α-tocopherol, and the RRR stereoisomer (d-α-tocopherol) is the naturally occurring form. Vitamin E activity in food is expressed as α-tocopherol equivalents (α-TE) and 1 α-TE is defined as 1 mg d-α-tocopherol. In the Norwegian Food Composition Table, only α-tocopherol is accounted for as vitamin E (NFSA, 2016). Vitamin E activity can also be expressed in International Units (IU) where 1 IU = 0.67 α-TE or (d-α-tocopherol).

Vegetable oils, nuts, seeds, whole grains, egg yolk and green leafy vegetables are important food sources of vitamin E. Vitamin E is available in food supplements, most oftenas the synthetic form α-tocopheryl acetate, a more stable form of the vitamin. α-Tocopheryl acetate consists of a racemic mixture of eight stereoisomers (the R and S isomers), named all-rac-α-tocopherols (= dl-α-tocopherol). The esters are hydrolysed and absorbed equally efficient as α-tocopherol (Cheeseman et al., 1995). All-rac-α-tocopheryl acetate has the activity of 0.67 of d-α-tocopherol due to lower affinity of the S-isomers in the body.

The physiological role of vitamin E is to react with free radicals in cell membranes and other lipid milieu, thereby preventing polyunsaturated fatty acids (PUFA) from being damaged by lipid peroxidation (Traber and Stevens, 2011). This antioxidant activity is important to maintain membrane integrity and takes place in all cells in the body. Vitamin E can influence cellular responses to oxidative stress by modulating signal-transduction pathways (Azzi et al., 2004). Because vitamin E is an important antioxidant agent, vitamin E supplementation has been studied with respect to development of cardiovascular disease, cancer, diabetes mellitus, and central nervous system disorders. So far no benefits of supplementation have been documented in otherwise well-nourished populations (Traber and Stevens, 2011). Vitamin E has also been suggested to improve immune function in elderly and prevent cognitive impairment, but the evidence is inconsistent (NNR Project Group, 2012).

Absorption of vitamin E requires presence of fat and involves molecular, biochemical and cellular processes related to lipid and lipoprotein metabolism (Rigotti, 2007). Dietary vitamin E is solubilised into mixed micelles by bile salts and other lipids in the intestinal lumen before uptake in the intestinal epithelial cells. Absorption of α-tocopheryl acetate seems to require hydrolysis before entering the micelles, making pancreatic lipase and bile important (Rigotti, 2007). On average diet absorption ranges between 20 to 79% influenced by the amount and quality of dietary fat and food matrix (Traber and Stevens, 2011). Unabsorbed vitamin E is

excreted in faeces and metabolised vitamin E is excreted through bile, making faeces the main route of vitamin E elimination (Kayden and Traber, 1993).

Normal plasma concentration of vitamin E range from 12-42 µmol/L, and is strongly correlated to fat intake (Bramley PM, 2000). All forms of vitamin E are transported to the liver but only α-tocopherol is conjugated with α-tocopherol transfer protein and transported for vitamin E specific activity in the body. The other forms of vitamin E are metabolised in the liver and excreted, resulting in low blood concentrations of these forms.

Vitamin E deficiency symptoms include peripheral neuropathy, ataxia, myopathy, retinopathy and anaemia in preterm babies (IOM, 2000a). Vitamin E is dependent on lipid and lipoprotein metabolism and it takes decades for body depletion (Traber and Stevens, 2011). There is no evidence of adverse effects from the consumption of vitamin E naturally occurring in foods. Animal studies have shown that α-tocopherol is not mutagenic, carcinogenic or teratogenic. However, high doses of α-tocopherol supplements can cause haemorrhage and interrupt blood coagulation.

# 2 Recommendations and tolerable upper intake levels vitamin E

## 2.1 Recommendations

Vitamin E requirement has been established with use of different methods by Institute of Medicine, USA (IOM, 2000b), the European Food Safety Authorities (EFSA, 2015), Expert Group on Vitamins and Minerals, UK (EVM, 2003) and Nordic Nutrition Recommendations (NNR Project Group, 2012) because no biomarkers have been found to correctly reflect vitamin E status.

IOM used an in-vitro hydrogen peroxide erythrocyte haemolysis test described by Horwitt et al.(Horwitt Mk Fau - Century et al., 1963). A plasma concentration of 12 µmol/L of α-tocopherol was chosen as the concentration associated with normal hydrogen peroxide induced haemolysis. From this, IOM derived at an estimated average requirement (EAR) of 12 mg/day of α-tocopherol in men (IOM, 2000a). The same EAR was used for women arguing that in spite of lower weight, women have higher fat mass requiring vitamin E. EAR for α-tocopherol was then multiplied with a factor of 1.20 for inter-individual variation and to cover 97 to 98% of the population, resulting in recommended dietary allowances (RDA) of 15 mg α-tocopherol/day for men and women. EAR and RDA for children were derived through extrapolation from the values for adults based on lean body mass and need for growth.

