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ORIGINAL ARTICLE

CONTACT DERMATITIS | WILEY

An emerging epidemic of allergic contact dermatitis due to phytonadione epoxide (oxidised vitamin K1)

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Abstract

Background: Reports of allergic contact dermatitis (ACD) to phytonadione epoxide (PE) in cosmetics suggest that PE is as powerful a sensitiser as its parent compound phytonadione.

Objective: To evaluate a case series of ACD to PE in Spain.

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Methods: We reviewed the records of 20 patients with ACD to cosmetics containing PE diagnosed across Spain between January 2019 and June 2023.

Results: All 20 patients developed patch test (PT) or repeated open application test (ROAT) reactions to cosmetics containing PE. All involved women with eyelid eczema. PT or ROAT with PE preparations were positive in 17/20 (85%). PE at 1%, 5%, 10% and 20% in pet. was patch-tested in 8/17, 14/17, 11/17 and 8/17 patients; being positive in 6/8 (75%), 13/14 (92.85%), 11/11 (100%) and 8/8 (100%), respectively.

Conclusion: Regulators should, not only ban the specific dangerous cosmetic ingredients, but also consider to ban or keep under close surveillance those closely related products or derivatives that might potentially cause similar harmful effects. PTs with PE are suggested to be performed at a 5% concentration in pet. Higher concentrations (10% pet.) should be tested whenever PTs with 5% pet. PE are negative.

KEYWORDS

allergic contact dermatitis, CAS no 25486-55-9, cosmetics, epidemic, eyelid dermatitis, patch test, phytonadione, phytonadione epoxide, vitamin K1, vitamin K1 oxidised

1 | INTRODUCTION

Vitamin K1 (phytonadione; CAS no. 84-80-0) is a liposoluble vitamin naturally present in green leafy vegetables and dairy products and, additionally provided by the intestinal bacterial flora. It is involved in blood clotting, bone and kidney metabolism.[1]

Vitamin K1 is medically indicated as a therapy in several types of coagulation disorders.[1]

Severe reactions, have occurred following intravenous or intramuscular injections of phytonadione, resembling anaphylaxis.[1] Additionally, it has been reported to cause eczematous lesions surrounding the injection site, morphea-like plaques, or, diffuse maculopapular exanthema.[2–4]

Claimed uses for vitamin K1 in cosmetic products include moisturising, skin lightening, periorbital hyperpigmentation, purpura and bruising after laser therapy. Several cases of allergic contact dermatitis (ACD) to vitamin K1 have been published[5,6] including some cases involving Spanish patients.[7–9]

In 2005, the French authorities reported 11 cases of severe ACD following the topical application of products containing vitamin K1 in France, including two severe cases related to oxidised vitamin K1. The use of vitamin K1 in cosmetics was thereafter forbidden in the European Union[1] by the Directive 2009/6/EC in Annex II, entry 1371 Phytonadione [INCI], phytomenadione [INN] CAS no. 84-80-0/81 818-54-4 and EC no. 201-564-2.[10,11]

An oxidised form of vitamin K1, phytonadione epoxide (PE) (CAS no. 25486-55-9; syn.: phytonadione 2,3-epoxide; (2,3-epoxyphytyl) menaquinone); phylloquinone 2,3-epoxide,[12,13] with an astringent function according to the Cosmetic Ingredient database was subsequently introduced by the cosmetic industry to replace phytonadione. It did not take long for the first cases of ACD to PE to be published.[14,15] Some additional cases were reported by Spanish authors[16,17] including two patients with severe erythema-multiforme-like lesions[16] (a woman and a child). A case of photo-induced reaction to PE was additionally later reported[18] (Table 1).

In 2019, three new patients presented with ACD to an eye-contour product containing PE (namely, K-Ox Eyes Isdin, Barcelona, Spain) at the University Hospital of Toledo. In one of them, patch tests (PTs) with a PE preparation provided by the manufacturer at an unknown concentration were positive; thus, the diagnosis was straightforward. In the remaining two cases, diagnosis was elusive because PTs with PE <1% pet. (unknown concentration) were, however, negative. It was not until 3 years later when both cases were diagnosed after further PTs with 5%, 10% and 20% pet. PE preparations were performed.

