

RISK PROFILE

Vitamin E

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1. Identification of substance

Chemical name (IUPAC):	3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-benzopyran-6-ol; Alpha-tocopherol; Vitamin E
INCI	Tocopherol (Common name: Vitamin E) Tocopheryl acetate Tocopheryl linoleate Tocopheryl succinate
Synonyms	Tocopherols are a class of naturally occurring chemical compounds related to Vitamin E
CAS No.	Alpha-Tocopherol: 59-02-9; 10191-41-0 Alpha-Tocopheryl acetate: 58-95-7 Alpha-Tocopheryl linoleate: 36148-84-2 Alpha-Tocopheryl succinate: 4345-03-3
EINECS No.	Alpha-Tocopheryl acetate: 231-710-0 Alpha-Tocopheryl linoleate Alpha-Tocopheryl succinate: 224-403-8
Molecular formula	C ₂₉ H ₅₀ O ₂ – Tocopherol

Chemical structure	
Molecular weight	430.71 (α -Tocopherol)
Contents (if relevant)	
Physiochemical properties	<p>Melting Point: 3 °C Boiling point: 210 °C at 0.1 mm Hg Solubility: Insoluble in water. Soluble in alcohol, ether, acetone, chloroform; in water, 1.9×10^{-6} mg/L at 25 °C (est) Octanol/Water Partition Coefficient: log Kow = 12 (est); i.e. lipophilic.</p> <p>References: Toxnet [online].</p>

2. Uses and origin

Uses	<p>➤ Cosmetic products:</p> <p><i>Functions according to</i></p> <ul style="list-style-type: none"> • CosIng database: <ul style="list-style-type: none"> - “Antioxidant” – “Inhibits reactions promoted by oxygen, thus avoiding oxidation and rancidity” - “Masking” – “Reduces or inhibits the basic odour or taste of the product” - “Skin conditioning” – occlusive - “Maintains the skin in good condition” • Other: <p>Used in cosmetic emulsions such as sun care products, hand and body lotions, hair care products, decorative cosmetics, e.g. anti-chap lipsticks, mascara, eye shadow, rouge, face powder and foundation cream, and anti-aging products.</p> <p><i>Frequency of use</i></p> <p>The Environmental Working Group (EWG) cosmetic database lists the following cosmetic products containing various tocopherol compounds:</p> <ul style="list-style-type: none"> • CAS no 10191-41-0 α - Tocopherol • moisturizer (1,210 products) • facial moisturizer/ treatment (1,060 products) • anti-aging (525 products) • lip balm (500 products) • lipstick (469 products) • A total of 7,482 products containing tocopherol
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- **CAS no 59-02-9 – D- α -Tocopherol,**
- moisturizer (8 products)
- facial moisturizer/ treatment (19 products)
- anti-aging (15 products)
- mask (7 products)
- around-eye cream (3 products)
- A total of 36 products containing D- α tocopherol.

- **CAS 58-95-7 α -Tocopheryl acetate**
- lipstick (879 products)
- facial moisturizer/ treatment (800 products)
- moisturizer (744 products)
- anti-aging (631 products)
- sunscreen: makeup (481 products)
- A total of 6,710 products containing tocopheryl acetate

- **CAS no 4345-03-3 α -Tocopheryl succinate**
- facial moisturizer/ treatment (2 products)
- lip balm (1 products)
- exfoliant/ scrub (1 products)
- mask (1 products)
- conditioner (1 products)
- A total of 5 products containing Vitamin E succinate.

- **CAS 36148-84-2 α -Tocopheryl linoleate**
- foundation (23 products)
- concealer (15 products)
- mascara (15 products)
- sunscreen: makeup (11 products)
- lipstick (6 products)
- A total of 67 products containing Tocopheryl linoleate

(EWG's Skin Deep [online])

The German database codecheck.info results in more than 19000 products listed on the web site (Codecheck.info [online]).

A Norwegian survey from 1999 showed that 81% sunscreen products contained vitamin E variants; α -tocopherol acetate most frequent (87%; 79 out of 91 products), followed by α -tocopherol (11%) and α -tocopheryl linoleate (2%) (cited in Council of Europe, 2008). By comparison, 62% and 69% of sunscreen products contained vitamin E variants in US and Finnish surveys in the '90s (cited in Council of Europe, 2008).

Concentrations of vitamin E being applied

Tocopherol, Tocopheryl acetate, and Tocopheryl linoleate are generally used at concentrations up to 5%, 36%, and 2%, respectively, but may be found at conc. up to 100% in vitamin E oil (Zondlo Fiume, 2002). On average 0.5 % vitamin E variants were found in cosmetic sunscreen products in a Norwegian survey from 1999 (Council of Europe, 2008). Typical use levels of vitamin E in cosmetics were much lower than 5% (range 0.0001 - more than 20%) according to data compiled by the cosmetic, toiletry, and fragrance association (CFTA) in the U.S., and modified from Zondlo Fiume (2002), (Annex 6; see Thiele & Ekanayake-Mudiyanselage, 2007).

	<p>➤ Food</p> <p>The main natural sources of Vitamin E are fresh vegetables, vegetable oils, cereals and nuts, but also animal fats, meat, poultry and eggs (Council of Europe, 2008). Almond is a particularly good source, containing approx. 26 mg per 100g (Evans & Johnsen, 2010).</p> <p>➤ Medicinal products</p> <p>E.g. Bio-E-Vitamin (Pharma Nord). Tablet formulation, each containing 350 mg (525 IE) d-α-tocopherol (Felleskatalogen [online]).</p> <p>➤ Other products</p> <p>In household products, tocopherol and tocopheryl acetate are present in 141 and 371 personal care products, respectively, whereas only four products contain tocopheryl linoleate (National Institute of Health [online]).</p>
<p>Origin</p> <p>Natural (exo /endo) Synthetic</p>	<p>Approx. eight naturally occurring vitamin E compounds have been described, including four <i>tocopherols</i> (alpha, beta, gamma and delta) and four <i>tocotrienol</i> compounds (alpha, beta, gamma and delta).</p> <p>Only four of the many isomers of α-tocopherol (RRR-, RSR-, RRS-, and RSS) are efficiently maintained in human plasma. Synthetic vitamin E contains all eight isomers of α-tocopherol (“all racemic”). Only the RRR-form is present in food.</p> <p>Both topical preparations and oral supplements most often use the inactive esters (e.g. α-tocopheryl acetate) instead of α-tocopherol, which is inherently instable (dependent upon source, formulation, storage conditions, exposure to UV light, alkalies, and oxidation etc).</p> <p><u><i>Alpha-tocopherol equivalents and international units:</i></u></p> <p>The new recommendations for vitamin E are expressed as milligrams of RRR-α-<i>tocopherol equivalents</i> (α-TE), which accounts for about 90% of the activity in human tissue; the relative potency of alpha-, beta-, gamma-, and delta-tocopherol is reported to be approximately 100:50:25:1.</p> <p>Dietary supplements of vitamin E are labeled in terms of <i>international units (IU)</i>¹ (Hatchcock et al., 2005).</p> <p>For more information on the properties of Vitamin E, see the Tocopherol/Tocopherol esters monograph (Council of Europe, 2008).</p>

3. Regulation

<p>Norway</p>	<p>The maximum concentration of α-tocopherol acetate allowed in cosmetic products is 5 % (w/w)², according to The Norwegian Cosmetics regulation.³</p>
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¹ One mg of synthetic vitamin E (all-rac- α -tocopheryl acetate) is equivalent to 1 IU vitamin E, but only 0.45 mg RRR- α -tocopherol. One mg of natural vitamin E (RRR- α -tocopherol) provides 1.5 IU. E.g. 1000 mg (any α -tocopherol form) is equivalent to 1500 IU RRR- or 1000 IU all-rac- α -tocopherol.