NNR (2012) set Recommended Intake (RI) based on a plasma α-tocopherol kinetics study among healthy adults with use of a stable isotope-labelled method (Bruno et al., 2006). The estimated rate of α-tocopherol metabolism was 5 mg/day, and with the use of an absorption rate of 55-79% (Traber and Stevens, 2011), an average requirement (AR) of 6-9 mg/day was established for adults. A higher vitamin E requirement with higher intake of PUFAs was discussed. However, intake of PUFAs in the Nordic countries had not changed since 2004 and therefore no increases in RIs from 2004 were suggested. For children the RIs are based on estimated PUFA intakes and calculated with use of the equation suggested by the Scientific Committee on Food (SCF) from 1993 (RI for vitamin E = 0.4 * α-TE/g total PUFA). The Norwegian recommended intakes for vitamin E for the different age groups, based on NNR (2012), are given in Table 2.1-1 (Helsedirektoratet, 2014; NNR Project Group, 2012).

**Table 2.1-1** Recommended intakes (RI) for vitamin E in Norway, both sexes.

| Age, both sexes | Vitamin E, α-TE/day | |
|---|---|---|
| | Men | Women |
| **6-11 mo.** | 3 | 3 |
| **1-2 years** | 4 | 4 |
| **2-5 years** | 5 | 5 |
| **6-9 years** | 6 | 6 |
| **10-13 years** | 8 | 7 |
| **14- >75 years** | 10 | 8 |
| **Pregnant** | - | 8 |
| **Lactating** | - | 8 |

In 2015, the European Food Safety Authority (EFSA) concluded that data were insufficient to derive Average Requirements (ARs) or Population Reference Intakes (PRIs) for alpha-tocopherol. EFSA therefore defined Adequate Intakes (AIs) from observed intakes in healthy populations in the EU with no apparent alpha-tocopherol deficiency (EFSA, 2015), See Table 2.1-2.

**Table 2.1-2** EFSA recommendations for vitamin E intakes, both sexes.

| Age, both sexes | Vitamin E, α-TE/day | |
|---|---|---|
| | Men | Women |
| **7-11 mo.** | 5 | 5 |
| **1-3 years** | 6 | 6 |
| **3-10 years** | 9 | 9 |
| **10-18 years** | 13 | 11 |
| **14- >75 years** | 13 | 11 |
| **Pregnant** | - | 11 |
| **Lactating** | - | 11 |

## 2.2 Tolerable upper intake levels

There is no evidence of adverse effects from the consumption of vitamin E naturally occurring in foods. Animal studies have shown that α-tocopherol is not mutagenic, carcinogenic or teratogenic. However, high doses of α-tocopherol supplements can cause haemorrhage and delay blood coagulation (IOM, 2000a). Several authorities have established ULs for alpha-tocopherol in food supplements.

### Institute of Medicine (IOM, 2000), USA

IOM used three dose-response studies in rats to derive a UL for vitamin E in food supplements (Abdo Km Fau - Rao et al., 1986; Takahashi et al., 1990; Wheldon Gh Fau - Bhatt et al., 1983). In a chronic oral toxicity study in rats by Wheldon et al., Charles River CD strain rats were fed 500, 1000 or 2000 mg dl-α-tocopheryl acetate/kg body weight (bw) per day for 104 weeks. Haemorrhages from the gut, the urinary tract, orbit, meninges and claws were observed in the male rats in week 15 with 2000 mg dl-α-tocopheryl acetate/kg bw, in

week 16 with 1000 mg/kg bw and by week 18 with 500 mg/kg bw. Prothrombin time was prolonged after 4 weeks in all male treatment groups, but this was reversed by vitamin K1 supplementation. It was reported that the massive dosages of dl-α-tocopheryl-acetate were capable of causing reaction in the liver, manifesting as the presence of foamy macrophages and a tendency towards higher relative liver weight. Increased growth rate and food intake were reported among females receiving 1000 or 2000 mg/kg bw per day. A lowest observed adverse effect level (LOAEL) of 500 mg/kg bw per day was identified.

In a subchronic toxicity study in rats, the diet was supplemented with 600 or 1000 mg of d-α-tocopheryl acetate/kg bw per day for 7 days to rats (Takahashi et al 1990). A dose-dependent increase in prothrombin time was reported. A LOAEL was set at 600 mg dl-α-tocopheryl acetate/kg bw per day. The study was criticised because of short duration and absence of lower doses.