In 2021, three further cases of ACD to PE in cosmetics were notified to the Spanish Agency for Medicines and Health Products Cosmetovigilance programme through REIDAC (Spanish Contact Dermatitis and Skin Allergy Registry). An additional case was reported in the Annual Meeting of the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) and 10 additional cases were subsequently identified. One of these cases involving one patient who was also additionally sensitised to bisabolol has recently been published.[19]

We describe this emerging epidemic of ACD caused by PE in cosmetics in our country and the notable challenges posed by the diagnostic approach in some cases.

2 | MATERIALS AND METHODS

We revised the clinical records of 20 patients with ACD reactions to cosmetic products containing PE diagnosed across 15 Dermatology Departments in Spain between January 2019 and June 2023. Patients with positive PTs or repeated open application tests (ROATs) to PE preparations were identified as proven cases of ACD to PE.

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TABLE 1 literature review on cases of allergic contact dermatitis from phytonadione epoxide.

Author/year	Country	Age/sex	Product	Outcome of the patch tests (PTs), prick test (PICKT) and intradermal test (IDT)
García Gavín (2010)	Belgium/Spain	47/F	Auriderm XO	Auriderm (PT): ++; Vitamin K_1 oxide 1% pet. (PT): ++
		63/F		
		51/F		Auriderm (PT): +
Aerts (2012)	Belgium		Auriderm XO	Auriderm (PT): ++ (D4); Konakion 10 mg/mL (PT): ++ (D4); Konakion 10 g/mL (IDT): +++ (D4); Konakion 10 mg/mL (PCKT): negative; Konakion 1 mg/mL (PT): + (D4)
Pastor-Nieto (2017)	Spain	6/M	Arnika gel	vitamin K1 oxide (5% pet.): +D2 and D4, Arnika gel: ++D2 y D4
		35/F	Arnika gel	vitamin K1 oxide (5% pet.): +++ D7, Arnika gel +++D7
Schneller-Pavelescu (2018)	Spain	57	Eye correct Platinum	Eye correct Platinum (++) on D3, PE 1% pet. (++) and PE 5% pet. (++) on D4; and, Konakion (++) on D5
Cameli (2020)	Italy	63/F	VigorSkinK1	Photodermatitis: in the irradiated area: VigorSkinK1 cream "as is" (++) and Vitamin K1 Konakion (++) at D4.
de la Rosa-Fernández E (2024)	Spain	39/F	Sensitive Vitamin K Ox Cream	PE 1% pet. (++) on D3, PE 5% pet. (++) on D3 and bisabolol 5% pet. (++) on D3

Abbreviations: F, female; M, male.

We analysed clinical and epidemiological variables, including the year of diagnosis; sex, age, anatomical site involved; severity of the lesions in terms of requirement of systemic corticosteroids or medical attention at the emergency care department; name of the cosmetic product with PE involved in the ACD reactions; PT and/or ROAT results.

Patients were patch-tested with the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) baseline series. Allergens were provided by either Chemotechnique Diagnostics (Vellinge, Sweden) or AllergEAZE (SmartPractice, Calgary, Canada), based on the availability at each centre. Additional supplementary series, as well as the patients' personal cosmetic products containing PE and their individual ingredients, were added to the baseline series in some cases. Heterogeneous pet. PE preparations provided by manufacturers were performed, including PET 1% (in 8/17 cases), PE 5% (in 14/17), PE 10% (in 11/17) and PE 20% (in 8/17) cases. Exposure times and scoring readings were conducted according to ESCD guidelines[20] on Day (D) 2 and D4. An additional reading of D7 or later was performed in some cases. In order to trigger a booster effect, the occlusion time was extended to 96 h in two patients.

3 | RESULTS

From January 2019 to June 2023, 20 patients evaluated in 15 Dermatology Departments across Spain developed positive PT and/or ROAT reactions to cosmetic products containing PE. Seventeen (85%) showed positive PT or ROAT reactions to PT preparations of different dilutions of PE. One case was diagnosed in 2019, three in 2021, eight in 2022 and five in the first 6 months of 2023. Three of the 20 cases evaluated in three centres were excluded because PTs with PE preparations were negative (two cases where the manufacturer provided with PE at unknown concentration) or not performed (one case); thus, evidence of sensitisation to PE in them could not be confirmed.