EU	No regulation ⁴
Rest of the world	<p>In Japan, <i>tocopherol</i> (as <i>natural vitamin E</i>) has precedent for unrestricted use. <i>Synthetic DL-α-tocopherol</i> is also used without restrictions, except at concentrations \leq 1% in Cosmetic Licence Standard (CLS) categories such as hair care, makeup, fragrant, suntan, sunscreen, eyeliner, lip, oral and bath preparations.</p> <p><i>D-α-tocopheryl acetate</i> has precedent for use without restrictions in CLS categories cleansing- and nail polish preparations and for use at \leq 1% in all other categories.</p> <p><i>DL-α tocopheryl linoleate</i> has precedent for use without restriction in the CLS categories, cleansing preparations and nail makeup preparations and at \leq1% in all other CLS categories, except eyeliner and bath preparations, in which it is not used.</p> <p>(Zondlo Fiume, <i>Cosmetic Ingredient Review</i>, 2002: pp. 60).</p>

4. Relevant toxicity studies

Absorption	<p><i>For data on absorption, distribution, metabolism and excretion (see reports on safety assessment of vitamin E: Zondlo Fiume, <i>Cosmetic Ingredient Review</i>, 2002: pp. 62 – 70; SCF, 2003; Council of Europe, 2008).</i></p>
Skin	<p>There is conflicting evidence as concerns skin penetration and systemic bioavailability of vitamin E (Council of Europe, 2008). In a dermal absorption study using human subjects, absorption of α-tocopheryl-acetate was substantial, but systemic availability was not observed (Alberts et al., 1996). Also, systemic conversion to tocopherol was not seen. In a rat study, 6% of the applied dose penetrated into the epidermis after 5 days (Zondlo Fiume, 2002). Webster et al (1997) found that in human skin <i>in vivo</i>, at least 2% α-tocopherol(?) was available in the circulation after 24 h (cited in Council of Europe, 2008).</p> <p>Skin bioconversion of vitamin E was investigated using a hairless mouse skin <i>in vitro</i>. The appearance rate of vitamin E increased gradually during the entire period of the permeation and bioconversion experiment (72 h), but with a long time lag (24 h), indicating that vitamin E may bind strongly to the skin tissue. Since vitamin E is a very lipophilic compound, a considerable amount of vitamin E that is bio-converted in the viable skin is expected to diffuse back into the stratum corneum. It is conceivable that the findings obtained from hairless mouse also are applicable to humans, because the relevant enzyme (esterase) is distributed in human skin (Toyo & Lee, 1987).</p>
GI tractus	<p>For data on oral absorption, see Zondlo Fiume, 2002: pp. 67-70. Oral absorption of α-tocopherol is variable. The absorption rate of dietary α-tocopherol ranges from 50% to 70%. However, absorption decreases to less than 10% at high pharmacologic doses (200 mg) (Norsk Legemiddelhåndbok [online]). Absorption depends on the presence of</p>

² With reference to the risk of attracting allergic contact dermatitis, urticaria (itching) and *erythema multiforme*.

³ Regulation to be lifted by 11 July 2013.

⁴ "On the basis of current knowledge, the SCCNFP is of the opinion that alpha-tocopherol acetate does not pose a threat to the health of the consumer and therefore does not propose any restrictions or conditions on the use of alpha-tocopherol acetate in cosmetic products (SCCNFP, 2001).

	<p>bile; it is reduced in conditions of malabsorption; water miscible preparations are better absorbed than oil preparations (UpToDate(b) [online])</p>
Distribution	<p><i>For data on absorption, distribution, metabolism and excretion (Zondlo Fiume, Cosmetic Ingredient Review, 2002: pp. 62 – 70; SCF, 2003; Council of Europe, 2008).</i></p> <p>Vitamin E is a fat-soluble vitamin that is distributed to all body tissues, especially in the liver and fat cells where levels in excess of daily requirements are stored (unlike water-soluble vitamins that are excreted daily). Vitamin E deficiency is uncommon in humans, except in unusual circumstances and disorders e.g. celiac disease and Crohn disease (UpToDate [online]).</p> <p>In plasma and red blood cells, vitamin E is the main lipid-soluble antioxidant that protects cell membrane lipids (polyunsaturated fatty acids) from peroxidation and scavenges free radicals (UpToDate [online]).</p>
Metabolism	<p><i>For data on absorption, distribution, metabolism and excretion (Zondlo Fiume, Cosmetic Ingredient Review, 2002: pp. 62 – 70; SCF, 2003; Council of Europe, 2008).</i></p> <p><i>The anti-oxidant effect of vitamin E pertains to α-tocopherol, and not the esters (e.g. tocopheryl acetate), which must be hydrolyzed for activity (Adams and Connolly, 2010). There is conflicting evidence as to what extent the conversion of esters into free α-tocopherol takes place in biological meaningful amounts in the skin (reviewed in Thiele & Ekanayake-Mudiyanselage, 2007). Some examples indicate that vitamin E is bioconverted (Toyo & Lee, 1987) and metabolized (Norkus et al., 1993), whereas others don't (Alberts et al., 1996) - both references cited in Council of Europe (2008).</i></p> <p>Metabolic studies have shown a short half-life (ca. 12 min) for plasma α-tocopherol, with predominant accumulation in liver, adipose tissue and muscle 24 h after intravenous injection of intestinal lymph labeled with radioactive vitamin E in rats (reviewed in Rigotti, 2007).</p>
Excretion	<p><i>For data on absorption, distribution, metabolism and excretion (Zondlo Fiume, Cosmetic Ingredient Review, 2002: pp. 62 – 70; SCF, 2003; Council of Europe, 2008).</i></p> <p>Approx. 70% is excreted in the feces in the course of a few days – ca. 50% as the unchanged form (i.e. d-α-tocopherol). In urine, only metabolites of tocopherol are present, usually as conjugated glucuronide forms (Norsk legemiddelhåndbok [online]).</p>
Local toxic effects Irritation Sensitivity	<p>Overall vitamin E is considered to be <i>non-irritating</i> to skin and eyes. In clinical studies, tocopherol, tocopheryl acetate and tocopheryl succinate were not irritants (Zondlo Fiume, 2002).</p> <p>Tocopheryl acetate produced <i>skin sensitization</i> in one animal test, was not sensitizing in the “guinea pig maximation test” (GPMT)⁵, but can cause sensitization in the “open epicutaneous test” (OET)² (>30% tocopheryl acetate).⁶ In clinical studies, tocopheryl acetate was not sensitizing (Zondlo Fiume, 2002).</p> <p>Although vitamin E and derivatives are widely used in many topical</p>

⁵ Kimber et al. (2001) for description of different skin sensitization tests.