In a third study d-alpha-tocopheryl acetate was given by gavage to groups of ten male and ten female rats at doses of 0, 125, 500 or 2000 mg/kg bw daily for 13 weeks (Abdo et al 1986). Deaths occurred in males at 2000 mg/kg bw. In this study, the vitamin E dosages had no effect on body weight or food consumption. The liver-to-body weight ratio of females was significantly increased at 2000 mg/kg bw. In males, 2000 mg/kg bw caused prolongation of both prothrombin time and activated partial thromboplastin time (APTT), caused reticulocytosis and a decrease in haematocrit values and haemoglobin concentrations. APTT was also lengthened in females at this dose. The 2000 mg/kg bw dosage caused haemorrhagic diathesis in both males and females but no adverse haemorrhagic effect was seen at a dose of 500 mg/kg bw.

IOM used the study by Wheldon et al. to set a LOAEL at 500 mg vitamin E/kg bw per day, because of the long exposure period and of the dosage given via diet.

To derive a UL, the LOAEL of 500 mg/kg bw per day was divided with an uncertainty factor (UF) of 36. This composite UF encompassed a factor 2 to get from LOAEL to a no observed adverse effect level (NOAEL), another factor 2 going from sub-chronic to chronic intake, a factor 3 going from animals to humans, and finally a factor 3 for interindividual variation in sensitivity (= 2*2*3*3= 36). The resulting UL is 14 mg/kg bw per day and in a 68.5 kg individual this is almost 1000 mg/day. The UL for children and adolescents were extrapolated from adult on the basis of body weight.

A couple of early clinical human studies were also discussed as well as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC study) (Albanes et al., 1994). In the ATBC study Finnish male smokers aged 50-69 years were randomised to consume 50 mg/day of all rac-alpha-tocopherol or placebo for median six years. The main results showed a tendency to increased mortality from haemorrhage in the 50 mg/day group compared with the placebo group, but the result was not statistically significant. IOM did not take the early clinical studies into account arguing the uncertainty of the studies, and that the ATBC study was preliminary and provocative, but not convincing until it could be corroborated or refuted in

further large-scale clinical trials. The ULs for vitamin E from IOM (2000) are given in Table 2.2-1.

**Table 2.2-1** Tolerable upper intake levels for supplementary vitamin E in different age groups adjusted by body weight suggested by the Institute of Medicine (2000).

| Age (years) | UL mg/day |
|---|---|
| **1-3** | 200 |
| **4-8** | 300 |
| **9-13** | 600 |
| **14-18** | 800 |
| **19 and older** | 1000 |

A vulnerable group for high vitamin E intakes is reported to be patients using anticoagulant or antiplatelet medication which could prolong bleeding time (IOM, 2000a).

## Scientific Committee for Food (SCF, 2003), EU

The SCF sat a NOAEL of 540 mg/day for vitamin E (alpha-tocopherol) in food supplements based on no effect on blood clotting or other adverse effects in older adults reported in a study by Meydani et al.(Meydani et al., 1996). In this double-blind, placebo-controlled trial supplementation with 60, 200, or 800 IU (40, 134, or 537 mg α-tocopherol) of all-rac-α-tocopherol/day were studied in 88 healthy subjects aged >65 years for 4 months. Vitamin E supplementation had no effect on body weight, concentrations of plasma proteins or haemoglobin, blood glucose, lipid metabolism, liver or kidney functions, blood cells, bleeding time or thyroid hormones. Furthermore, vitamin E supplementation had no significant effects on plasma concentrations of other antioxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase or total homocysteine. There was no significant effect of vitamin E on serum nonspecific immunoglobulin concentrations or anti-DNA and anti-thyroglobulin antibodies. The cytotoxic ability of neutrophils against Candida albicans was not compromised. Thus, it was concluded that 4 months of supplementation with up to 800 IU (537 α-TE) vitamin E/day had no adverse effects.

SCF decided that the critical effect was blood clothing, and that Meydani et al. provided the best basis for setting a UL. SCF used this study to set a NOAEL for vitamin E at 540 mg/day and used an uncertainty factor of 2 for interindividual differences. A UL for supplemental vitamin E for adults was thus established at 270 mg/day and rounded up to 300 mg/day. The ULs for children were set using 300 mg/day for adults and adjusting for body surface area (body weight$^{0.75}$) (SCF, Expressed 2003).

