

Vitamin E and Allergic Contact Dermatitis

Payman Kosari, Ali Alikhan, Mary Sockolov, and Steven R. Feldman

Reports of vitamin E-induced allergic contact dermatitis (ACD) and frequent use of vitamin-E derivatives (tocopherol, tocopheryl linoleate, tocopherol acetate, etc) in skin care products deserves further investigation into tolerability and suitability of vitamin E in skin care preparations. A PubMed search was conducted to review the prevalence of vitamin E-induced ACD. It revealed 931 cases of vitamin E-induced ACD mainly from one large study. There were no reported deaths and only three patients required hospitalization for treatment. It appears that vitamin E-induced ACD is an uncommon phenomenon; incidence is low despite its widespread use in skin care products. Given its antioxidant and photoprotective properties, vitamin E should remain an ingredient in skin care products.

VITAMIN E protects skin by absorbing the ultraviolet (UV) wavelengths that are most damaging to skin and by forming stable nonradical intermediates in the presence of oxidative stress.^{1,2} Although there are no conclusive data on its efficacy, vitamin E is postulated to minimize photoaging,³ decrease UV-induced damage,⁴ increase stratum corneum hydration,² and help accelerate wound healing.⁵ Although dietary vitamins provide some oxidative protection, topical antioxidant supplementation of lipophilic substances such as vitamin E help further protect the skin.⁶ With hopes of hastening scar resolution and erasing wrinkles, manufacturers commonly include vitamin E in topical cosmetics, lotions, and sunscreens. However, it has long been reported that topical vitamin E formulations are a source of allergic contact dermatitis (ACD). This may lead to speculation about its continued use in cosmetics and skin care products. We report the results of a literature review undertaken to explore the issue of vitamin E-induced ACD.

From the Center for Dermatology Research, Departments of Dermatology, Pathology, and Public Health Sciences, Wake Forest University School of Medicine; Winston-Salem, NC.

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Address reprint requests to Steven R. Feldman, MD, PhD, Department of Dermatology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1071. E-mail: sfeldman@wfubmc.edu

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Methods and Results

Studies describing vitamin E-induced ACD were identified with a literature search of the PubMed database. The search used the terms “vitamin E,” “tocopherol,” and “contact dermatitis.” Date restriction was not used, and only articles in English were considered. The articles obtained were screened for additional references to work not obtained through the initial search. Our search revealed 931 cases of vitamin E-induced ACD, most coming from one large study (Table 1).

Discussion

Since the beginning of the use of vitamin E as a topical agent, reports of vitamin E-induced ACD have surfaced. Vitamin E was discovered in 1922 as an essential component in animal reproduction; further studies postulated that its topical use might confer health benefits. Vitamin E effectively protects against acute and chronic UV-induced damage that is clearly associated with human skin cancers.^{7,8} When it effectively penetrates the skin, vitamin E neutralizes lipid peroxyl radicals while preventing further unsaturated fatty acid peroxidation.⁹ The remaining vitamin E that has not penetrated the epidermis continues to provide protection by absorbing UV radiation.¹ Vitamin E may be found in products as tocopherol (usually α -tocopherol) or as the esterified form, tocopheryl. Both are absorbed by the body at similar rates, but the ester is thought to be less susceptible to oxidation.¹⁰

Brodtkin and Bleiberg reported the first case of ACD after the use of a vitamin E-based cream.¹¹ Since then, others have reported similar dermatitic symptoms in patients who used vitamin E-containing skin care products (see Table 1). Vitamin E-induced ACD has been