⁶ http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/dhi_report_app2_081211_en.pdf

	<p>cosmetic products, reports of side effects such as allergic or irritant skin reactions are rare (Adams & Connolly, 2010). Clinical studies similarly demonstrated that tocopherol and tocopherol acetate were safe for use in topical skin formulations (Thiele & Ekanayake-Mudiyanselage, 2007).</p> <p>In case reports, however, <i>contact dermatitis</i>, <i>contact urticaria</i>, and <i>erythema multiforme</i>-like eruptions have been described after topical application of vitamin E (Council of Europe, 2008; Zondlo Fiume, 2002: pp. 105 – 108, summarized in Table 13). E.g. one study reported four cases of <i>contact dermatitis</i>⁷ caused by cosmetic creams that contained 10% tocopheryl acetate (de Groot, 1991). Ohko et al. (2012) reported a case of ACD with erythema multiforme-like eruptions caused by a topical ointment (5% synthetic <i>DL-α</i>-tocopherol acetate). There was no reaction to 0.5% <i>DL-α</i>-tocopherol acetate. However, Matsumura et al. (2004) has reported a case of allergy elicited by much lower concentrations (0.5%, 0.25%). When testing alternative treatments for scars, vitamin E is possibly worsening a scar's appearance and causing contact dermatitis, contact urticaria (itching), and erythema (redness) multiform-like reactions in a large percentage of patients” (Taylor, 2008). Contact dermatitis and eczema have been reported with topical vitamin E preparations, such as ointments or vitamin E-containing deodorants. (Mayo, 2011).</p> <p>In a survey of moisturizers, vitamin E was present in 55% of the products, but <i>allergic contact dermatitis (ACD)</i> due to vitamin E was relatively rare, possibly due to its low concentration in cosmetic products (Zirwas and Stechschulte, 2008).</p> <p>A PubMed scientific literature search revealed 931 cases of vitamin E-induced allergic contact dermatitis (ACD), mainly (905 cases) related to a brand of cosmetics containing <i>tocopheryl linoleate</i> (Perrenoud et al., 1994; Kosari et al., 2010). The reaction was believed to be caused by oxidation products of the vitamin, rather than by the vitamin itself. Tocopheryl linoleate continues to be used in 67 cosmetic products, but is relatively rare compared to the α-tocopherol and its acetate ester (EWG's Skin Deep [online]). Thus, patch tests have been proposed to identify whether problems are related to vitamin E derivatives or other components; e.g. breakdown products and contaminants (Thiele & Ekanayake-Mudiyanselage, 2007).</p> <p>Adams and Connolly (2010) determined the incidence of ACD from vitamin E in 2950 patients, by retrospectively analysing patch-test data during the period from 1987 to 2007. The results showed that 18 patients (0.61%) had positive reactions to α-tocopherol; 6 (0.53%) of 1,136 patients tested from June 1987 through December 1997, and 12 (0.66%) of 1,814 patients tested from January 1998 through December 2007 ($p = .69$). The study concluded that Vitamin E appears to be a relatively rare contact allergen.</p> <p>In conclusion, despite evidence for vitamin E as a skin toxicant, <i>the incidence of vitamin E-induced ACD is rare given its widespread use in cosmetics</i> (EWG's Skin Deep [online]; Zondlo Fiume, 2002).</p>
<p>Systemic toxic effects Acute</p>	<p>The acute oral toxicity of α-tocopherol is very low, with LD50 values of synthetic α-tocopherol and α-tocopheryl acetate greater than 2000 mg/kg</p>

⁷ The term contact dermatitis sometimes is used incorrectly as a synonym for allergic contact dermatitis. Contact dermatitis is inflammation of the skin induced by chemicals that directly damage the skin (see Irritant Contact Dermatitis) and by specific sensitivity in the case of allergic contact dermatitis. <http://tinyurl.com/y8kvy3p>. Allergic contact dermatitis (ACD) is a delayed type of induced sensitivity (allergy) resulting from cutaneous contact with a specific allergen to which the patient has developed a specific sensitivity. This allergic reaction causes inflammation of the skin manifested by varying degrees of erythema, edema, and vesiculization.

<p>Repeated dose</p>	<p>body weight in mice, rabbits, and neonatal and adult rats (SCF, 2003). LD50, mouse: 5000 mg/kg (MSDS).</p> <p>The US Food and Nutrition Board (FNB) concluded that available data (dose-response relationships) from several large human intervention trials and other clinical trials were insufficient to determine a NOAEL for α-tocopherol. The panel used animal data to establish a LOAEL of 500 mg/kg bw/day, with hemorrhage (abnormal bleeding) as the critical effect (DRI, 2011; ERNA [online]). An uncertainty factor of 2 was used to set a tolerable upper intake limit (UL) for α-tocopherol of 1000 mg/day; i.e. the maximum daily intake unlikely to cause adverse health effects.</p> <p>The EC scientific Committee on Foods (SCF) (SCF, 2003), used a placebo controlled dose response supplementation study in 88 healthy humans to set the NOAEL at 540 mg α-tocopherol equivalents (α-TE), with hemorrhagic effects as the critical event. An uncertainty factor of 2 was used to adjust for inter-individual differences in sensitivity, giving an UL of 270 mg α-TE (rounded to 300 mg α-TE). (ERNA [online]).</p> <p>The UK expert group on Vitamins and Minerals (EVM) – a scientific committee of the UK Food Standards Agency – established a NOAEL of 540 - 970 mg α-TE based on three placebo controlled human studies (atherosclerosis, angina pectoris). The UL was established at 540 mg α-TE, as a safety factor was not considered necessary. (ERNA [online]).</p> <p>A subchronic oral toxicity study of mixed tocopheryl phosphates in rats, reported NOAEL values equivalent to 587 and 643 mg /kg bw/day for male and female rats, respectively (Gianello et al., 2007).</p> <p>A short-term repeated dose toxicity study (28 days) resulted in the following NOAEL values (racemic tocopheryl acetate): Rat: 1111 mg/kg bw; Dog: 360 mg/kg bw (unpublished).</p> <p>A subchronic toxicity study (90 days) found a NOAEL of 2000 mg/kg bw/d in both rats and minipig (unpublished report)⁸.</p>
<p>Mutagenicity /genotoxicity</p>	<p>There is no evidence of a mutagenic/genotoxic potential of tocopherols.</p>
<p>Carcinogenicity</p>	<p><u>Skin cancers:</u> (for more details, see monograph on Tocopherol /Tocopherol esters (Council of Europe, 2008).</p> <p>No epidemiological studies investigating the relationship between topically applied α-tocopherol and skin cancer. Clinical trials suggest that both <i>dietary</i> and <i>topical</i> vitamin E may provide photoprotection, but reports not entirely consistent (Evans & Johnson, 2010).</p> <p>Multiple studies in mice treated topically with α-tocopherol and esters provide strong evidence of photoprotection (summarized in Annex 5, taken from table 2, Thiele & Ekanayake-Mudiyanselage, 2007; Evans and Johnsen, 2010, and references therein). However, <i>esterified forms</i> of α-tocopherol have not been found to offer the same protection, or even lack a protective effect. This is possibly related to the antioxidant effect of vitamin E, which depends on a free hydroxyl group on the aromatic ring for scavenging free radicals. It appears that limited cleavage of vitamin E esters into biologically active α-tocopherol takes place in the skin. Also, the photo-protective effect in sunscreens is likely to involve conversion of ester forms into free α-tocopherol (Hanson and Clegg, 2003).</p>

