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Sensitisation to ethylhexyl salicylate: Another piece of the frontal fibrosing alopecia puzzle

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Abstract

Background: There is speculation that some environmental factors may be impacting the increasing incidence of frontal fibrosing alopecia (FFA). In a recent publication, sensitisation to benzyl salicylate was shown to be prevalent among 36 patients with FFA. Ethylhexyl salicylate (EHS), a light stabiliser, ultraviolet (UV) B absorber and UV filter, frequently found in photoprotectors/cosmetics and, rarely reported as a sensitiser, was not patch tested in said research.

Methods: From January 2021 to February 2022, 33 patients with FFA were patch-tested with the European Photopatch Series, including EHS 10% pet. in two hospitals. In addition, we conducted a literature review and a market survey.

Results: Patch test reactions to EHS were identified in 9 of 33 (27.3%). Four of nine also reacted to their personal sunscreens (containing EHS). All involved women with a mean age of 54 (30–65). Five patients had been diagnosed with FFA before the patch tests; and, four were diagnosed with FFA during the patch test investigations.

Conclusion: Sensitisation to EHS was frequently found in a selected population of patients with FFA. We propose to expand the spectrum of contact allergens described in patients with FFA to include EHS and discuss the possible need for optimization of the patch test preparation.

KEYWORDS
allergic contact dermatitis, cosmetics, cross-reactions, patch test

1 | INTRODUCTION

Frontal fibrosing alopecia (FFA) may involve, not only postmenopausal women, but also younger women and men. Locations other than the forehead, eyebrow and preauricular areas, such as the occipital region, may also be compromised. It has been speculated that some environmental factors may be impacting the increasing incidence of the disease by modulating individual genetic predisposing factors.[1]

Retrospective studies based on questionnaires as well as clinical cases have shown an association of the FFA with the use of photoprotectors as well as other facial cosmetics in both female and male patients.[2–4] In addition, patch test investigations performed on patients with FFA in Europe, Brazil and the USA[2,5–9] have shown that contact sensitisation may be a frequent comorbidity of the disorder.

Case reports of relevant sensitisation to emerging allergens in cosmetics involving patients with FFA have recently been published, such as facial allergic contact dermatitis (ACD) from *Magnolia officinalis* bark extract and ethylhexyl salicylate (EHS) involving one patient with FFA and *lichen planus pigmentosus*[10]; ACD to shellac in a hair spray in one patient with FFA[11]; one case of ACD to diethylamino hydroxybenzoyl hexyl benzoate

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in a sunscreen, as well as cinnamal and cinnamyl alcohol in a facial moisturiser, involving one patient with acquired dermal macular hyperpigmentation (ADMH), subsequently diagnosed with FFA[12]; and, ACD to drometrizole trisiloxane and EHS in a woman, eventually diagnosed with FFA.[13]

2-EHS (IUPAC name: 2-ethylhexyl 2-hydroxybenzoate; molecular formula: $C_{15}H_{22}O_3$; CAS no. 118-60-5; syn. ethylhexyl salicylate; octisalate, octylsalicylate; salicylic acid-2-ethylhexyl ester; *trans*-2-hexenyl salicylate) is the ester of 2-ethylhexanol and salicylic acid.[14,15] This substance is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area at ≥1000 to <10 000 tonnes per annum. It is used by consumers, by professional workers, in formulation or re-packing, at industrial sites and in manufacturing.[16]

EHS was not patch tested in previous research[8,9] identifying sensitisation to benzyl salicylate, octyl gallate, propolis and limonene hydroperoxides to be frequent among a group of 36 patients with FFA in Spain,[8,9] with the exception of a single case involving a woman who developed positive patch test reactions to three salicylates (EHS, benzyl salicylate and homosalate), as well as propolis and butylmethoxydibenzoyl methane (BMDM).[8] Regarding said previous research,[8,9] we may speculate whether benzyl salicylate was not the primary allergen but a cross reactor of another compound.

Subsequently, in 2021, we implemented a protocol to patch test FFA patients using an extended photoallergen series, including EHS, due to its widespread use in sunscreens and reported cross-reactions with benzyl salicylate.[17]

2 | MATERIALS AND METHODS

2.1 | Case series

From January 2021 to February 2022, 33 patients with FFA were patch tested with the European Photopatch Extended Series[18] including EHS 10% petrolatum (pet.) (Chemotechnique Diagnostics) in two Spanish Dermatology Departments, namely the University Hospital of Guadalajara (HUG) and the University Hospital Complex of Toledo (HUT) (20 patients in HUG and 13 in HUT). Some patients were diagnosed with FFA before patch test investigations (which had been indicated due to the FFA itself or other symptoms). Other patients were diagnosed with FFA during the patch test investigations indicated due to other symptoms.