3.1 | Demographics and clinical features

All 17 patients were female and the mean age at diagnosis was 48.17 years (range: 32–67 years). The features of the patients regarding the MOAHLFA index were: male: 0; occupational: 0; atopy: 2/17 (11.1%); hand involvement: 0; leg involvement: 0; face involvement: 17/17 (100%); older than 40 years old: 13/17 (76.4%).

All patients presented with eyelid involvement (Figure 1A,B), which was especially severe in four cases, including one woman who was initially misdiagnosed with angioedema (Case 14). In some patients, the lesions spread to involve other areas such as the cheeks (two cases), the neck (two) (Figure 1A), the thorax (one) and the antecubital folds (one). One patient (Case 12) developed coalescent erythematous papules reminiscent of erythema multiforme affecting the anterior neck (Figure 1A).

Nine of the 17 (52.9%) patients required medical attention at the emergency care unit, and 8 of the 17 (47%) required oral corticosteroids. Ten of the 17 (58.8%) patients required either medical attention at the emergency department and/or oral corticosteroids.

3.2 | PT results and culprit cosmetic products

Cosmetics containing PE causing the reactions were identified to be eye contour products in 14 of the 17 cases (82.35%). Most patients (12/17; 70.58%) recalled reactions to the product K-Ox Eyes (Isdin, Barcelona, Spain), 2 of the 17 patients (11.76%) to Sensitive Vitamin K Ox Cream (Chantelet S.A, Madrid, Spain), 1 patient to D'E Global

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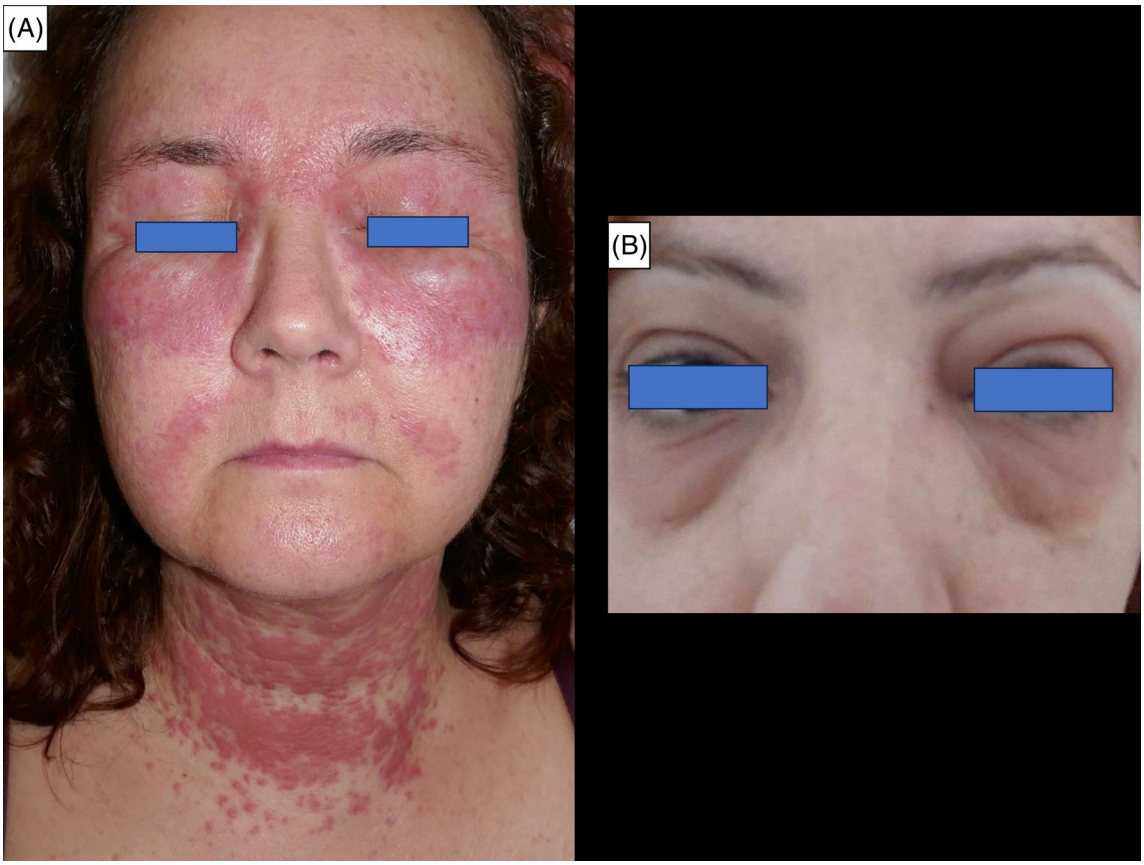