Table 1. Case Reports and Studies of Contact Allergy to Vitamin E

<i>Study</i>	<i>Patient No.</i>	<i>Sex, Age (yr)</i>	<i>Medium Used</i>	<i>Clinical Features</i>	<i>Patch-Test Results*</i>
Brodkin et al, 1965	1	F, 18	Tashan Cream (Hoffman, La Roche, Basel, Switzerland) (α -tocopherol)	Two episodes of erythema, edema, vesiculation, and crusting of left ear lobe and helix after application of Tashan cream	Reaction (+) to d- α -tocopherol
Minkin et al, 1973	1–3	NR	Mennen E (vitamin E) deodorant (Colgate-Palmolive, New York)	Erythema and edema of underarms with a blotchy morbilliform dermatitis spreading to trunks and arms	Patch testing not performed.
Aeling et al, 1973	1–3	M, 18 M, 22 M, 16	Vitamin E-based aerosol deodorant (dl- α -tocopherol)	All patients experienced pruritus and erythema of the axillae extending onto the thorax and upper extremities.	Two patients were patch-tested with dl- α -tocopherol (–); (third patient was not tested); 1 patient (the other two were not tested) had positive (2+) patch-test reaction to mixture of α -, β -, γ -, and δ -tocopherol (nonacetate form).
Roed-Peterson et al, 1975	1	M, 21	dl- α -tocopherol 20% pet (5% pet was negative)	Patch testing of 97 patients resulted in one report of ACD of the hands and forearms.	Reaction (2+) to dl- α -tocopherol 20% pet 22 days after application of test (probably patch-test sensitization as follow-up test results were negative)
Saperstein et al, 1984	1	F, 31	Contents of “pure vitamin E” capsule	Extensive eruption in a generalized distribution after application of vitamin E oil on right thigh and right hemithorax	Reaction (4+) to dl- α -tocopherol acetate
	2	F, 32	Vitamin E cream	Postoperative wound care (s/p augmentation mammoplasty) with vitamin E cream resulted in numerous erythematous edematous patches and plaques, papules, and macules around breast, axillae, and arms.	Reaction (2+) to dl- α -tocopherol
Goldman et al, 1986	1	F, 63	Contents of “pure vitamin E” capsule	Erythematous, eczematous, and pruritic eruption over upper chest, neck, and face after application of vitamin E oil in vitiliginous areas of body	Reaction (2+) to “pure vitamin E” oil (no mention of other ingredients)
Fisher 1987	1	F, 46	Moisturizing cream (vitamin E)	Acute pruritic edematous dermatitis of face after use of facial cream for wrinkles	Patch testing not performed.
Hunter et al, 1991	1	F, 48	Contents of “pure vitamin E” capsule	Redness, swelling, stinging, and infection of face requiring antibiotics after mixing of contents of vitamin E oil with Crisco shortening (J.M. Smucker Co., Orville, OH) for facial care after full-face chemical peel	Patch testing not performed.

Table 1. Continued

<i>Study</i>	<i>Patient No.</i>	<i>Sex, Age (yr)</i>	<i>Medium Used</i>	<i>Clinical Features</i>	<i>Patch-Test Results*</i>
De Groot et al, 1991	2	M, 41	Contents of "pure vitamin E" capsule	Swelling, stinging, and intense redness of face after application of vitamin E oil to face s/p dermabrasion of both cheeks	Patch testing not performed.
	3	F, 51	Contents of "pure vitamin E" capsule	Burning, erythema, and exudation of face after application of vitamin E oil to face s/p perioral chemical peel	Patch testing not performed.
	1	F, 40	Cosmetic creams (tocopheryl acetate)	Erythema and urticarial papules on face and neck with edema of eyelids after first-time use of a cream on face.	Reaction (2+) to tocopheryl acetate 10% pet
	2	F, 45	Cosmetic creams (tocopheryl acetate)	Dermatitis of face and hands after use of moisturizing cream	Reaction (1+) to tocopheryl acetate 10% pet
	3	F, 38	Cosmetic creams (tocopheryl acetate)	Papulovesicular dermatitis of abdomen, thighs, and buttocks after first-time use of moisturizing cream for treatment of striae	Reaction (2+) to tocopheryl acetate 10% pet
Garcia-Bravo et al, 1992	4	F, 27	Cosmetic creams (tocopheryl acetate)	Erythematous papular dermatitis on upper legs and thighs with papular dissemination to arms and trunk after use of moisturizing cream for treatment of cellulitis	Reactions (2+) to tocopheryl acetate 10% pet and tocopheryl nicotinate 10% pet
	1	M, 28	Soapy oats lotion (water-soluble tocopherol acetate)	Acute generalized eczema after use of soapy oats lotion	Reaction (1+) to tocopherol acetate 1% aq
Manzano et al, 1994	1	M, 17	Glaan cream (Neo-Farmaceutica, Lisbon, Portugal) (tocopheryl acetate)	Eczema development on right leg 2 months after application of moisturizing cream on a third-degree burn	Reactions (3+) to tocopheryl acetate 20% and 10% pet
Perrenoud et al, 1994	905 [†]	NR	Cosmeceutical vitamin E lineolate (mainly tocopheryl linoleate)	Papular, follicular, widely distributed pruritic contact dermatitis	Not all patients were patch-tested.
Bazzano et al, 1996	1	F, 19	Topical ointment (5% vitamin E)	Development of eczematous lesions scattered over arms and legs after application of topical formulation	Reaction (1+) to tocopherol acetate 2.5%
Harris et al, 1997	1	F, 17	Contents of "pure vitamin E" capsule	Erythema and edema of entire face after application of vitamin E oil to facial laceration	Negative reactions to dl- α -tocopherol 4% pet, contents of vitamin E capsule, and cosmeceuticals containing tocopheryl acetate
Parsad et al, 1997	1	F, 30	Contents of 400 IU vitamin E, Evion capsule (Merck, Darmstadt, Germany)	Erythematous papules and vesicles, progressing to xanthomatous reaction, after application of vitamin E oil to face for postinflammatory hyperpigmentation after superficial injury to right cheek	Patch testing not performed.
Oshima et al, 2003	1	F, 32	Medicated cream for hands and fingers	Itchy eruptions and edematous erythema on trunk and extremities	Reaction (1+) to dl- α -tocopheryl nicotinate 0.1% pet