We reviewed the clinical histories of patients with positive patch test reactions to EHS for clinical and epidemiological data. Patch tests with the Spanish Contact Dermatitis Research Group (GEIDAC) (TRUE-Test, AllergEaze, SmartPractice, Calgary, Canada), and supplementary allergens (propolis, hydroxyethyl methacrylate, sodium metabisulfite, *Compositae* mix II, linalool hydroperoxides 1%, limonene hydroperoxides 0.3%, benzisothiazolinone, octylisothiazolinone, decyl glucoside and lauryl polyglucoside) were also performed. In most cases, additional patch tests with the cosmetics and fragrance series (Chemotechnique), as well as the patients' personal cosmetics and sunscreen products, were also performed (simultaneously or in prior tests). The allergens were prepared on Curatest chambers (Lohmann & Rauscher, Neuwied, Germany) in HUG; or Finn Chamber Aqua (SmartPractice) in HUT; and fixed with Omnifix E (Hartmann, Heidenheim an der Brenz, Germany). Exposure times and scoring readings were conducted according to the European Society of Contact Dermatitis guidelines.[19] Photopatch tests involved applying two sets of the European Photopatch Extended Series, including 10% EHS pet. supplemented with benzyl salicylate 10% pet. (Chemotechnique) as well as the patients' personal sunscreens for 48 h. One of the sets was irradiated on Day 2 (D2) with 5 J/cm^2 ultraviolet A (UVA).

In addition, one patient (Case 7) was also patch-tested with EHS 10% pet. AllergEaze (octisalate). Case 8 was also patch-tested with a 10% EHS pet. preparation, as part of the ingredient breakdown of one sunscreen (Anthelios lotion Confort SFP 50+) provided by the manufacturer (La Roche Posay, L'Oréal, Paris, France). Subsequently, the same preparation was also patch-tested in Case 9.

The authors obtained informed written consent from our patients for the attached data and photographs to be published.

2.2 | Literature review on contact allergy to EHS

We conducted a literature review with PubMed and the *Contact Dermatitis* browser, which we consulted up to October 2021. Search terms used were 'ethylhexyl salicylate' OR 'octisalate' AND 'contact dermatitis' OR 'sensitisation' OR 'allergy' with no restrictions on language or publication year. We collected demographic data as well as information regarding the body sites involved; source of exposure to EHS; results of diagnostic procedures; vehicle used and concentration of EHS in the patch test preparations; reactions to other allergens, with special attention to other salicylates; and results of patch tests in controls when provided.

2.3 | Market survey

We screened the labelling of 518 dermo-cosmetics available to be purchased at pharmacies for EHS by consulting the *Vademecum Dermatología Cosmetica 2020*[20] in October 2021. We evaluated products from five popular brands frequently prescribed by dermatologists in Spain, including Bioderma; Cantabria Labs; Eucerin; Isdin; and, La Roche Posay. Cosmetic products sold in supermarkets, perfume stores or online, were not evaluated.

We registered the label listing order of EHS; the number of UV filters/absorbers used in each product; the format of the product (cream/lotion, spray, powder, etc.); and, whether the products were marketed for children or special locations (lips or eyes).

We evaluated the combined used of EHS and other UV filters/absorbers (including BMDM, homosalate, octocrylene, diethylamino hydroxybenzoyl hexyl benzoate, bis-ethylhexyloxyphenol methoxyphenyl triazine, diethylhexyl butamido triazone, ethylhexyl methoxycinnamate, ethylhexyl triazone, phenylbenzimidazole sulfonic acid, methylbenzylidene camphor, drometrizole trisiloxane, terephthalylidene dicamphor sulfonic acid or benzophenones); as well as, fragrance ingredients (namely, 'parfum', limonene, linalool and benzyl salicylate).

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3 | RESULTS

3.1 | Case series

Positive patch test reactions to EHS were identified in 9 of 33 (27.3%) cases, including 7 of 20 (35%) patients in HUG and 2 of 13 (15.4%) in HUT. All involved women with a mean age of 54 (30–65) (Table S1). Five patients had been diagnosed with FFA before the patch tests, while four patients were diagnosed with FFA during the patch test investigations. Indications for patch testing in all cases are summarised in Table S1.

In seven cases, the patch test reactions to EHS 10% pet. were equally intense in both the UVA-irradiated and non-irradiated areas; in one patient, photosensitisation was suspected; and, in one patient, photo-aggravation was suspected (Figure 1). Reactions to a variety of additional allergens were identified in all cases, being gallates (5/9); and propolis (3/9) the most frequent. Regarding other salicylates, patch test reactions to benzyl salicylate were identified in 5 of 9 cases (+ or more in three and ?+ in two) and to homosalate in 2 of 9 (Table S1).