FIGURE 1 Two cases of allergic contact dermatitis allergic to cosmetic products with phytonadione epoxide (PE). (A) Patient with intense periorbital reaction that affected the area of application of the product and extended to the neck where confluent erythematoedematous papules reminiscent of erythema multiforme were identified. (B) Patient with notable eyelid involvement in the form of intense erythema and oedema.

Contour (D'E Global Contour, Murcia, Spain), 1 patient to Eye Correct Day and Night (Martiderm, Cervelló, Spain) and 1 patient to Vitamina-K-Oxido-Skin 10 Medichy Model (Tres Cantos, Madrid, Spain). Five patients (29.4%) recalled reactions to other cosmetic products containing PE.

PTs with cosmetic products containing PE were performed in 14 of the 17 patients. Positive results were identified in 13 of the 14 cases (92.85%), and 12 of the 14 cases (85.7%) developed strong-to-extreme PT reactions (++ in 5/12 and +++ in 7/12); however, only 6 of the 13 became positive as early as on D2 (Table 2).

ROAT with cosmetic products containing PE was performed on 10 of the 17 patients and positive results were observed in all (including one patient with prior negative PT responses and three patients who had not been patch-tested to the same cosmetic products). Nine of the 10 patients (90%) developed strong-to-extreme positive ROAT reactions (+++ in 5/10, ++ in 4/10 and + in 1/10) (Table 2). Mean reading day for the ROAT to become positive was D4 (range: D2–D7).

PTs with heterogeneous PE preparations provided by manufacturers were performed in all patients across 15 centres. A 1% pet. preparation of PE was patch-tested in 8 of the 17 cases and was positive in 6 of the 8 cases (75%) (++ or +++ in all). Two of the eight remained negative throughout readings from D2 to D7.

Preparations of PE 5%, PE 10% and PE 20% in pet. were patch-tested in 14/17, 11/17 and 8/17 cases; being positive in 13/14 (92.85%), 11/11 (100%) and 8/8 (100%) patients, respectively. Reactions were strong-to-extreme in 9/13 (69.2%), 9/11 (81.8%) and 8/8 (100%), respectively.

In six patients, individual ingredients of K-Ox Eyes provided by the manufacturer, including PE at an unknown concentration, were patch-tested. Positive results to PE were identified in two of the six cases (33.3%) including one woman who became positive on D7. In two patients (Cases 5 and 6), PTs with PE at unknown concentrations were performed on three and two different occasions, respectively, with negative results on several readings (as late as D7–D11). In both, we tried to boost a reaction by extending the occlusion time to 96 h and a positive response was only observed in Case 5 (on D7 and D9 following an *in crescendo* pattern). On the other hand, the patient involving Case 6 remained negative on D7, D9 and D11. Additionally, PE at 5%,10% and 20% in pet. triggered an *angry back* reaction in both cases (on D4 in Case 5 and on D7 in Case 6). We subsequently, re-applied PE 5%,10% and 20% in pet. separately and positive reactions were observed in both patients on D5 (to all concentrations of PET in case 5 and to PE 20% in Case 6) (Figure 2).

Three additional patients were patch-tested with unknown concentrations of PE with negative results. Regarding three patients with

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TABLE 2 New case series of allergic contact dermatitis from phytonadione epoxide: epidemiological and clinical features, culprit cosmetic product and results of patch tests (PTs) and ROAT.