⁸ http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/dhi_report_app2_081211_en.pdf

<p>Reprotoxicity / teratogenicity</p> <p>Other effects</p>	<p>In contrast, Gensler et al. (1996) reported that tocopheryl acetate and tocopheryl succinate appeared to <i>enhance</i> photocarcinogenesis in mice, whereas α-tocopherol was protective using the same treatment protocol (Zondlo Fiume, 2002). This conclusion was not supported by an SCCNFP in 2001, whereas the Council of Europe requested additional studies to gain full insight and clarification as concerns the photo carcinogenicity issue in connection with the acetate esters (Council of Europe, 2008). It might be speculated that a putative photo-carcinogenic effect of vitamin E acetate is related to a (dose-dependent) shift from anti-oxidant to pro-oxidant activity, similar to what has been reported in other systems (e.g. Soni et al., 2010).</p> <p>Adverse effects of vitamin E on reproductive function have not been observed in humans (at oral doses up to 2% in the diet) and vitamin E was not teratogenic in mice (SCF, 2003; Thiele & Ekanayake-Mudiyansele (2007); Tomassi and Silano (1986)⁹.</p> <p><i>Modulation of carcinogenicity:</i> tocopherol appears protective in most cases, but one study reported that it can act as a complete tumor promoter (Zondlo Fiume, 2002: pp. 102).</p>
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5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	<p>A LOAEL of 500 mg/kg bw/day has been established for α-tocopherol, based on the potential for hemorrhagic effects.</p> <p>NOAEL = LOAEL /3 = 500/3 = 167 mg /kg bw/day. ^{10,11,12}</p>
Exposure cosmetic products	<p>For assessment of systemic exposure dose (SED), the following premises were used:</p> <ul style="list-style-type: none"> - Conc. of Vitamin E in the products: 5% (illustrative purpose); likely very conservative as typical use levels are approximately 0.5%. - Skin penetration rate: 2% - The estimated daily exposure levels for body and face are 123.20 and 24.14 mg/kg bw/day, respectively¹³ <p style="text-align: center;">• Total body</p> <p>Calculated relative daily exposure of product : 123.20 mg/kg bw/day The concentration of vitamin E in product: 5% = 0.05 Dermal absorption / skin penetration rate: 2% = 0.02</p> <p>SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 123.20 mg/kg bw/day x 0.05 x 0.02 = 0.123 mg/kg bw/day</p>

⁹ Vitamin E was administered subcutaneously (sc) in amounts of 150 or 300 mg/kg/day to pregnant mice on days 6, 8 and 10 of gestation. Growth retardation and fetal survival were increased in the treated group, and the incidence of cleft palate was increased. Similar studies with 75 mg/day vitamin E in rats were negative (Toxnet [online]).

¹⁰ For the purpose of calculating the margin of safety (MoS), an additional factor of three is taken into consideration when using the LOAEL value, cf. SCCS notes of Guidance, 7th revision (SCCS, 2010).

¹¹ <http://www.epa.gov/risk/dose-response.htm>

¹² By comparison, the NOAEL values set by SCF and EVM were 300 mg/kg bw/day and 540 mg/kg bw/day, respectively.

¹³ SCCS notes of Guidance, 7th revision (SCCS, 2010).

	<ul style="list-style-type: none"> • Face <p>Calculated relative daily exposure of product : 24.14 mg/kg bw/day The concentration of vitamin E in product: 5% = 0.05 Dermal absorption / skin penetration rate: 2% = 0.02</p> <p>SED = A (mg/kg bw/day) x C(%) / 100 x Dap (%) / 100 = 24.14 mg/kg bw/day x 0.05 x 0.02 = 0.024 mg/kg bw/day</p> <p>Overall SED from cosmetic products: Body lotion + face cream: 0.123 + 0.024 = 0.147 mg/kg bw/day Daily exposure of a 60 kg person: 0.147 * 60 = 8.8 mg /day.</p>
Margin of Safety (MoS)	<p>MoS (NOAEL / SED): NOAEL = 167 mg/kg bw/day</p> <p>MoS for total body: SED = 0.123 mg/kg bw/day MoS = 167 / 0.123 = 1358</p> <p>MoS for face cream: SED = 0.024 mg/kg bw/day MoS = 167 / 0.024 = 6958</p> <p>Overall MoS (body lotion + face cream): SED = 0.147 MoS = 167 / 0.147 = 1136</p>