The ATBC study described above was also discussed in the SCF opinion. Later analyses from the ATBC study showed increased risk of subarachnoidal haemorrhage and higher mortality in hypertensive men receiving alpha-tocopherol supplementation of 50 mg/day (Leppala et al., 2000). However, since no other study had reproduced these results, the ATBC study was not

taken into consideration. The ULs for supplemental alpha-tocopherol from SCF (2003) is given in Table 2.2-2.

**Table 2.2-2** Tolerable upper intake levels for supplemental alpha-tocopherol and for different age groups adjusted for body surface area suggested by the Scientific Committee for Food (2003).

| Age (years) | UL mg/day |
|---|---|
| **1-3** | 100 |
| **4-6** | 120 |
| **7-10** | 160 |
| **11-14** | 220 |
| **15-17** | 260 |
| **Adults** | 300 |

## Expert Group on Vitamins and Minerals (EVM, 2003), UK

EVM stated that vitamin E has low toxicity and that humans as well as animals can tolerate 670 to 1340 mg/day (EVM, 2003). However, signs indicative of antagonism with the function of other fat-soluble vitamins have been reported with adverse effects like headache, fatigue, nausea, double vision, muscle weakness, mild creatinuria and gastrointestinal distress in humans consuming 670 mg of vitamin E per day. EVM used three supplementation studies in humans to set a safe upper level (SUL) for vitamin E (Gillilan Re Fau - Mondell et al., 1977; Meydani et al., 1996; Stephens et al., 1996).

In the first study 48 patients with stable angina were treated with 1600 IU/day d-α-tocopherol succinate (equivalent to 1070 mg d-α-tocopherol per day) or placebo in a double-blind crossover study of two 6 month periods (Gillilan et al.1977) (Gillilan Re Fau - Mondell et al., 1977). No statistically significant differences were apparent in a number of cardiac parameters including systolic time interval assessment of left ventricular function and the multistage maximal exercise test. The subjects were questioned regarding possible side effects and underwent urinalysis, blood count and blood chemistry analysis, measures of prothrombin time, chest X-ray and ECG. No adverse effects were observed. It was stated that there was no exacerbation of hypertension, congestive heart failure or skeletal muscle complaints attributable to vitamin E therapy.

The second study was the abovementioned study by Meydani et al. used by the SCF (Meydani et al., 1996). The third study referred to was the Cambridge Heart Antioxidant Study (CHAOS) (Stephens et al. 1996) (Stephens et al., 1996). In this study 546 patients with atherosclerosis were given 800 IU vitamin E (537 mg as d-α-tocopherol/day) while 489 patients received 400 IU/day (268 mg/day as d-α-tocopherol) and 967 patients received identical placebo capsules in a double-blind placebo-controlled study for a median of 510 days (range 3-981). Treatment significantly reduced the risk of non-fatal myocardial infarction (MI) (RR, 0.23, 95% CI, 0.11-0.47; p=0.005), but there was a slight non-significant excess of cardiovascular deaths in the treatment groups (27 vs. 23). The authors concluded that in patients with angiographically proven symptomatic coronary

atherosclerosis, alpha-tocopherol treatment substantially reduced the rate of non-fatal MI, with beneficial effects apparent after 1 year of treatment. The authors stated that the effect of alpha-tocopherol treatment on cardiovascular deaths required further studies. There were no significant differences between the treatment groups for diarrhoea, dyspepsia or rash.

In the two first studies (Gillilan 1977 and Meydani 1996) the biochemical and physiological effects of vitamin E were investigated in detail and the findings indicated that supplementation with doses of 800 to 1600 IU/day (equivalent to 536 to 1200 mg/day) were without adverse effects. However, these results were derived from relative small and perhaps not representative groups making use of an uncertainty factor (UF) necessary. The CHAOS study was large enough to take the interindividual variation into account and hence EVM suggested a NOAEL of 540-1070 mg d-alpha-tocopherol per day with an UF of 1. Based on this SUL was set at 540 mg/day, equivalent to 9 mg/kg/body weight in a 60 kg adult.

The ATBC study was also discussed in the EVM report, but it was noted that the results were only significant in smoking and hypertensive subjects and that the results of increased risk of subarachnoidal haemorrhage and mortality had not been reproduced in other studies (Leppala et al., 2000).

### Nordic Nutrition Recommendations (NNR Project Group, 2012)

NNR acknowledged the ULs for alpha-tocopherol set by SCF in 2003 due to lack of more recent research (NNR Project Group, 2012).

## 2.2.1 Summary and discussion tolerable upper intake level

Table 2.2.1-1 summarises available upper intake levels for vitamin E.