				Culprit product with PE			PT with PE provided by manufacturers					
No.	Year	Sex/age	Severe	Name	PT (*as is*)	ROAT (*as is*)	at UC	PE 1% pet.	PE 5% pet.	PE 10% pet.	PE 20% pet.	ROAT with PE
1	2019	F/41	Yes	K-Ox Eyes Isdin	NP	++ +D7	−D2; ++D7	NP	NP	NP	NP	+++D3 (UC)
2	2021	F/41	No	K-Ox Eyes Isdin	−D2; + +D4	++D2	−D2, D4, D7	NP	NP	NP	NP	++D2 (UC)
3		F/60	No	Vitamina-K-Oxido-Skin10 Medichy Model	−D2, D3	++ +D3	NP	+++UD	NP	NP	NP	NP
4		F/50	Yes	Eye Correct Day and Night, Martiderm	++D2; + ++D4, D7	NP	NP	+++D2, D4, D7	+++D2, D4, D7	NP	NP	NP
5	2022	F/47	No	K-Ox Eyes Isdin	NP	++UD	−D2, D4, D7 (three times). Booster (occluded 96 h): −D4; +D7; ++D9	NP	−D2; AB D4 Reapplied on the arm separately: −D2; ? +D5; +D7	−D2; AB D4 Reapplied on the arm separately: −D2; +D5; + +D7	−D2; AB D4 Reapplied on the arm separately: −D2; +++D5, D7	− Twice with different samples (UC)
6		F/34	Yes	K-Ox Eyes Isdin	−D2; +D4, D7	++D5	−D2, D4, D7 (twice) Booster: −D7, D9, D11	NP	−D2, D4; AB D7 Reapplied on the arm separately: −D5, D11	−D2; +D4; AB D7 Reapplied on the arm separately: −D5, D11	−D2; +D4; AB D7 Reapplied on the arm separately: ++D5, D11	− (UC)
7		F/67	No	K-Ox Eyes Isdin	++D2; + ++D4	++ +D5	NP	++UD	++UD	+++UD	+++UD	NP
8		F/46	No	K-Ox Eyes Isdin	++D2; + ++D4	++ +D4	NP	++UD	++UD	++UD	+++UD	NP
9		F/46	No	K-Ox Eyes Isdin	−D4; ++ +D7	NP	NP	−D4, D7	+++D4, D7	+++D4, D7	+++D4, D7	NP
10		F/36	Yes	K-Ox Eyes Isdin	+D2; ++ +D4	NP	-D2, D4	NP	+D2; +++D4	+D2; +++D4	NP	NP
11		F/51	No	K-Ox Eyes Isdin	−D2; + +D4, D7	NP	NP	−UD	−D2, D4; + +D7	−D2, D4; + +D7	−D2, D4; + +D7	++D7 (20%)
12		F/53	Yes	K-Ox Eyes Isdin	+D2; ++ +D4	+D3	NP	+++UD	+++ UD	+++ UD	+++ UD	+++D3 (UC)

(Continues)

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TABLE 2 (Continued)

No.	Year	Sex/age	Severe	Culprit product with PE			PT with PE provided by manufacturers					ROAT with PE
				Name	PT (*as is*)	ROAT (*as is*)	at UC	PE 1% pet.	PE 5% pet.	PE 10% pet.	PE 20% pet.	
13	2023	F/32	Yes	K-Ox Eyes Isdin	+++D2; +++D4	NP	−D2, D4	NP	+++D2, D4	+++D2, D4	NP	NP
14		F/44	Yes	DGlobal Contour	−D2; ++D4	NP	NP	NP	−D2; +D4	NP	NP	NP
15		F/66	Yes	Sensitive Vitamina K Ox Deliplus	−D2; ++D4	++D4	NP	NP	−D2; +D4	−D2; +D4	NP	NP
16 Published[19]		F/39	Yes	Sensitive Vitamina K Ox Deliplus	NP	++ +D3	NP	−D2; ++ +D4; ++D7	−D2; +++D4; ++D7	NP	NP	NP
17		F/65	No	K-ox Eyes Isdin	−D2; ++D3	NP	NP	NP	−D2; +D4	−D2; +++D4	−D2; +++D4	NP

Abbreviations: AB, angry back; D, day; F, female; NP, not performed; pet., petrolatum; PE, phytonadione epoxide; ROAT, repeated open application test; UC, unknown concentration; UD, unknown day.

negative PT to PE at unknown concentration, sensitisation to PE could be demonstrated by performing ROAT with the same preparation (one case); or by patch testing PE 5% and 10% pet. (three cases); or PE 20% pet. (one case) (Figure 2).