Table 1. Continued

Study	Patient No.	Sex, Age (yr)	Medium Used	Clinical Features	Patch-Test Results*
Matsumura et al, 2004	1	M, 31	Mentholatum AD cream (ROHTO, Osaka, Japan)	Edematous erythema and serous papules on face, penis, and upper extremities and hands	Reactions (+) to tocopherol acetate 0.5% and 0.25%

ACD = allergic contact dermatitis; aq = aqueous; F = female; IU = international units; M = male; NR = not reported; pet = in petrolatum; s/p = status post.

*A “+” indicates that the patch-test result was positive but that the intensity of the reaction was not reported; a number preceding the “+” indicates the intensity as reported by the author(s).

†Dermatologists saw 263 patients, and 642 patients self-reported.

reported from underarm aerosol deodorant (namely, Mennen E, Colgate-Palmolive, New York, NY),^{12,13} chemical peels,¹⁴ and concentrated vitamin E oil (“pure vitamin E”) capsules.^{14–18} Rash presentation is predominantly eczematous and papular but can range from xanthomatous eruptions to erythema multiforme-like lesions.^{15,18}

The type of vitamin E derivative also plays a role in ACD. Roed-Petersen and Hjorth patch-tested 97 patients with d,l- α -tocopherol in 20% petrolatum, resulting in just one positive result.¹⁹ Furthermore, solutions of dl- α -tocopherol (5%), d- α -tocopherol (5% and 20%), and d- α -tocopheryl succinate (5% and 20%) did not induce a positive test result in this subject. Other studies have confirmed that dl- α -tocopherol (of synthetic origin) induces dermatitis more frequently than d- α -tocopherol (of natural origin).²⁰

The North American Contact Dermatitis Group (NACDG) tested 4,435 patients with 100% dl- α -tocopherol and observed 0.7% reactivity in 2005 to 2006, compared with 1.1% reactivity in 2003 to 2004 and 0.5% in 2001 to 2002.²¹ Wetter and colleagues patch-tested with 10% tocopherol and found that 0.8% of the 711 participants had a positive reaction.²² This rate is similar to the positive-reaction rates of mercapto mix 1%, sesquiterpene lactone mix 0.1%, benzophenone-3 3%, and hydrocortisone-17-butyrate 1%.²¹ Although there is a low rate of reaction to dl- α -tocopherol, the increasing use of vitamin E in skin care products suggests that many may benefit by including it in standard patch tests.