In two cases (Cases 5 and 6), patch tests were performed as an extension of preceding patch testing performed 1-year prior that did not include EHS.[8,9] Regarding Case 5, sensitisation to two personal sunscreens containing EHS had been identified in the previous patch tests in 2020 (not including EHS).[8] Subsequently, in 2021, patch-test reactions to EHS without photo-aggravation were identified on D4. Case 6 involved one woman with intolerance to sunscreens and eyelid eczema who had first been patch tested in 2020[8] (not including EHS) with positive reactions to benzyl salicylate, homosalate and octyl gallate. Her symptoms notably improved upon avoidance of salicylates in cosmetics. One year later, additional patch tests (including EHS) showed intense reactions to EHS with photo-aggravation (Figure 1).

Two patients (Cases 3 and 7) presented with neck hyperpigmentation. Both were sensitised to oak moss absolute of unknown relevance. In both cases, avoidance of fragrances and salicylates in cosmetics led to a resolution of the pigmentation. Case 3 involved one woman referred for patch testing due to neck pigmentation and eyelid/forearm erythema. We became aware of the typical clinical features of FFA during the patch test investigations. Case 7 involved one woman who consulted for symmetrical lateral neck pigmentation in 2006 (Figure 2). A biopsy was taken and histopathological examination showed vacuolar-type interphase dermatitis with melanophages (Figure 2). The patient was initially diagnosed with Berloque dermatitis, treated with hydroquinone, and instructed to avoid the use of

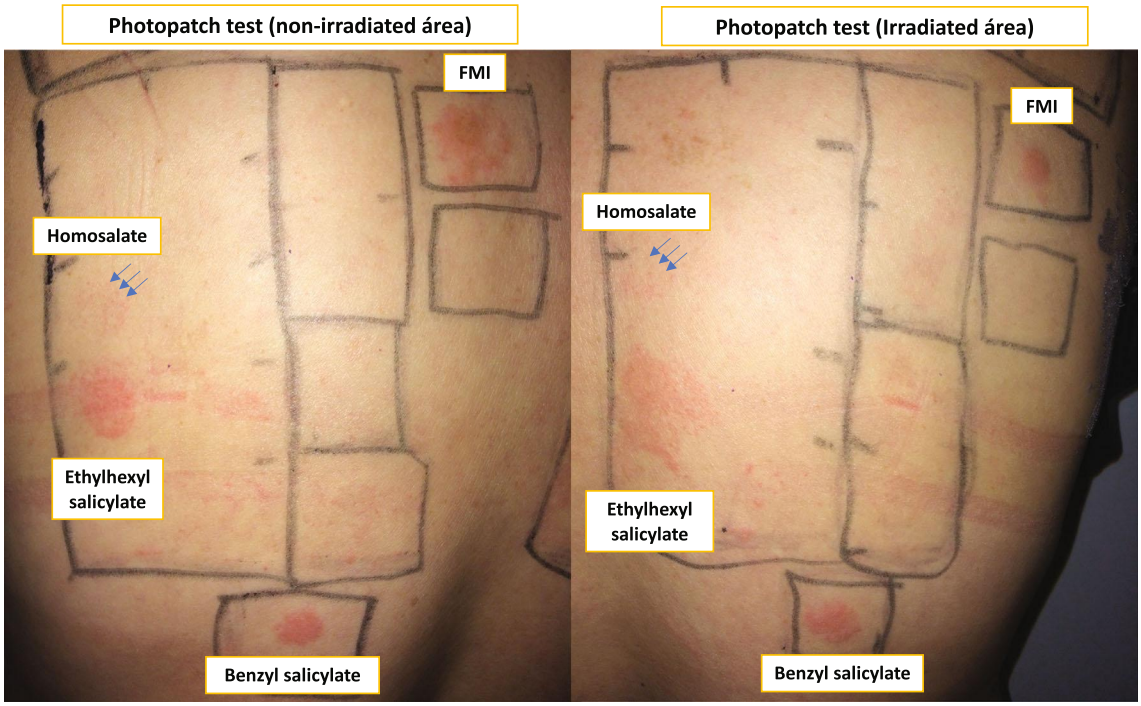

FIGURE 1 A patient diagnosed with frontal fibrosing alopecia and intolerance to sunscreens and deodorants, generalised pruritus with summer aggravation, and eyelid eczema. We published this patient in prior research because of positive patch tests to benzyl salicylate, homosalate octyl gallate, jasmine absolute and propolis, among other allergens. Avoidance of salicylates in personal care products led to resolution of her symptoms. Subsequently, further patch testing with an extended series of photoallergens including ethylhexyl salicylate (EHS) (which had not been patch tested initially) were positive to EHS 10%, benzyl salicylate, and homosalate and fragrance mix I (FMI). Regarding EHS, the reaction was more extensive at the irradiated site; thus, possible photo-aggravation was suspected. The reaction to FMI was stronger in the non-irradiated area likely due to the application of dissimilar amounts of the FMI preparation at the irradiated and non-irradiated areas. Photoinhibition (reduced photopatch reaction caused by the anti-inflammatory and immune modulating effects of UVA irradiation), could not, however, be ruled out.