We identified several patients sensitised to additional allergens of past or unknown relevance in 10/17 (58.8%), such as metals (nickel sulphate in 7/17; potassium dichromate in 2/17 and cobalt chloride in 1/17); preservatives (methylchoroisothiazolinone/methylisothiazolinone in 3/17 and formaldehyde in 1/17); and fragrance-related allergens (linalool hydroperoxides in 2/17; limonene hydroperoxides in 2/17; fragrance mix in 2/17 and propolis in 1/18).

ROAT with PE preparations, performed in six cases, showed positive results in four of the six (66.6%) (three at unknown concentration and one at 20% pet. on D7).

4 | DISCUSSION

ACD to vitamins in cosmetics is possibly underdiagnosed/underreported because PTs are not standardised; preparations are generally unavailable; and, in many instances, PTs are not performed because vitamins are considered safe natural ingredients generally not suspected to be the culprit.

Phytonadione (vitamin K1) was prohibited in cosmetics in 2009 following a French report on 11 cases of severe ACD.[1] Subsequently, the cosmetic industry replaced it with its oxidised derivative, PE (oxidised vitamin K1). Soon, ACD caused by PE in cosmetics was first reported,[14] and, subsequently, further cases were published,[15] some involving Spanish consumers.[16,17] The prototypical patient was a woman older than 40 presenting with facial (predominantly eyelid) non-occupational eczema.

We report a series of 17 additional proven cases of ACD to PE diagnosed in 12 Dermatology Departments across Spain during the last 3 years. More than half were caused by one eye-contour product (K-Ox Eyes, Isdin).

Possibly, awareness of the condition among physicians as well as an increasing popularity and exposure to cosmetics with PE in recent years, and, particularly, to K-Ox Eyes in our area, have contributed to the growing numbers of patients diagnosed in this period.

A woman who had been applying the product to the periorbital area developed distant reactions on her neck reminiscent of erythema multiforme (Case 12; Figure 1A). This type of reaction has been previously described in other patients sensitised to PE.[16]

PT and/or ROAT with the cosmetic products containing PE *as is* were positive in all cases and the majority of patients showed strong-to-extreme responses. However, sensitisation to PE was difficult to confirm in some cases because of negative results of PTs with the individual ingredients, especially when PE preparations were provided by the manufacturer at an unknown concentration. Given the difference between the sensitivity of PTs performed with PE preparations at an unknown concentration (33.3%) and PTs performed with preparations at a known concentration (5%–20%) (75%–100%), we suspect that the preparation provided at an

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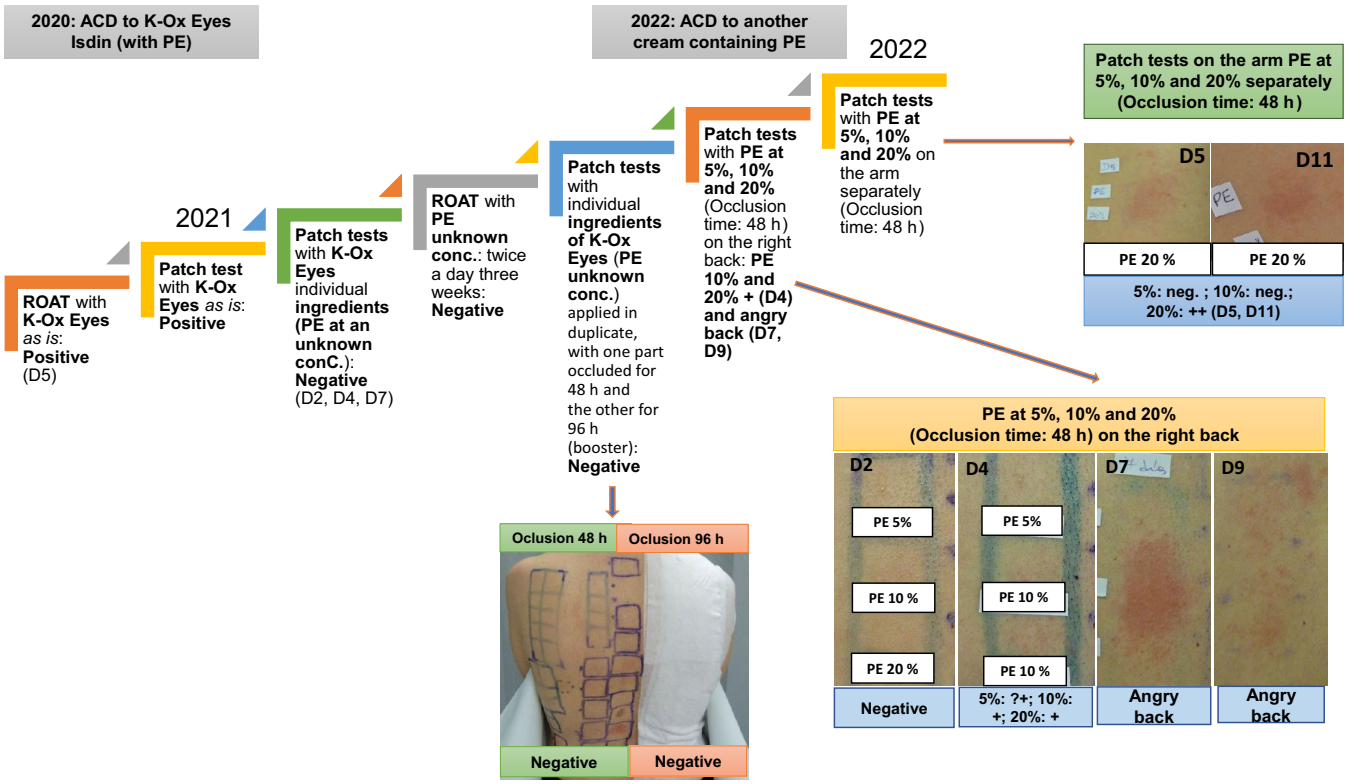