Table 2.2.1-1: Overview of ULs or SULs for vitamin E in adults set by various authorities.

| | UL/SUL mg/day | | Based on | NOAEL mg/day | LOAEL mg/kg bw/day | UF |
|---|---|---|---|---|---|---|
| **IOM, 2000** | 1000 | α-tocopherol | Animal studies | - | 500 | 36 |
| **SCF, 2003** | 300 | vitamin E | 1 human study | 540 | - | 2 |
| **EVM, 2003** | 540 | d-alpha-tocopherol equivalents | 3 human studies | 540-1200 | - | 1 |
| **NNR, 2012** | 300 | Vitamin E | Acceptance of SCF´s UL | 540 | - | 2 |

The hazard identification revealed haemorrhage as the most sensitive adverse health effect of vitamin E supplementation. The IOM (2000) UL is based on animal studies, while both SCF and EVM based their UL on human clinical studies. In general it is stated by EFSA that human data are preferable to animal studies to set ULs and animal studies should only be

used when data from human studies are insufficient (EFSA, 2010). For vitamin E, only one clinical dose-response study was identified (Meydani et al., 1996). SCF included only this dose-response study in setting a UL, while EVM also included the two clinical studies evaluating one-dose effect on angina pectoris and myocardial infarction, respectively. Although these studies reported on some adverse events, they were not designed to fully evaluate adverse advents.

VKM proposes to use the UL set by SCF comprising one human dose response study. Hence, the proposed UL to be applied for adults is 300 mg/day for supplemental vitamin E, and for children and adolescents the appropriate ULs should be derived by allometric scaling of the adult UL on the basis of body surface area (body weight$^{0.75}$) (see Table 2.1.2-1).

# 3 Intakes and scenarios vitamin E

## 3.1 Short description of the Norwegian dietary surveys

The calculated intakes of alpha-tocopherol presented in this opinion are based on data from the national food consumption surveys in children and adolescents (2-, 4-, 9- and 13-year-olds) and adults (aged 18 to 70 years). In the Norwegian Food Composition table, vitamin E is given as alpha-tocopherol. The national food consumption surveys were conducted by the Department of Nutrition, University of Oslo in collaboration with the Directorate of Health, the Norwegian Food Safety Authority and the Norwegian Institute of Public Health. Different methodologies were used in the tree different surveys and thus direct comparisons between the age groups may be misleading.

A description of the food consumption surveys and the different methodologies used is given below.

Adults: "Norkost 3" is based on two 24-hour recalls by telephone at least one month apart. Food amounts were presented in household measures or estimated from photographs (Totland et al., 2012). The study was conducted in 2010/2011, and 1787 adults (925 women and 862 men) aged 18-70 participated.

9- and 13-year-old children/adolescents: "Ungkost 3" is based on a 4-day food intake registration with a webbased food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2016). The study was conducted in 2015 and 636 9-year-old children and 687 13-year-old adolescents participated.

4-year-old children: "Ungkost 3" is based on a 4-day food intake registration with a webbased food diary. All food items in the diary were linked to photographs for portion estimation (Hansen et al., 2017). The study was conducted in 2016, and 399 4-year-olds participated.

2-year-old children: "Småbarnskost 2007" is based on a semi-quantitative food frequency questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. The study was conducted in 2007, and a total of 1674 2-year-olds participated (Kristiansen et al., 2009).

## 3.2 Dietary intakes of vitamin E in the Norwegian population

Intake of vitamin E (only the content of alpha-tocopherol is reported in the Norwegian Food Composition Table (NFSA, 2016)) in the various age groups and in groups of users of alpha-tocopherol supplements are presented in tables in Appendix 1. The tables in Appendix 1 also include calculations for P25 and P75. Vitamin E intake from fortified products is not included in the calculations, but are evaluated to be very low

### Adults (n=1787)

The mean intake of alpha-tocopherol from the diet alone is 11 mg/day (median 10 mg/day) in adults (n=1787). The P5 intake is 4.5 mg/day and the P95 intake is 20 mg/day.

In Norkost 3, 750 participants (42%) reported use of alpha-tocopherol-containing supplements. Their mean total intake of alpha-tocopherol including that from food supplements is 25 mg/day (median 22 mg/day), P5 intake is 9.8 mg/day and P95 intake is 47 mg/day.

Mean intake of alpha-tocopherol from supplements alone in adults reporting use of alpha-tocopherol-containing supplements is 14 mg/day (median 11 mg/day), P5 intake is 2.5 mg/day and P95 intake is 33 mg/day.

### 13-year-olds (n=687)

The mean intake of alpha-tocopherol from the diet alone is 9 mg/day (median 8 mg/day) in 13-year-olds. The P5 intake is 4 mg/day and the P95 intake is 16 mg/day.