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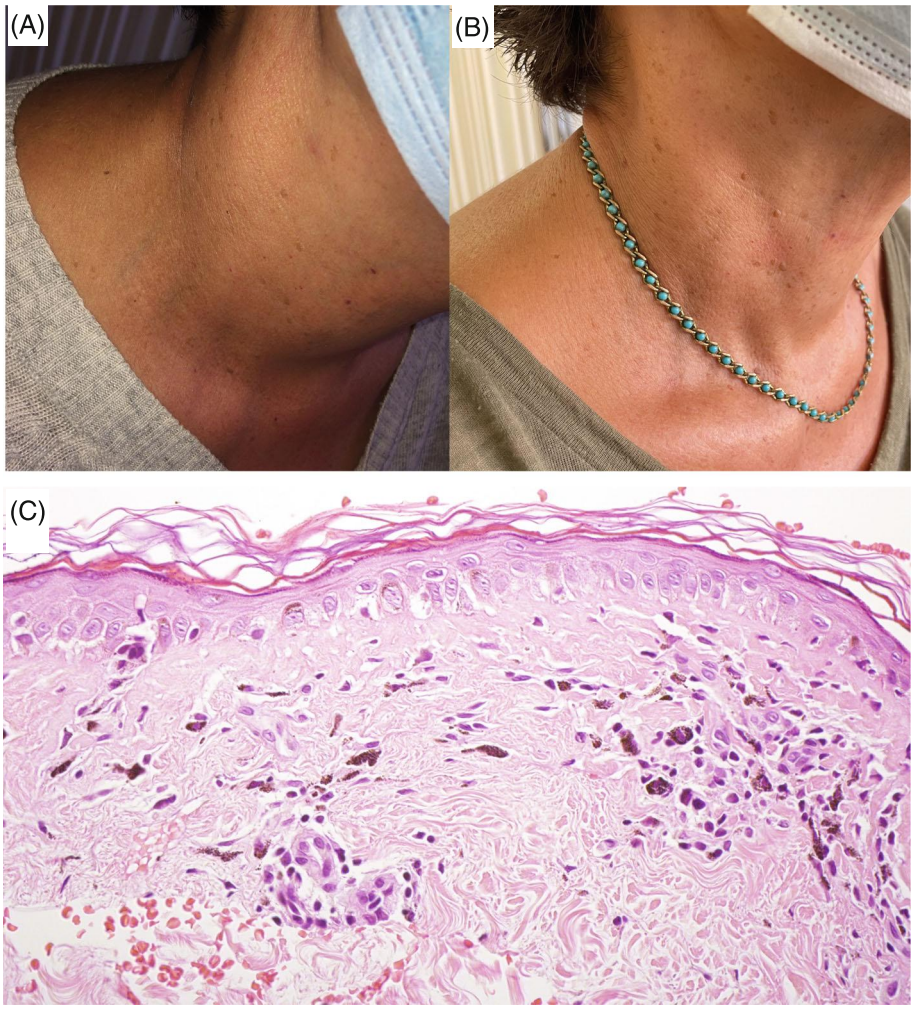

FIGURE 2 (A) Bilateral symmetrical neck pigmentation involving one patient who was thereafter diagnosed with frontal fibrosing alopecia. The patient recalled episodic erythema involving the pigmented areas. (B) Avoidance of fragrances and salicylates led to the disappearance of the pigmentation. (C) Skin biopsy was initially taken and histopathological examination showed vacuolar-type interface dermatitis with melanophages.

perfumes and sunscreens. Subsequently, in 2020, she consulted for eyelid erythematous reactions and persistent neck pigmentation with episodic erythema. Cosmetics were replaced by unscented products and a mineral sunscreen was prescribed. One year later, the patient consulted for frontal-temporal-eyebrow hair loss; and, FFA was diagnosed (15 years after she first consulted for pigmentation). Patch tests were performed in 2021, and, ?+ reactions to EHS 10% pet. (Chemotechnique) and benzyl salicylate were identified, involving both UV-irradiated and non-irradiated skin. Subsequent patch tests were performed 2 years later, with the same Chemotechnique 10% EHS pet. preparation, as well as an additional 10% EHS pet. preparation provided by AllergEaze, yielded ?+ and + reactions, respectively.