6. Other sources of exposure than cosmetic products

Food stuffs	<p>There are no adverse effects caused by vitamin E from <i>natural</i> dietary sources (DRI [online]). The recommended daily intake (RDI) of Vitamin E in food (e.g. vegetable oils and cereals) is 8-10 mg (Norsk Legemiddelhåndbok [online]). Mean intakes of vitamin E in Europe are between 7 and 15 mg α-TE (SCF, 2003), and between 5 and 20 mg in the US.</p> <p>As a dietary supplement, vitamin E is used for its antioxidant effects. In Norway, the maximum recommended daily dose of vitamin E in vitamin allowed in supplements is 30 mg α-TE (Forskrift om kosttilskudd [online]).</p> <p>In US, the recommended dietary allowances (RDAs) is 15 mg of vitamin E per day - or 22 IU of natural RRR-or 33 IU of synthetic all rac-α-tocopherol (issued by the US Food and Nutrition Board (FNB); cf. GRAS Substances (SCOGS) Database, http://tinyurl.com/bn7a3z8).</p> <p>The <i>tolerable upper intake level (UL)</i> -- the amount most people can take without developing toxic effects -- is 1000 mg (1500 IU) / day for natural vitamin E and 500 mg (1100 IU) /day for synthetic vitamin E.</p> <p>In EU, the European Food Safety Authority (EFSA) has set the UL at 300 mg/day (for adults), 100 mg/day (ages 1-3 years) and 260 mg/day (ages 15-17 years) (EFSA, 2008; Mayo, 2011).</p>
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Pharmaceuticals	<p>Large clinical trials have failed to demonstrate medicinal uses of vitamin E (Swedish Health Library [online]); e.g. vitamin E supplementation offered no benefit for heart disease, and it slightly increased overall mortality (Byers, 2010 and references therein; Soni et al., 2010). The Selenium and vitamin E cancer prevention trial (SELECT) showed increased prostate cancer risk from vitamin E supplements (Klein et al., 2011): men who took 400 IU (180 mg) of vitamin E (DL-α-tocopheryl acetate) daily had more prostate cancers compared to the placebo group; 76 vs. 65 cases per 1000, respectively.</p> <p>Most studies have used between 50 IU and 800 IU daily doses (some even higher), corresponding to about 50 mg to 800 mg of synthetic vitamin E or 25 mg to 400 mg of natural vitamin E (Swedish Health Library [online]).</p> <p>Thus, there is no evidence for an optimal (if any) therapeutic dosage of vitamin E.</p>
Other sources	
Adverse side effects - from uses other than cosmetics	<p>A literature review on vitamin E toxicity revealed no adverse effects using up to 3200 IU/day of vitamin E, concluding that up to 1600 IU/day of vitamin E appears to be safe for most adults (Hathcock et al. 2005)</p> <p><i>Bleeding:</i> High doses of α-tocopherol supplements can cause hemorrhage and interrupt blood coagulation in animals (DRI [online], Table 3; EFSA, 2008; Mayo, 2011).</p> <p><i>Skin cancer:</i> Epidemiological studies and intervention studies support a role for diets rich in nutrients such as α-tocopherol and others (e.g. flavonoids, β-carotene, lycopene and lutein) and decreased risk of photoaging and cancer, but conclusions are not entirely consistent (Evans & Johnson, 2010, Thiele & Ekanayake-Mudiyanselage, 2007). Studies in mice also indicate that topical α-tocopherol is photo protective. However, there is a report that vitamin E may increase the risk of developing basal cell carcinoma (Heinen et al., 2007), but the clinical relevance is unclear. Serum concentrations of α-tocopherol were not associated with later skin cancer incidence (van der Pols et al., 2009).</p> <p><i>Dermabrasion / chemical peel:</i> Hunter DH et Frumkin (1991) reported that: —Three women and one man aged forty-one to sixty-five years experienced a severe burning sensation following the application of Aloe Vera or vitamin E preparations to a skin area that had been subjected to a chemical peel or dermabrasion. Subsequently, a severe dermatitis occurred that required hospitalisation of one patient and intravenous administration of ster-oids....Patients undergoing dermabrasion or chemical peel procedures should be cautioned specifically against the use of Aloe vera or vitamin E topically in the first weeks after surgeryll (Aloe extracts, Europarâdet, pp. 18)</p> <p><i>Interactions:</i></p>

	<p>Pharmacologic doses (more than 300–400 mg/day) of vitamin E may increase the risk of bleeding in patients treated with anticoagulants. Vitamin E at RDA does not increase bleeding time or affect warfarin except at megadoses (~10x RDA or higher) - adjustment of warfarin may be necessary for such doses (DRI [online]). Unexpected results obtained from interactions of vitamin E and vitamin C (and/or CoQ10) has also been reported (Trueba et al., 2004).</p> <p><i>General adverse effects:</i> Vitamin E is known to cause gastro-intestinal symptoms (e.g. nausea, diarrhea and flatulence) at high doses. Very modest but statistically significant increase in all-cause mortality with supplemental intake of vitamin E =400 IU/day.</p>
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7. Assessment

According to the EWG's cosmetic safety database (EWG's Skin Deep [online]), more than 14000 currently marketed products contain tocopheryl acetate or tocopherol, and vitamin E is used in approximately 55% of moistening lotions / creams (Zirwas & Stechschulte, 2008). These substances are present in moisturizers, sunscreens, lip products, foundations, cleansers, conditioners, and other topical products. With the steadily increased interest in anti-aging and rejuvenation products, the number is likely to increase in the future.

General toxicity:

No adverse systemic effects are related to the use of vitamin E in the form of cosmetic products.

There are concerns that too much vitamin E can cause abnormal bleeding (hemorrhage), and safety authorities have established UL for vitamin E in adults of 1000 mg/day (U.S.) and 300 mg/day (Europe). EFSA has set a lower UL of 100 mg/day for children 1 – 3 years of age (EFSA, 2008; Mayo, 2011). Thus, people who consume more than this amount place themselves at greater risk of hemorrhagic damage because the nutrient can act as an anticoagulant.

Cosmetic products:

Vitamin E is considered to be non-irritating to skin and eyes. Allergic contact dermatitis (ACD) appears to be an uncommon phenomenon given the widespread use of vitamin E variants in skin care products, possibly related to its relatively low usage levels. In addition to ACD, contact urticaria and erythema multiforme-type eruptions have been reported in connection with vitamin E. Both these side effects are rare, with case reports in the literature only.

For hypothetical risk assessment calculations, we used a derived NOAEL of 167 mg/kg bw/day, with hemorrhage as the critical effect (based on animal experiments). An overall SED of 0.147 mg/kg bw/day was estimated from exposure to the whole body (i.e. body lotion + face cream¹⁴): $0.123 + 0.024 = 0.147$ mg/kg bw/day.

The resulting MoS (NOAEL/SED) amounts to $167/0.147 = 1136$.

Since the NOAEL is based on animal data, a MoS of 100 is sufficient as a safety margin¹⁵.

Food and dietary supplements:

There is no evidence of adverse effects from the consumption of vitamin E *naturally* occurring in foods. Adverse effects from vitamin E containing *supplements* may include hemorrhagic toxicity. The UL for vitamin E applies to any form of α -tocopherol obtained from supplements, fortified foods, or a combination of the two.

Total exposure:

The total exposure of vitamin E from cosmetic products (0.147 mg /kg bw/ day)¹⁶ and food supplements (0.25 mg/kg bw/day)^{17,18}: 0.40 mg/ kg bw/day.

The **combined MoS** (cosmetics + dietary supplements) = $167 / 0.40 = 418$, represents an acceptable safety margin, which agrees well with calculated mean intake from cosmetics and dietary supplements not more than 25 mg/ day for most users – i.e. much lower than UL at 300 mg/day for adults and 100 mg/day (ages 1-3 years) (EFSA, 2008; Mayo, 2011).

Thus, there is no reason for concerns relating to systemic toxic effects of vitamin E at *recommended* use levels in adults.

¹⁴ Concentration of 5% α -tocopherol as an illustrative example.

¹⁵ Considered to be very conservative as FNB and EFSA have set the NOAEL to 1000 mg/day and 300 mg/day –

¹⁶ SED of 0.147 mg/kg bw/day equals 8.8 mg /day ($0.147 * 60$) for an adult person weighing 60 kg.

¹⁷ Occasional use of vitamin E in the form of (unproven) medicinal products (e.g. 180 mg; cf. SELECT trial) has not been taken into consideration.