In Ungkost 3, 259 13-year-olds (38%) reported use of alpha-tocopherol -containing supplements. Their mean total intake of alpha-tocopherol including that from food supplements is 17 mg/day (median 16 mg/day), P5 intake is 7 mg/day and P95 intake is 32 mg/day.

Mean intake of alpha-tocopherol from supplements alone in 13-year-olds reporting use of alpha-tocopherol-containing supplements is 8 mg/day (median 7 mg/day), P5 intake is 3 mg/day and P95 intake is 20 mg/day.

### 9-year-olds (n=636)

The mean intake of alpha-tocopherol from the diet alone is 8 mg/day (median 8 mg/day) in 9-year-olds. The P5 intake is 4 mg/day and the P95 intake is 14 mg/day.

In Ungkost 3, 296 9-year-olds (47%) reported use of alpha-tocopherol -containing supplements. Their mean total intake of alpha-tocopherol including that from food supplements is 15 mg/day (median 14 mg/day), P5 intake is 8 mg/day and P95 intake is 24 mg/day.

Mean intake of alpha-tocopherol from supplements alone in 9-year-olds reporting use of alpha-tocopherol-containing supplements is 7 mg/day (median 6 mg/day). P5 intake is 2 mg/day and P95 intake is 16 mg/day.

### 4-year-olds (n=399)

The mean intake of alpha-tocopherol from the diet alone is 7 mg/day (median 7 mg/day) in 9-year-olds. The P5 intake is 4 mg/day and the P95 intake is 11 mg/day.

In Ungkost 3, 233 4-year-olds (58%) reported use of alpha-tocopherol -containing supplements. Their mean total intake of alpha-tocopherol including that from food supplements is 14 mg/day (median 13 mg/day), P5 intake is 7 mg/day and P95 intake is 23 mg/day.

Mean intake of alpha-tocopherol from supplements alone in 4-year-olds reporting use of alpha-tocopherol-containing supplements is 7 mg/day (median 7 mg/day). P5 intake is 4 mg/day and P95 intake is 11 mg/day.

### 2-year-olds (n=1674)

The mean intake of alpha-tocopherol from the diet alone is 5 mg/day (median 4 mg/day) in 2-year-olds. The P5 intake is 2 mg/day and the P95 intake is 8 mg/day.

In Småbarnskost 2007, 927 2-year-olds (55%) reported use of alpha-tocopherol-containing supplements. Their mean total intake of alpha-tocopherol including that from food supplements is 13 mg/day (median 12 mg/day). The P5 intake is 5 mg/day and the P95 intake is 24 mg/day.

Mean intake of alfa-tocopherol from supplements alone in 2-year-olds reporting use of alpha-tocopherol-containing supplements is 8.5 mg/day (median 7.7 mg/day). P5 intake is 1.3 mg/day and P95 intake is 18 mg/day.

# 4 Assessment of the intakes of vitamin E

Dietary calculations for alpha-tocopherol have been performed for intake in P5, P25, mean, P50, P75 and P95 in children (2-, 4- and 9-year-olds), adolescents (13-year-olds) and in adult men and women.

Mean and median intakes of vitamin E are above the recommended intakes for all age groups. No age group reaches the recommended intake at P5. At P25, adult women reach the recommended intake, while adult men do not. At P25 boys, 9- and 13-year-old and girls, 9-year-old do not reach the recommended intake. At P25, 2-year old children do not reach the recommended intake.

# 5 Uncertainties

It should be noted that the intakes have been calculated based on various dietary surveys for the different age categories and a comparison of calculations across age groups can be misleading. The calculated intakes in the higher and lower percentiles are always associated with a higher degree of uncertainty than mean or median intakes.

The percentile estimates of dietary intake are prone to random error due to the limited number of participants in the dietary surveys. The largest degree of uncertainty is present in the estimated percentiles for 4-year-olds with a sample size of n=399, corresponding to about 20 observations below the 5-percentile and above the 95-percentile, respectively.

Another issue is the validity of the estimated exposure data. Low participation rates in the national dietary surveys give rise to systematic errors and limit the representativeness of the participants compared with the background population in Norway. The participation rates among adults, 13-, 9-, 4- and 2-year-olds in the dietary surveys were 37%, 53%, 55%, 20%, and 56%, respectively. In general, those participating had a considerably higher education level than the background population, and they are expected to represent a health-conscious subgroup of the population. Some population subgroups are not covered, e.g. ethnic minorities.