Four patients reacted to their personal sunscreens (containing EHS), including three patients who reacted to two sunscreen products each; and, one patient who reacted to one sunscreen. In all, equal reactions were observed in both UVA-irradiated and non-irradiated areas except for one patient who only reacted to the sunscreens applied to the irradiated skin.

In both patients diagnosed in HUT with EHS sensitisation (Cases 8 and 9), the patch tests with a preparation of 10% EHS pet. provided by one sunscreen manufacturer were positive, while the patch tests with Chemotechnique EHS 10% pet. were negative. Case 8 involved one patient previously patch tested[8] due to eyelid eczema, intolerance to cosmetics and sunscreens showing positive reactions to EHS 5% pet., homosalate, benzyl salicylate, gallates mix and one personal sunscreen (Anthelios Lotion Confort, La Roche Posay). Two years thereafter (2021), the patient was further patch tested with the European Photopatch Extended Series (Chemotechnique), including EHS 10% pet. and homosalate 10% pet.; and the individual ingredients of Anthelios Lotion Confort provided by the manufacturer (including EHS 10% pet. and homosalate). The patient reacted to the EHS and homosalate preparations provided by the manufacturer, however, EHS and homosalate (Chemotechnique) were negative.

Case 9 was initially patch-tested due to cheilitis and trichodynia in 2017. ACD to triclosan (in toothpaste) and benzyl salicylate (in hair care products) was diagnosed. Allergen avoidance led to a notable improvement in both cheilitis and trichodynia. Subsequently, in 2021, FFA was diagnosed on the basis of total eyebrow hair loss, receding frontal hairline, 'solitary hair' sign and perifollicular hyperkeratosis. Patch tests performed in 2021 yielded positive reactions to the EHS 10% pet. La Roche Posay preparation available from research regarding Case 8. On the other hand, 10% EHS pet. (Chemotechnique) only yielded a doubtful reaction only at the non-irradiated site on D2 being negative at the irradiated site as well on readings performed on D4, D7 and D9.

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3.2 | Literature review

Twelve cases of sensitisation to EHS were identified in 10 articles published from 2004 to 2023[8,10,13,17,21–26] (Table S2) across Europe and in the USA. Sex was not specified in two cases and the remaining 10 cases involved women. The mean age of 9 of 12 cases was 53 (40–64). In three cases, the age was not specified.

The sources of exposure to EHS (mentioned in 10/12 cases) were sunscreens (6/10 cases), facial creams (3/10 cases), one perfume and one sunscreen (in one case). The face was involved in 7 of 12 cases (including one case presenting with cheilitis and two cases with eyelid involvement). In four cases, extra-facial sites were identified.

Three patients had FFA.[8,10,13] One of them, initially presented with facial ADMH, and was, subsequently, diagnosed with FFA and ACD.[10]

The concentration of EHS used for patch testing was 10% pet. in six cases (four publications); 5% in three; 2% and 5% in one; and not specified in two. The maximum intensity of the reactions was described as + in four cases; ++ in three; +++ in three (one turning positive on D14); and, not specified in two. In three cases with ++ or +++ reactions, the preparations had been provided by manufacturers (La Roche Posay in two cases and Isdin in one case). According to four publications, patch tests with EHS were performed in control populations ($n = 35$, 29, 243 and 320) with positive results in 0%, 0%, 1.2% and 0.9% respectively.[17,22,24,26]

Photopatch tests with EHS were performed in five cases. In four, no augmentation was observed with UVA irradiation; and, in one case, reaction occurred only in the non-irradiated site.

Patch tests with salicylates other than EHS were performed in 10 cases. Reactions to benzyl salicylate were identified in 6 of 10 cases (?+ in two; + in two; ++ in one; and, +++ in one). Homosalate was positive in one patient; and, repetitive open application test (ROAT) with *cis*-3-hexenyl salicylate, in another patient. A wider range of salicylates was patch-tested in two cases (two publications), however, no other positive results were observed.

Eight patients were patch-tested with their personal cosmetic products containing EHS, all of them yielding positive patch-test reactions.

Additional sensitisation to other UV absorbers/filters was identified in three cases, such as: BMDM (two cases); and, drometrizole trisiloxane (one case). Other positive allergens were: nickel sulphate (four cases); propolis (two); *Magnolia officinalis* bark extract (one); *Myroxylon pereirae* (one); and, gallate mix and dodecyl gallate (one).

3.3 | Cosmetic products assessment

We evaluated the labels of 518 dermo-cosmetic products available in the Spanish market. EHS was labelled in 76 of 518 (14.7%). Of them, 59 of 76 (77.6%) were sunscreens; 17 of 76 (22.4%) were a miscellany of products with a sun protection factor (SPF) (namely, 10 moisturisers; 3 scar-healing creams; 1 depigmenting-product; 1 eye-contour cream; 1 anti-imperfections corrector; and 1 cream for rosacea).