FIGURE 2 The diagnostic approach in some cases was particularly complex, as in Case 6. Patch tests were initially carried out with an unknown concentration of PE provided by the manufacturer, resulting in negative results. Subsequently, we performed additional patch tests with the 13 individual ingredients of K-Ox Isdin (including PE at an unknown concentration) in duplicate on the patients' back under occlusion for 48 and 96 h, respectively, also with negative results. Additionally, 5%, 10% and 20% pet. PE preparations were simultaneously patch tested triggering *angry back* reactions on D7. The same concentrations were subsequently patch-tested separately on the arm, with only one clear positive reaction being observed to PE 20% pet. on D5. PE, phytonadione epoxide.

unknown concentration was likely excessively diluted thus unable to elicit a positive reaction.

Triggering a booster effect by re-patch testing the substance, increasing the occlusion time and performing readings on D7 or later may help to diagnose patients showing false negative PT results when the preparations are provided at an unknown concentration, as in two of our cases.

According to our results, we suggest that the PT PE preparation is applied at least a concentration of 5% in pet. Whenever a 5% concentration is negative and the clinical suspicion is high, PTs with a 10% pet. PE preparation should be considered.

Sensitisation to PE in cosmetics poses an especially concerning risk for consumers because future systemic treatments with parenteral vitamin K for significant internal diseases may potentially be jeopardised.

The assessment of vitamin K derivatives such as K2, K3 and K4 has been suggested,[21] as cosmetic manufacturers could feel tempted to increase their use as a consequence of the banning of vitamin K1 in the cosmetic setting.

We share our experience with an emerging epidemic of severe contact dermatitis to PE likely caused by the widespread use of cosmetics containing PE in our country. Restrictions on the use of PE in cosmetics are direly needed. Since the sensitising potential of PE and its parent molecule, phytonadione, are likely analogous, we believe the authorities should immediately implement effective policies to prevent the cosmetic industry from replacing banned cosmetic ingredients with twin molecules carrying equivalent risks.

AUTHOR CONTRIBUTIONS

María E. Gatica-Ortega: Conceptualization; investigation; writing – original draft; methodology; visualization; writing – review and editing; project administration; supervision; resources. **María A. Pastor-Nieto:** Conceptualization; investigation; writing – original draft; methodology; visualization; writing – review and editing; project administration; supervision; resources. **Ana María Giménez-Arnau:** Investigation; resources; writing – review and editing. **Pedro Mercader-García:** Investigation; writing – review and editing; resources. **Esther Serra-Baldrich:** Writing – review and editing; investigation; resources. **Violeta Zaragoza-Ninet:** Investigation; writing – review and editing; resources. **Tatiana Sanz-Sánchez:** Investigation; writing – review and editing; resources. **Araceli Sánchez-Gilo:** Investigation; writing – review and editing; resources. **David Pesqué:** Resources; investigation; writing – review and editing. **Fátima Tous-Romero:** Investigation; writing – review and editing; resources. **Francisco Javier Ortiz-de-Frutos:** Investigation; writing – review and editing; resources. **Eduardo de la Rosa-Fernández:** Investigation; writing – review and editing; resources. **Sara Dorta-Alom:**