For the determinations of the ULs for vitamin E, EFSA, IOM and EVM have not reached the same conclusions, indicating uncertainty regarding establishment of these ULs both for adults, and even more for children and adolescents. Long-term clinical studies are requested by all these scientific bodies to ascertain ULs

# 6 Answers to the terms of reference vitamin E

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of vitamin E from the diet, including fortified products, in all age groups in the population above 1 year in relation to tolerable upper intake levels (ULs).

VKM was also requested to conduct scenario estimations to illustrate the consequences of amending the existing maximum limit for vitamin E (to 15, 50, 100, 150, 200 or 300 mg/day, as examples) in food supplements. The existing maximum limit for vitamin E in food supplements is 30 mg/day.

The ULs set for vitamin E concern only intakes from supplements, since intake of vitamin E from the diet is considered safe. VKM has therefore not conducted or evaluated scenarios with intake from both diet and supplements. The tolerable upper intake levels for vitamin E for the various age groups therefore equals the amounts that can be tolerated in food supplements.

Dietary calculations have however been performed for intakes in the P5, P25, mean, P50, P75 and P95 in children 2-, 4- and 9-year-olds, adolescents 13-year-olds and among adult men and women. Mean and median intakes of vitamin E from diet alone are above the recommended intakes for all age groups.

An overview of the conclusions is presented in Table 6-1.

**Table 6-1** An overview of the conclusions for vitamin El according to doses in supplements.
Green: No exceedance of the UL.
Red: Exceedance of the UL.

| Doses in supplements / Age group | 15 mg/day | 50 mg/day | 100 mg/day | 150 mg/day | 200 mg/day | 300 mg/day |
|---|---|---|---|---|---|---|
| **Adults** | | | | | | |
| **13 years** | | | | | | |
| **9 years** | | | | | | |
| **4 years** | | | | | | |
| **2 years** | | | | | | |

# 7 Data gaps

Long-term RCTs with vitamin E that also thoroughly address adverse health effects are missing.

More age groups should be included in dietary surveys in addition to subgroups like different ethnical groups.

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# Appendix I

## Summary tables of alpha-tocopherol intake for all age groups

Intakes of alpha-tocopherol in the various age groups are presented in the tables below. The tables summarise intakes from the diet alone, alpha-tocopherol containing supplements alone (users only) and total intakes from both diet and supplements (Tables 7-12). Intakes are also given for both genders.

**Table 1** Alpha-tocopherol intakes from diet alone in various age groups (mg/day).

| | Adults (n=1787) | 13 years (n= 687) | 9 years (n=636) | 4 years (n=399) | 2 years (n=1674) |
|---|---|---|---|---|---|
| **Alpha-tocopherol from diet alone, mean** | 11 | 9 | 8 | 7 | 5 |
| **Alpha-tocopherol from diet alone, median** | 10 | 8 | 8 | 7 | 4 |
| **Alpha-tocopherol from diet alone, P5** | 5 | 4 | 4 | 4 | 2 |
| **Alpha-tocopherol from diet alone, P25** | 8 | 6 | 6 | 5 | 3 |
| **Alpha-tocopherol from diet alone, P75** | 14 | 11 | 10 | 8 | 5 |
| **Alpha-tocopherol from diet alone, P95** | 20 | 16 | 14 | 11 | 8 |

**Table 2** Alpha-tocopherol supplement users intake of total Alpha-tocopherol from diet and supplements, and from supplements alone (users only), in various age groups (mg/day).

| | Adults (n=750) | 13 years (n= 259) | 9 years (n=296) | 4 years (n=233) | 2 years (n=927) |
|---|---|---|---|---|---|
| **Total alpha-tocopherol from diet and supplements, mean** | 25 | 18 | 15 | 14 | 13 |
| **Total alpha-tocopherol from diet and supplements, median** | 22 | 16 | 14 | 13 | 12 |
| **Total alpha-tocopherol from diet and supplements, P5** | 10 | 7 | 8 | 7 | 5 |
| **Total alpha-tocopherol from diet and supplements, P25** | 16 | 12 | 11 | 10 | 8 |
| **Total alpha-tocopherol from diet and supplements, P75** | 31 | 21 | 18 | 17 | 17 |
| **Total alpha-tocopherol rom diet and supplements, P95** | 47 | 32 | 24 | 23 | 24 |
| **Alpha-tocopherol from supplements alone, mean** | 14 | 8 | 7 | 7 | 5 |
| **Alpha-tocopherol from supplements alone, median** | 11 | 7 | 6 | 7 | 4 |

| | Adults (n=750) | 13 years (n= 259) | 9 years (n=296) | 4 years (n=233) | 2 years (n=927) |
|---|---|---|---|---|---|
| **Alpha-tocopherol from supplements alone, P5** | 3 | 3 | 2 | 4 | 2 |
| **Alpha-tocopherol from supplements alone, P25** | 5 | 4 | 4 | 5 | 3 |
| **Alpha-tocopherol from supplements alone, P75** | 18 | 10 | 9 | 8 | 5 |
| **Alpha-tocopherol from supplements alone, P95** | 33 | 20 | 16 | 11 | 8 |