¹⁸ Average daily dietary dose of vitamin E is 8 mg in the Nordic countries (Council of Europe, 2008). Mean intake in Europe: 7 -15 mg α -TE, corresponding to $15 \text{ mg}/60 \text{ kg} = 0.25 \text{ mg}/\text{kg bw}/\text{day}$.

8. Conclusion

Systemic toxicity:

The risk assessment calculations of vitamin E in cosmetic products are based on a deduced NOAEL value for vitamin E of 167 mg/kg bw/day (hemorrhagic effect in animal experiments), a skin penetration rate of 2%, and a use level of 5% for illustrative purposes.

We find that there is no reason for concerns as regards systemic toxic effects of vitamin E, based on an overall MoS in cosmetics (body lotion + face cream) of 1136 (MoS = 100 is sufficient).

Skin irritation and sensitization:

Overall vitamin E is considered to be non-irritating to skin and eyes. However, α -tocopherol acetate failed some of the criteria regarding skin sensitization as an end-point:

α -tocopheryl acetate produced skin sensitization in one animal test, was not sensitizing in the "guinea pig maximization test" (GPMT), but can cause sensitization in the "open epicutaneous test" (OET) (>30% tocopheryl acetate). In clinical studies, tocopherol, tocopheryl acetate and tocopheryl succinate were not irritants (Zondlo Fiume, 2002).

Case reports suggest that vitamin E is associated with sensitization and allergic contact dermatitis (ACD).

Thus, we propose the following restriction in use levels:

Maximum use levels allowed in all cosmetic products: 5 % (w/w) α -tocopherol acetate.

Special considerations in some consumer groups:

Patients on anticoagulant therapy should be monitored when taking vitamin E supplements (> 300 mg/day?)¹⁹.

Comments:

At the proposed maximum allowed use levels for vitamin E variants, systemic toxicity is of no concern for the general consumer²⁰, and we would assume that problems with allergic skin dermatitis and sensitization are largely avoided.

¹⁹ The UL for vitamin E (vitamin supplements) is 1000 mg of α -tocopherol per day for adults. People who consume more than this amount place themselves at greater risk of hemorrhagic damage because the nutrient can act as an anticoagulant.

²⁰ In Germany, users of food supplements have, on average, an intake approx. 22% higher than non-users, corresponding to a MoS of $167 / (0.25 * 1.22 + 0.147) = 370$.

UK data indicates a highest average daily intake of vitamin E from supplements of 270 mg (270/60 = 4.5 mg /kg bw /day) in women aged between 50 and 64 years (97.5 percentile), corresponding to a MoS of $167 / (0.147 + 4.5) = 36$, which represents an insufficient margin of safety (ERNA [online]).

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9. Annexes

Annex I:

Tolerable upper intake levels of Vitamin E

Table II. Tolerable Upper Intake Levels (ULs) of Vitamins and Essential Minerals for Adults.					
Nutrient	UL ^a (per day)	Reasons given by the Institute of Medicine, National Academy of Sciences for UL	Basis for UL (NOAEL or LOAEL ^b /per day)	RDA or AI ^c (per day) Men/Women	Daily Value ^d (per day)
Vitamin E ^{f,g}	1,000 mg α-tocopherol	No adverse effects from consumption of vitamin E naturally occurring in foods. The critical adverse effect of high intakes from fortified foods, dietary supplements, or pharmacologic agents is increased tendency to hemorrhage. Adults deficient in vitamin K, including those taking coumarin drugs, have increased risk of coagulation defects.	LOAEL = 500 mg/kg	15/15 mg α-tocopherol	30 IU (22 mg of natural d-α-tocopherol acetate ^h)

^aUL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects.

^bNOAEL = No-observed-adverse-effect level; LOAEL = Lowest-observed-adverse-effect level.

^cRDA = Recommended Dietary Allowance; AI = Adequate Intake.

^dThe Daily Value is used in nutritional labeling of food products and dietary supplements. The values given are for individuals age 4 years and above.

^e5 mcg vitamin D for 19-50 year olds, 10 mcg for 51-70 year olds, and 15 mcg for those above 70 years.

^fAs α-tocopherol; applies to any form of supplemental α-tocopherol.

^gThe ULs for vitamin E, niacin, and folate apply to synthetic forms from supplements, fortified foods, or a combination of supplements and fortified foods.

^hThe conversion of IUs to mg α-tocopherol depends on the form.

Annex 2:

Human Health Effects:

Human Toxicity Excerpts:

/SIGNS AND SYMPTOMS/ Some adults given [repeated doses](#) of 2 to 3 g/day, in an attempt to reduce angina pectoris, developed skin rashes and mild GI irritation with diarrhea, but 1 g daily was consumed for months without untoward effects.

[Gosselin, R.E., R.P. Smith, H.C. Hodge. *Clinical Toxicology of Commercial Products*. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-266] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ /Side effects/ ... with larger doses (greater than 400 to 800 Units per day for prolonged periods) /include/... blurred vision ... breast enlargement in males and females ... diarrhea ... dizziness ... flu-like symptoms ... headache ... nausea or stomach cramps ... unusual tiredness or weakness.

[Thomson.Micromedex. *Drug Information for the Health Care Professional*. 25th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2005., p. 2969] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Very high doses of vitamin E (greater than 800 Units per day for prolonged periods) have also been associated with increased bleeding tendencies in vitamin K deficient patients, altered metabolism of hormones (thyroid, pituitary, and adrenal), altered immunity, impaired sexual function, and may increase the risk of thromboembolism in susceptible patients.

[Thomson.Micromedex. *Drug Information for the Health Care Professional*. 25th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2005., p. 2969] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Vitamin E is usually nontoxic. However, large doses (more than 300 units daily) have rarely caused nausea, diarrhea, intestinal cramps, fatigue, weakness, headache, blurred vision, rash, gonadal dysfunction, creatinuria, increased serum creatine kinase, creatine phosphokinase, increase serum cholesterol and triglycerides, increased urinary estrogens and androgens, and decreased serum thyroxine and triiodothyronine. These effects disappeared after discontinuing the vitamin.

[McEvoy, G.K. (ed.). *American Hospital Formulary Service. AHFS Drug Information*. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 3583] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Necrotizing enterocolitis has been associated with oral administration of large dosages (eg, 200 units daily) of a hyperosmolar (measured osmolality of 2025 mOsm/kg for a twofold dilution of the preparation) vitamin E preparation in low-birthweight infants.

[McEvoy, G.K. (ed.). *American Hospital Formulary Service. AHFS Drug Information*. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 3583] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ High dosages of vitamin E (400 units daily or greater) for 1 year or longer in individuals with chronic disease was associated with an increase in all-cause mortality in one pooled analysis that evaluated the dose-dependent effect of vitamin E on all-cause mortality. Findings from this pooled analysis of data were unclear regarding risks and benefits of lower dosages of vitamin E. However, a dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with an increased risk at dosages exceeding 150 units daily.