In 1992, an epidemic outbreak of papular, follicular, and widely distributed rashes with pronounced pruritus occurred in Switzerland following the release of a new line of cosmetics. In fact, the cosmetic line induced ACD at least three times per 1,000 units sold. Perrenoud and colleagues, using patch tests on affected patients and

biochemical studies on the cosmetic line, found the offending agent to be vitamin E linoleate, a mixture of fatty acid esters of d,l- α -tocopherol, primarily composed of tocopheryl linoleate but also tocopheryl oleate, tocopheryl palmitate, and tocopheryl myristate.²³ Because of its lipophilic properties and possible active metabolite production in vivo, tocopheryl linoleate may be more allergenic than other derivatives of vitamin E. Furthermore, both delayed- and immediate-type presentations were reported. However, the Cosmetic Ingredient Review Expert Panel concluded that all vitamin E derivatives, including tocopheryl linoleate, are safe for topical use, and tocopheryl linoleate continues to be used in many skin care and cosmetic products.²⁴

According to the National Institutes of Health National Library of Medicine database on household products, 126 personal care products contain tocopherol, 309 products contain tocopheryl acetate, 11 products list tocopherol acetate as an ingredient, and 4 products still contain tocopheryl linoleate.²⁵ The Environmental Working Group’s Skin Deep cosmetic safety database lists 11,931 products containing tocopheryl acetate, 8,944 containing tocopherol, and 210 containing tocopheryl linoleate.²⁶ Although tocopheryl linoleate appears to be the more problematic form of vitamin E, it continues to be included in at least 210 cosmetic products.²⁶

Review of the literature on vitamin E-induced ACD suggests several important principles: (1) higher concentrations of vitamin E produce ACD more often than do low concentrations,¹⁹ and many cases have occurred after the use of high-concentration vitamin E oil (“pure vitamin E”)^{14–18}; (2) vitamin E-induced ACD is an uncommon phenomenon—incidence is low despite its widespread use in skin care products; and (3) several of the case reports of vitamin E-induced ACD were not confirmed by patch testing, casting some doubt upon their claim.

Although the healing properties of vitamin E are controversial, its photoprotective properties have been used in various cosmetic and skin care products.²⁷ Soon after the addition of vitamin E to skin care products, reports of vitamin E-induced ACD began to surface, implicating d,l- α -tocopherol, tocopheryl acetate, and tocopheryl nicotinate, along with concentrated vitamin E oil ("pure vitamin E"). However, these reports represent only a minute percentage of the population that uses products that contain vitamin E. Of note, most cases involved eczematous lesions, papular rashes, acute edematous urticaria-like lesions, and erythema multiforme-like eruptions; only three reported patients have required hospitalization.^{14,15} When one suspects a patient is experiencing vitamin E-induced ACD from a particular product, patch testing with the suspected type of vitamin E as well as with all of the other ingredients in the product is called for, along with detailed history and other types of appropriate testing (use testing, dilutional testing, repeat open application testing). There are no conclusive data on the best form, concentration, and vehicle for patch-test screening. De Groot and colleagues recommended vitamin E derivatives at a 10% concentration in petroleum,²⁸ but the extended and comprehensive NACDG patch test series include 100% dl- α -tocopherol. Other commercially available patch tests include tocopherol acetate 100% and dl- α -tocopherol acetate 10% in petrolatum.^{29,30} Vitamin E allergy testing is not currently available on the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test ready-to-use patch-test system. Further research is necessary to determine the best form, concentration, and vehicle for patch-test screening.