EHS was listed among the first 10 ingredients in 74 of 76 (97.4%) products; and, among the first five ingredients in 32 of 76 (42.1%) products. The median order of listing of EHS was 6 (range: 3–12).

EHS was always used in combination with other UV absorbers or filters (mean: 5.1; range: 3–8), such as BMDM (67/76, 88.1%); bis-ethylhexyloxyphenol methoxyphenyl triazine (47/76, 61.8%); octocrylene (46/78; 59%); homosalate (40/76; 52.6%); ethylhexyl triazone (35/76; 46%); diethylamino hydroxybenzoyl hexyl benzoate (11/76; 14.5%); and, ethylhexyl methoxycinnamate (10/76; 13.1%). Unspecified 'parfum', linalool and limonene were labelled in 38 of 76 (50%); 8 of 76 (10.5%); and, 3 of 76 (3.9%) of the sunscreens, respectively. No product labels identified benzophenones, benzyl salicylate or gallates as being present.

Twenty-five (32.9%) products were sprays and two (2.6%) were powders. Eleven (14.5%) products were specifically advertised for children; two (2.6%) for 'atopic' or 'allergic' skin; two (2.6%) for lips; and, one (1.3%) to be used around the eyes.

4 | DISCUSSION

4.1 | Consumer uses of EHS

EHS is used in cosmetics and personal care products; perfumes and fragrances; and, for the manufacture of chemicals and furniture.[16] It can be used as a cosmetic ingredient at a maximum concentration of 5%.[27]

Its properties as a light stabiliser, UVB absorber and UV filter,[15] allow EHS to prevent sunburn, but not reactions associated with UVA light. It is insoluble in water,[28] thus, suitable for use during bathing,[25] however, it is able to solubilise water-insoluble substances such as benzophenones.[28] For these reasons, it is usually used in combination with other UV filters.

Clear elimination kinetics with detection of EHS metabolites in urine samples collected after dermal application of sunscreens with EHS in volunteers has been identified. The kinetic profiles with a prolonged systemic availability indicate a skin depot and accumulation during consecutive multi-day exposure.[29–31]

According to our market survey (September 2021), 76 of 518 (14.7%) dermo-cosmetics (products sold at pharmacies) were labelled to contain EHS. The majority of the products were sunscreens, but we also identified other cosmetics with SPF. Four years prior, we had investigated the labels of 100 best-selling dermo-cosmetics in Spain, including 22 sunscreens (GEIDAC Annual Meeting 2018, personal communication). Six (6%) products, including 5 of 22 (22.7%) sunscreens and one anti-age cream with SPF, contained EHS, while six cosmetics (none of them being sunscreens) contained benzyl salicylate.

Sensitisation to EHS may, thus, occur as a result of exposure, not only to sunscreens, but also to a variety of cosmetics with SPF.

In most products, EHS was labelled among the first (thus, more concentrated) ingredients. In addition, EHS was usually listed in combination with other UV filters/absorbers. BMDM was labelled in most

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products with EHS (88.1%), which may explain concomitant reactions (likely caused by co-sensitisation) identified in two patients[8] of our case series, and, in one additional case reported in the literature.[8,24]

Often, EHS was labelled in association with other salicylates. Concomitant patch test reactions to EHS and homosalate involved two cases in our series,[8] which could be explained by either co-exposure and/or cross-reactivity.

All products evaluated were available at pharmacies (cosmetics sold in supermarkets, or perfume stores such as fine fragrances were not included), which may have caused a possible selection bias. In addition, label disclosure of EHS is not mandatory regarding medical product sunscreens. For these reasons, we may have underestimated the actual frequency of EHS. On the contrary, a high proportion of the dermo-cosmetics evaluated were sunscreens, which may have biased our results to a higher frequency of products with EHS.

Primary and secondary prevention of EHS sensitisation or ACD elicitation involves consulting the labels of sunscreens and other cosmetic products. Since EHS is not mandatory to be disclosed in medical product sunscreens, it may be challenging for sensitised patients to fully avoid it.

EHS was labelled in some products, marketed to be specifically applied in children, atopic/allergic skin, lips or periocular skin, which may pose a higher risk of sensitisation. In addition, accidental or unnoticed airborne exposure may be caused by spray or powder sunscreen formats used by the patients or their relatives; and, lip products may lead to systemic exposure to EHS through ingestion. Since it is a low water-soluble substance, we could speculate that it may be difficult to rinse off during a routine washing, leading to prolonged contact with the skin, thus, increased risk for sensitisation.

4.2 | EHS as a sensitiser and cross-reactions with other salicylates

Sensitisation to salicylates is not uncommon in patients with relevant exposure.[26] Preparations of EHS are available to be patch/photopatch tested at 5% pet. (Sunscreen and the North American Photopatch Series); and at 10% pet. (European Photopatch Extended Series).