**Table 3** Alpha-tocopherol intakes from diet alone in various age groups, women/girls (mg/day).

| | Women (n=925) | Girls 13 years (n= 355) | Girls 9 years (n= 341) |
|---|---|---|---|
| **Alpha-tocopherol from diet alone, mean** | 10 | 9 | 8 |
| **Alpha-tocopherol from diet alone, median** | 10 | 8 | 7 |
| **Alpha-tocopherol from diet alone, P5** | 4 | 4 | 4 |
| **Alpha-tocopherol from diet alone, P25** | 7 | 6 | 6 |
| **Alpha-tocopherol from diet alone, P75** | 12 | 10 | 9 |
| **Alpha-tocopherol from diet alone, P95** | 18 | 15 | 12 |

**Table 4** Alpha-tocopherol supplement users intake of total Alpha-tocopherol from diet and supplements, and from supplements alone, in various age groups, women/girls (mg/day).

| | Women (n=415) | Girls 13 years (n= 135) | Girls 9 years (n= 171) |
|---|---|---|---|
| **Total alpha-tocopherol from diet and supplements, mean** | 23 | 16 | 14 |
| **Total alpha-tocopherol from diet and supplements, median** | 20 | 15 | 13 |
| **Total alpha-tocopherol from diet and supplements, P5** | 9 | 6 | 7 |
| **Total alpha-tocopherol from diet and supplements, P25** | 15 | 11 | 10 |
| **Total alpha-tocopherol from diet and supplements, P75** | 29 | 20 | 17 |
| **Total alpha-tocopherol from diet and supplements, P95** | 43 | 29 | 23 |
| **Alpha-tocopherol from supplements alone, mean** | 12 | 8 | 6 |
| **Alpha-tocopherol from supplements alone, median** | 10 | 7 | 6 |
| **Alpha-tocopherol from supplements alone, P5** | 2.5 | 2 | 2 |
| **Alpha-tocopherol from supplements alone, P25** | 5 | 3 | 4 |
| **Alpha-tocopherol from supplements alone, P75** | 16 | 10 | 8 |
| **Alpha-tocopherol from supplements alone, P95** | 31 | 19 | 16 |

**Table 5** Alpha-tocopherol intakes from diet alone in various age groups, men/boys (mg/day).

| | Men (n=862) | Boys 13 years (n= 332) | Boys 9 years (n= 295) |
|---|---|---|---|
| **Alpha-tocopherol from diet alone, mean** | 12 | 9 | 9 |
| **Alpha-tocopherol from diet alone, median** | 11 | 9 | 8 |
| **Alpha-tocopherol from diet alone, P5** | 5 | 4 | 4 |
| **Alpha-tocopherol from diet alone, P25** | 8 | 7 | 6 |
| **Alpha-tocopherol from diet alone, P75** | 15 | 12 | 10 |
| **Alpha-tocopherol from diet alone, P95** | 23 | 16 | 14 |

**Table 6** Alpha-tocopherol supplement users intake of total Alpha-tocopherol from diet and supplements, and from supplements alone, in various age groups, men/boys (mg/day).

| | Men (n=335) | Boys 13 years (n= 124) | Boys 9 years (n= 125) |
|---|---|---|---|
| **Total alpha-tocopherol from diet and supplements, mean** | 28 | 19 | 16 |
| **Total alpha-tocopherol from diet and supplements, median** | 25 | 17 | 15 |
| **Total alpha-tocopherol from diet and supplements, P5** | 11 | 9 | 9 |
| **Total alpha-tocopherol from diet and supplements, P25** | 18 | 13 | 13 |
| **Total alpha-tocopherol from diet and supplements, P75** | 33 | 23 | 19 |
| **Total alpha-tocopherol from diet and supplements, P95** | 53 | 33 | 25 |
| **Alpha-tocopherol from supplements alone, mean** | 15 | 9 | 7 |
| **Alpha-tocopherol from supplements alone, median** | 11 | 7 | 6 |
| **Alpha-tocopherol from supplements alone, P5** | 3 | 3 | 2 |
| **Alpha-tocopherol from supplements alone, P25** | 5 | 5 | 5 |
| **Alpha-tocopherol from supplements alone, P75** | 22 | 12 | 10 |
| **Alpha-tocopherol from supplements alone, P95** | 41 | 22 | 16 |