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References

- Krol ES, Kramer-Stickland KA, Liebler DC. Photoprotective actions of topically applied vitamin E. *Drug Metab Rev* 2000;32:413–20.
- Manela-Azulay M, Bagatin E. Cosmeceuticals vitamins. *Clin Dermatol* 2009;27:469–74.
- Podda M, Grundmann-Kollmann M. Low molecular weight antioxidants and their role in skin ageing. *Clin Exp Dermatol* 2001;26:578–82.
- Dreher F, Gabard B, Schwindt DA, Maibach HI. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet-induced erythema: a human study in vivo. *Br J Dermatol* 1998;139:332–9.
- Nachbar F, Korting HC. The role of vitamin E in normal and damaged skin. *J Mol Med* 1995;73:7–17.
- Weber C, Podda M, Rallis M, et al. Efficacy of topically applied tocopherols and tocotrienols in protection of murine skin from oxidative damage induced by UV-irradiation. *Free Radic Biol Med* 1997;22:761–9.
- Burke KE, Clive J, Combs GF, et al. Effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. *Nutr Cancer* 2000;38:87–97.
- de Gruijl FR. Photocarcinogenesis: UVA vs. UVB radiation. *Skin Pharmacol Appl Skin Physiol* 2002;15:316–20.
- Serbinova EA, Packer L. Antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Methods Enzymol* 1994;234:354–66.
- Mathias PM, Harries JT, Peters TJ, Muller DP. Studies on the in vivo absorption of micellar solutions of tocopherol and tocopheryl acetate in the rat: demonstration and partial characterization of a mucosal esterase localized to the endoplasmic reticulum of the enterocyte. *J Lipid Res* 1981;22:829–37.
- Brodtkin RH, Bleiberg J. Sensitivity to topically applied vitamin E. *Arch Dermatol* 1965;92:76–7.
- Aeling JL, Panagotacos PJ, Andreozzi RJ. Letter: allergic contact dermatitis to vitamin E aerosol deodorant. *Arch Dermatol* 1973;108:579–80.
- Minkin W, Cohen HJ, Frank SB. Contact dermatitis from deodorants. *Arch Dermatol* 1973;107:774–5.
- Hunter D, Frumkin A. Adverse reactions to vitamin E and aloe vera preparations after dermabrasion and chemical peel. *Cutis* 1991;47:193–6.
- Saperstein H, Rapaport M, Rietschel RL. Topical vitamin E as a cause of erythema multiforme-like eruption. *Arch Dermatol* 1984;120:906–8.
- Goldman MP, Rapaport M. Contact dermatitis to vitamin E oil. *J Am Acad Dermatol* 1986;14:133–4.
- Harris BD, Taylor JS. Contact allergy to vitamin E capsules: false-negative patch tests to vitamin E? *Contact Dermatitis* 1997;36:273.
- Parsad D, Saini R, Verma N. Xanthomatous reaction following contact dermatitis from vitamin E. *Contact Dermatitis* 1997;37:294.
- Roed-Petersen J, Hjorth N. Patch test sensitization from d,l-alpha-tocopherol (vitamin E). *Contact Dermatitis* 1975;1:391.
- Oshima H, Tsuji K, Oh-I T, Koda M. Allergic contact dermatitis due to DL-alpha-tocopheryl nicotinate. *Contact Dermatitis* 2003;48:167–8.
- Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis* 2009;20:149–60.
- Wetter DA, Davis MD, Yiannias JA, et al. Patch test results from the Mayo Clinic Contact Dermatitis Group, 1998–2000. *J Am Acad Dermatol* 2005;53:416–21.
- Perrenoud D, Homberger HP, Auderset PC, et al. An epidemic outbreak of papular and follicular contact dermatitis to tocopheryl linoleate in cosmetics. Swiss Contact Dermatitis Research Group. *Dermatology* 1994;189:225–33.
- Zondlo Fiume M. Final report on the safety assessment of tocopherol, tocopheryl acetate, tocopheryl linoleate, tocopheryl linoleate/oleate, tocopheryl nicotinate, tocopheryl succinate, dioleoyl tocopheryl methylsilanol, potassium ascorbyl tocopheryl phosphate, and tocophersolan. *Int J Toxicol* 2002;21 Suppl 3:51–116.

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25. National Institutes of Health. Household Products Database. Bethesda (MD): National Institutes of Health National Library of Medicine Specialized Information Services; 2009.
 26. Environmental Working Group. Skin Deep cosmetic safety database. Washington (DC): Environmental Working Group; 2009.
 27. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. *Dermatol Surg* 2005;31:805–13.
 28. de Groot AC, Nater JP, Weyland JW. Unwanted effects of cosmetics and drugs used in dermatology. Amsterdam (NY): Elsevier; 1994.
 29. AllergEAZE: The art and science of patch testing. Calgary, Canada: SmartPractice Canada; 2009. Available at: <http://allergeaze.com/allergens.aspx?ID=NA> (accessed December 11, 2009).
 30. Chemotechnique Diagnostics: Allergens. Products 2009, Vellinge, Sweden. Available at: <http://www.chemotechnique.se/index2.htm> (accessed December 11, 2009).