[McEvoy, G.K. (ed.). *American Hospital Formulary Service. AHFS Drug Information*. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 3584] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Vitamin E can cause hemorrhage, increase prothrombin time, and cause

blood coagulation abnormalities at very high dosages in animals. Although evidence from several large clinical intervention studies in which adult humans receiving 300 to 800 units of vitamin E daily for 1.4 to 4.5 years showed no increased risk of stroke, at least one study (the α -Tocopherol, Beta-carotene (ATBC) Cancer Prevention study) reported an increased mortality from hemorrhagic stroke in male smokers receiving 50 units of vitamin E daily.

[McEvoy, G.K. (ed.). American Hospital Formulary Service. AHFS Drug Information. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 3584] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ A complex, potentially fatal syndrome of thrombocytopenia, hepatomegaly, splenomegaly, ascites, and renal, pulmonary, and hepatic (eg, cholestasis) dysfunction has occurred in several premature infants who received iv therapy with dl-alpha-tocopheryl acetate solubilized in polysorbates 20 and 80 (E-Ferol for iv Infusion). Infants at greatest risk appeared to be those with low birthweights, and development of the syndrome appeared to be related to daily and total vitamin E and polysorbates doses. A progressive, vasculocentric hepatotoxicity has been described in these infants, characterized initially by degeneration and exfoliation of Kupffer's cells, central lobular accumulation of these cells, and centrally accentuated panlobular congestion; prolonged exposure to the IV vitamin E formulation was associated with progressive intralobular cholestasis, inflammation of hepatic venules, and extensive fibrotic, sinusoidal veno-occlusion ... This syndrome in these infants ... may result from a cumulative toxic effect of one or more of the ingredients in the injection (eg, polysorbates).

[McEvoy, G.K. (ed.). American Hospital Formulary Service. AHFS Drug Information. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 3584] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ Reports of toxicity to enterally administered vitamin E are rare in infants. However, increased risks of sepsis and necrotizing enterocolitis have been reported after both enteral and parenteral vitamin E, primarily when plasma (or serum) vitamin E levels exceed 3.5 mg/dL. Levels this high are seldom seen with enteral vitamin E when intake is 25 mg d-tocopherol equivalent/(kg/day) or less. Intakes below this threshold will be provided by infant formulas with vitamin E to energy ratios of up to 20 mg/100 kcal (30 IU/100 kcal) so long as energy intake does not exceed 125 kcal/(kg/day).

[Bell EF; J Nutr 119 (12 Suppl): 1829-31 (1989)] **PEER REVIEWED** [PubMed Abstract](#)

Annex 3: Summary CIR 2002

Quick Reference Table - Cosmetic Ingredient Review reports through June 2010									
S - safe as used; SQ - safe with qualifications; I - insufficient data to support safety; Z - insufficient data, but no uses; U - unsafe									
IJT - International Journal of Toxicology; JACT - Journal of the American College of Toxicology; JEPT - Journal of Environmental Pathology and Toxicology									
Ingredient Name	Review Conclusion					Explanation Use concentration for "S" conclusion 6	Concentration or other limitation on use for "SQ" conclusion	Safety concern for "U" conclusion	Journal Citation
	S	SQ	I	Z	U				
Tocopherol	X					5%			IJT 21(S3):51-116, 2002
Tocophersolan	X					0.2%			IJT 21(S3):51-116, 2002
Tocopheryl Acetate	X					36% (100% in Vitamin E oil)			IJT 21(S3):51-116, 2002
Tocopheryl Linoleate	X					2%			IJT 21(S3):51-116, 2002
Tocopheryl Linoleate/Oleate	X					not in current use ¹			IJT 21(S3):51-116, 2002
Tocopheryl Nicotinate	X					1%			IJT 21(S3):51-116, 2002
Tocopheryl Succinate	X					not reported ²			IJT 21(S3):51-116, 2002

Annex 4: Absorption

Vitamin E (α-tocopherol acetate)

The percutaneous absorption of α-tocopherol acetate was assessed in 11 patients aged 36–77 years with actinic keratoses. The patients rubbed a cream containing this ingredient into the skin of their forearms twice daily (morning and night) for 3 months. Before the main study, the patients applied a placebo containing the base cream only for 1 month. Skin biopsy samples were taken for analysis at the end of the 3-month period and (presumably) at the end of the 1-month period to provide baseline data. Similarly, blood samples were taken. Analysis of plasma from all subjects showed no difference during the baseline and treatment periods in the concentrations of free α-tocopherol (13 ± 6.3 (SD) and 13 ± 6.1 μg/mL, respectively) or α-tocopherol acetate (2.1 ± 0.9 and 2.5 ± 1.3 μg/mL, respectively). The analysis of four lots of randomly pooled biopsy samples showed a substantial increase in the concentration of α-tocopherol acetate (baseline, 5.9 ± 12 (SD) μg/g; all values 0 except one outlier; treated, 260 ± 200 μg/g) but no difference in the concentration of α-tocopherol or γ-tocopherol. These data indicate that α-tocopherol acetate is not metabolized to the free form of α-tocopherol in plasma or skin (Alberts *et al.*, 1996).

Alberts DS, Goldman R, Xu MJ, Dorr RT, Quinn J, Welch K, Guillen-Rodriguez J, Aickin M, Peng YM, Loescher L, Gensler H. Disposition and metabolism of topically administered alpha-tocopherol acetate: a common ingredient of commercially available sunscreens and cosmetics. *Nutr Cancer*. 1996;26(2):193–201. PubMed PMID:8875556.

Annex 5:

Photoprotective potential of topical vitamin E and derivatives -table taken from Thiele & Ekanayake-Mudiyanselage, 2007.

Table 2
Studies on the photoprotective potential of topical vitamin E and its derivatives *in vivo*

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E Vitamin E acetate	Rabbit	Erythema (MED)	Vitamin E protective; vitamin E acetate not protective	BHT also protective; Vitamin E also protective when applied after UVR-exposure	Roshchupkin et al. (1979)
Vitamin E	Human	Mechanoelectrical properties of skin	Protection against UVR-, and PUVA-induced damage		Potapenko et al. (1983)
Vitamin E Vitamin E derivatives	Human, rabbit	PUVA-induced erythema and changes in mechanoelectrical properties of skin	Vitamin E and derivatives with shorter hydrocarbon chain protective; vitamin E acetate not protective	No protection of vitamin E and derivatives when applied after UVR- exposure	Potapenko et al. (1984)
Vitamin E	Mouse	Lipid peroxidation	Protective	Vitamin A, BHT, and β - carotene also protective	Khettab et al. (1988)
Vitamin E	Mouse	Skin wrinkling, skin tumor incidence, and histology	Protective		Bissett et al. (1989)
Vitamin E	Human	Erythema (MED)	Protective	SPF-determination	Möller et al. (1989)
Vitamin E Trolox [®] Vitamin E acetate Vitamin E succinate Vitamin E linoleate Vitamin E nicotinate	Mouse	Skin wrinkling and sagging, skin tumor incidence, and histology	Vitamin E esters not as protective as vitamin E or vitamin E analog Trolox [®] ; no protection against UVA-induced skin sagging	Glutathione, β -carotene, BHT, and mannitol not protective	Bissett et al. (1990)
Vitamin E	Mouse	Skin tumor incidence and immunosuppression	Protective	Prolonged pre-treatment	Gensler and Magdalen o (1991) (continued on next page)