Positive patch tests for EHS involved 1.2% of 243 patients in research performed in 2014–2016 in the USA.[26] In addition, positive patch tests in controls provided by other studies are identified in 0%–1.2%.[17,22,24] In Spain, according to the Spanish Contact Dermatitis Registry (REIDAC) data as of 2020, none of 25 patch tests (14 cases patch tested with EHS 5% pet. and 11 patch tested with EHS 10% pet.) and none of 36 photopatch tests (16 with EHS 5% pet. and 20 with EHS 10% pet.) were positive.

According to our literature review, 12 cases of sensitisation to EHS have been reported in 10 publications (involving 10 women and two patients of unspecified gender).[8,10,13,17,21–26] Sunscreens (often multiple) were the most frequent source of exposure and the clinical picture generally involved eczematous lesions frequently affecting the face (Table S2).

EHS was mainly reported to be patch tested in pet. at a concentration of 10%, however, reactions to 2% and/or 5% concentrations have also been identified. Regarding cases showing the strongest patch test reactions to EHS, the preparation had been provided by sunscreen manufacturers in half.

Concomitant patch test reactions to benzyl salicylate involved 6 of 12 (50%) of the reports. Cross-reactivity was suspected in some cases. Since patch tests with a series of salicylates were performed in a limited number of reports, evidence for potential cross-reactions among salicylates other than benzyl salicylate is lacking.[17] Concomitant sensitisation to *cis*-3-hexenyl salicylate,[22] likely as a result of cross-reactivity, was reported in one case.

Patch tests with cosmetic products brought in by patients are highly advisable since patch test-positive reactions to patients' personal cosmetics and sunscreens were common among our reported cases.

4.3 | Sensitisation to EHS involving patients with FFA

Sensitisation to sunscreen and cosmetic allergens has been described in patients with FFA.[2,5–9] A series of patients sensitised to EHS who were diagnosed with FFA before or during the patch test investigations in two Spanish Dermatology Departments from January 2021 to February 2022 is reported including two patients who presented with neck pigmentation before being diagnosed with FFA (15 years before in one case).

We are aware of a potential selection bias since most patients were referred for patch testing because of features other than FFA (e.g., intense trichodynia, pigmentation, rosacea, eczema, intolerance to sunscreens, etc.), which may be associated with a higher risk for sensitisation. In addition, three patients had a prior diagnosis of sensitisation to benzyl salicylate and/or personal sunscreens.[8]

Only one patient developed ++ reactions to EHS. In the remaining cases, reactions were scored as +. Regarding the latter, patch test reactions were double checked (involved both the UVA-irradiated and non-irradiated areas of the photopatch test), persisted until D7; and/or, were reproducible over time.

In both patients diagnosed with sensitisation to EHS in HUT, the patch tests with two 10% EHS pet. preparations (provided by Chemotechnique and one sunscreen manufacturer, respectively) yielded negative and positive results, respectively. These conflicting results regarding the outcome of two different EHS patch test preparations (at identical concentration in pet.) made us doubt the reliability of the commercial preparation supplied by Chemotechnique in HUT, which had been applied thus far in the remaining 11 cases evaluated in HUT with negative results. We suspect that cases of EHS sensitisation may have been missed (due to an excessive dilution or other reasons) among patients studied in HUT, which would explain the differences between the two hospitals regarding the results. Alternatively, patch test reactions to La Roche Posay EHS preparation could hypothetically be related to impurities or metabolites. In this respect, half the

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cases showing the strongest patch test reactions to EHS reported in the literature were described regarding patients patch tested with preparations provided by sunscreen manufacturers (La Roche Posay or Isdin, Barcelona, Spain). Unfortunately, we did not perform a chemical analysis of either EHS preparation and patients negative to EHS (Chemotechnique) were no longer available for further patch tests with La Roche Posay EHS preparation.

In addition, one patient (Case 7) evaluated in HUG developed a ? + reaction to EHS 10% pet. (Chemotechnique) and a + reaction to EHS 10% pet. (AllergEaze).

It has been suggested that a diagnosis of sensitisation to sunscreen compounds usually involves performing step-by-step complex patch and/or photopatch test investigations, ROAT with the patient's sunscreen products, as well as the breakdown of the individual ingredients at multiple readings (including D7 and D14 late readings).[13]

In our opinion, the patch test concentration of sunscreen ingredients likely needs to be optimised to reduce the occurrence of false negative results on conventional reading times.[13] As an example, relevant sensitisation to EHS was detected in one report by performing a late reading (D14) using a 5% EHS pet. preparation provided by one manufacturer.[13] Two prior investigations involving 5% and 2% pet. concentrations on D7 and D6, respectively, had previously been negative.[13] We believe concentrations of EHS higher than commercially available may possibly be needed in order to identify the EHS sensitisation. Further research on this subject, as well as chemical research on patch test preparations, are, however, possibly required.

In 1 year, we identified nine FFA patients to be sensitised to EHS, an allergen currently considered to be unusual (with no cases identified in a Spanish population, who underwent aimed patch/photopatch testing with EHS in the sunscreen or photoallergen series in the same period across Spain). The frequency of sensitisation to EHS involving the general population in our region is, however, unknown because this allergen has not been routinely patch tested in consecutive patients.

In prior research,[8,9] we described that contact sensitisation to benzyl salicylate was prevalent in a series of selected patients with FFA and speculated with a potential association between the two conditions. In said research, EHS was not patch tested, with the exception of one patient who reacted to three salicylates, namely, EHS, benzyl salicylate and homosalate.[8] According to the results of current research, we propose to expand the spectrum of contact allergens described in patients with FFA to include EHS, a UVB absorber frequently used in sunscreens.

We identified additional sensitisation to other chemically unrelated sunscreens such as BMDM or drometrizole trisiloxane in some patients, as well as, in other reported cases. It has been reported that sunscreens contain a median of four UV filters, perfumes contain a median of three filters, and creams contain a median of two filters.[32] The aggregated exposure to these ingredients may lead to hypersensitivity to more than one UV filter, often from unrelated chemical groups.[32]

Contact and photocontact allergy to sunscreen ingredients is more frequently reported in populations with suspected photodermatosis (2%–25%) than in the general population.[33] A higher use of sunscreens involving patients with FFA has been suggested by some authors,[2–4] which could hypothetically be stimulated by photosensitive FFA comorbidities (e.g., rosacea). Accordingly, high exposure to sunscreens in the context of FFA would theoretically lead to a higher risk of contact sensitisation to their ingredients. The sensitisation would thus be an effect and not necessarily a trigger for the FFA process. Conversely, whether sensitisation to EHS or other allergens can impact the pathogenesis of the FFA is a matter of controversy. Theoretically, inflammation, pruritus and scratching caused by contact allergy could aggravate the lichenoid reaction through a *Koebner* isomorphic phenomenon. Alternatively, other conjectural pathways, such as lichenoid contact dermatitis reactions involving the follicles or endocrine-disruptive effects, are mere hypothesis. In this respect, a case of severe acute lichenoid ACD from hair dyes containing PPD leading to both hyperpigmentation and cicatricial alopecia has recently been reported.[34] Sensitisation to PPD has also been reported in 36% of patients with facial and scalp ADMH showing interface dermatitis on histopathology.[35] In addition, regarding salicylates, follicular dermatitis has been described in relation to allergic sensitivity to homosalate in a suntan lotion,[36] and drug lichenoid reactions have been described with medicinal salicylates such as salicylic acid,[37] mesalazine[38] or salsalate.[39] Interestingly, two cases of hair part line scarring alopecia involving two patients who had long been daily applying sunscreen products specifically to that area have been reported. One patient had applied one spray-on sunscreen containing amyl salicylate and benzyl salicylate,[40] and the other patient had used a sunscreen with EHS and homosalate.[41] One developed isolated hair part line involvement and was diagnosed with lichen planus pilaris.[40] The other patient also experienced frontal-temporal hairline recess and was diagnosed with FFA.[41] Patch tests were not performed in said cases.

Interestingly, according to the literature review (Table S2), concomitant reactions to salicylates, propolis and/or gallates, involving patients with FFA have previously been reported. Whether this is related to cross-reactivity or co-exposure is uncertain. Propolis contains benzyl salicylate, thus, simultaneous reactions to both are expected.[8] On the other hand, gallates and salicylates have chemical structural similarities, both being hydroxybenzoic acid derivatives,[42] which could hypothetically result in cross-reactions among them. The clinical relevance of positive patch tests from gallates is difficult to determine because gallates are marginally labelled in cosmetics. In our patients, patch test reactions from gallates possibly resulted from cross-reactivity since we were unable to find any sources of gallates regarding our cases. Alternatively, our patients may have become sensitised in the past to foods or cosmetics.

An association between FFA and sensitisation to allergens contained in sunscreens and facial cosmetics is predictable, since the use of said products has been reported to be associated with FFA.[43] Contact sensitisation from these ingredients would be expected as a result of an increased exposure. Whether sensitisation to these allergens may impact the pathogenesis of FFA remains speculative.

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AUTHOR CONTRIBUTIONS

María Antonia Pastor-Nieto: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; data curation. **María Elena Gatica-Ortega:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; data curation. **Leopoldo Borrego:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; data curation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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