Table 2 (continued)

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E Vitamin E acetate	Rat	UVA-induced binding of 8-MOP and CPZ to epidermal biomacromolecules	Vitamin E protective after single application; vitamin E acetate only protective after prolonged application	Limited conversion of vitamin E acetate into vitamin E after single application	Schoonderwoerd et al. (1991)
Vitamin E acetate	Mouse	Lipid peroxidation and DNA-synthesis rate	Protective		Record et al. (1991)
Vitamin E	Mouse	Skin wrinkling, skin tumor incidence, and histology	Protective	Additive protection in combination with anti- inflammatory agents	Bissett et al. (1992)
Vitamin E acetate	Mouse	Erythema, edema, and skin sensitivity	Protective	Treatment immediately after UVR-exposure	Trevithick et al. (1992)
Vitamin E acetate	Mouse	Edema and histology	Protective	Delayed treatment after UVR-exposure; increased skin vitamin E concentration	Trevithick et al. (1993)
Vitamin E Vitamin E acetate Vitamin E sorbate	Mouse	Skin wrinkling	Vitamin E and sorbate ester protective; vitamin E acetate ester only modestly protective	Sorbate ester more protective than free vitamin E	Jurkiewicz et al. (1995)
Vitamin E Vitamin E acetate	Human	Erythema (skin color)	Moderate protection of vitamin E and vitamin E acetate when applied occlusively after UVR- exposure	No protection when applied occlusively before UVR-exposure	Montenegro et al. (1995)
Vitamin E Vitamin E acetate	Rat	UVA-induced binding of 8-MOP to epidermal biomacromolecules	Vitamin E protective; vitamin E acetate only protective after prolonged application	Conversion of vitamin E acetate into vitamin E slow	Beijersbergen van Henegouwen et al. (1995)

Vitamin E acetate Vitamin E succinate	Mouse	Skin tumor incidence and immunosuppression	No protection		Gensler et al. (1996)
Vitamin E	Yorkshire pig	Sunburn cell formation	Protection against UVR-induced damage	Minimal protection in reducing PUVA-induced damage	Darr et al. (1996)
Vitamin E	Mouse	Immunosuppression and lipid peroxidation	Protective	No protection when applied after UVR-exposure	Yuen and Halliday (1997)
Vitamin E	Mouse	Histology (sunburn cell formation and skin thickness)	Protective		Ritter et al. (1997)
Vitamin E Vitamin E acetate Vitamin E methyl ether	Mouse	Formation of DNA-photoadducts	Vitamin E derivatives less protective than vitamin E	Sunscreening properties of vitamin E	McVean and Liebler (1997)
Vitamin E	Mouse	Chemiluminescence after UVA-exposure	Protective	β -Carotene also protective	Evelson et al. (1997)
Vitamin E	Mouse	Formation of DNA-photoadducts in epidermal p53 gene	Protective		Chen et al. (1996)
Vitamin E	Mouse	Lipid peroxidation	Protective	Skin's enzymatic and non-enzymatic antioxidant capacity investigated	Lopez-Torres et al. (1998)

(continued on next page)

Table 2 (continued)

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E	Human	Erythema (skin color and skin blood flow)	Moderate protection	No protection when applied after UVR-exposure; SPF (determined in vitro) = 1	Dreher et al. (1999)
Vitamin E α -Tocopherol γ -Tocopherol Vitamin E acetate Vitamin E methyl ether	Mouse	Formation of DNA-photoadducts	Vitamin E, α -tocopherol and γ -tocopherol protective; vitamin E acetate and vitamin E methyl ether not protective	Application as dispersion in cream	McVean and Liebler (1999)
Vitamin E Vitamin E succinate	Mouse	Erythema, pigmentation, skin tumor incidence	Protective after prolonged application	No sign of toxicity observed for vitamin E and vitamin E succinate	Burke et al. (2000)
Vitamin E	Human	Formation of macrophage metalloelastase mRNA after UV-exposure	Protective with 5% Vitamin E occlusive application for 24 h prior UV-exposure	Pretreatment of skin with 20% NAC also protective	Chung et al. (2002)
Vitamin E	Yorkshire pig	Antioxidant protection factor, erythema, sunburn cells, thymine dimers	1% Vitamin E protective, but stronger protective in combination with 15% vitamin C	Application on 4 consecutive days	Lin et al. (2003)

BHT, butylated hydroxytoluene; CPZ, chlorpromazine; MED, minimal erythema dose; 8-MOP, 8-methoxypsoralen; PUVA, 8-methoxypsoralen and UVA-treatment; SPF, sun protection factor.

Annex 6:

Concentration of use, function and product formulation of vitamin E and its derivatives - table taken from Thiele & Ekanayake-Mudiyanselage, 2007

Table 3
Concentration of use, function and product formulation data of vitamin E and its derivatives

Compound	Concentration of use (%)	Antioxidant function	Function as skin-conditioning agent
Tocopherol	Baby products: 1 Bath products/shampoo/rinse off products: 0.01–0.8 Deodorants: 0.05 Hair products: 0.01–0.6 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.05–2 sun tan gels and creams: 0.001–0.3 Make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.001–0.9	Antioxidant; humectant; skin protectant	Occlusive; humectant; emollient; miscellaneous
Tocopheryl acetate	Baby products: 0.001–1 Bath products/shampoo/rinse off products: 0.0001–25 Deodorants: 0.2 Hair products: 0.001–0.3 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.001–25 sun tan gels and creams: 0.05–1 Cosmetics (e.g., make up liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.02–0.8	Antioxidant; humectant; skin protectant	Humectant; emollient; miscellaneous
Tocopheryl linoleate	Shaving cream: 2	Antioxidant	Miscellaneous
Tocopheryl linoleate/oleate	Moisturizing preparations, creams, lotions, body/hand ointments: 0.1–2 sun tan gels and creams: 2 Cosmetics (e.g., make up liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.1–2	Antioxidant	Emollient; miscellaneous
Tocopheryl nicotinate	Shampoo/rinse off products: 0.0001–1 Hair conditioner: 0.1–1 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.1 Make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.1	Antioxidant	Miscellaneous;
Potassium ascorbyl tocopheryl phosphate	Moisturizing preparations, creams, lotions, body/hand ointments: 0.02 sun tan gels and creams: 0.02 make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.02	Antioxidant	Anti-dandruff agent
Tocophersolan	Moisturizing preparations, creams, lotions, body/hand ointments: 0.2 ski freshener: 0.05	Antioxidant	
Tocopheryl succinate	Use in food supplementation; 1 mg D- α -tocopheryl succinate = 1.21 IU α -tocopherol	Antioxidant; humectant; skin protectant	Humectant; emollient;

According to data compiled by the cosmetic, toiletry, and fragrance association (CFTA); modified from Zondlo Fiume (2002).