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

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

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REFERENCES

1. Scientific Committee on Consumer Safety SCCS OPINION ON Vitamin K1 (Phytonadione). Opinion of the Scientific Committee on Consumer Products on vitamin K1 (europa.eu). Accessed April 28, 2024.
2. Zhang M, Chen J, Wang CX, Lin NX, Li X. Cutaneous allergic reaction to subcutaneous vitamin K_1: a case report and review of literature. *World J Clin Cases*. 2022;10(29):10742-10754.
3. Morell A, Betlloch I, Sevila A, Bañuls J, Botella R. Morphea-like reaction from vitamin K1. *Int J Dermatol*. 1995;34:201-202.
4. Tsuboi R, Ogawa H. Skin eruption caused by fat-soluble vitamin K injection. *J Am Acad Dermatol*. 1988;18:386-387.
5. Foti C, Calogiuri G, Nettis E, et al. Allergic contact dermatitis from vitamins: a systematic review. *Health Sci Rep*. 2022;5:e766.
6. Veneziano L, Silvani S, Voudouris S, Tosti A. Contact dermatitis due to topical cosmetic use of vitamin K. *Contact Dermatitis*. 2005;52:113-114.
7. Serra-Baldrich E, Dalmau J, Pla C, Muntanola AA. Contact dermatitis due to clarifying cream. *Contact Dermatitis*. 2005;53:174-175.
8. Ruiz-Hornillos FJ, Prieto A, de Castro FJ, et al. Allergic contact dermatitis due to vitamin K1 contained in a cosmetic cream. *Contact Dermatitis*. 2006;55:246-247.
9. Lopez-Lerma I, Vilaplana J. Contact dermatitis to vitamin K1 in an eye cream. *Ann Allergy Asthma Immunol*. 2013;111:227-228.
10. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products (Recast) (Text with EEA Relevance). Accessed April 6, 2024. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02009R1223-20160812&from=EN
11. The Cosmetics Directive of the European Union. Dir. 2009/6/EC. Amending Council Directive 76/768/EEC, Concerning Cosmetic Products, for the Purpose of Adapting Annexes II and III There to Technical Progress. 2009. Accessed April 6, 2024. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009L0006&qid=1492280649496&from=en
12. Pub Chem. Phytonadione Epoxide, (E,2S,3R) (Compound). Accessed April 6, 2024. https://pubchem.ncbi.nlm.nih.gov/compound/90479364#section=Depositor-Supplied-Synonyms
13. Cosing Ingredient: PHYTONADIONE EPOXIDE. Accessed April 6, 2024. https://ec.europa.eu/growth/tools-databases/cosing/details/82371
14. García-Gavín J, Goossens A, Tennstedt D. Allergic contact dermatitis due to cosmetics containing vitamin K1 oxide. *Contact Dermatitis*. 2010;62:248-250.
15. Aerts O, Duchateau N, Bervoets A, Matthieu L, Lambert J. Testing vitamin K1 when vitamin K1 oxide is the cause. *Contact Dermatitis*. 2012;66:54-55.
16. Pastor-Nieto MA, Gatica-Ortega ME, Melgar-Molero V, et al. Erythema multiforme-like reaction resulting from vitamin K1 oxide (phytomenadione epoxide). *Contact Dermatitis*. 2017;77:343-345.
17. Schneller-Pavelescu L, Ochando-Ibernón G, Vergara-de Caso E, Silvestre-Salvador JF. "Crossed" allergic contact dermatitis caused by oxidized vitamin K1 in a patient previously sensitized to non-oxidized vitamin K1. *Contact Dermatitis*. 2019;80:64-65.
18. Cameli N, Zanniello R, Mariano M, Cristaudo A. Vitamin K_1 photo-induced reaction during treatment with cetuximab. *Contact Dermatitis*. 2020;82(3):189-190.
19. de la Rosa-Fernández E, Gatica-Ortega ME, Feliciano-Divasson L, et al. Severe allergic contact dermatitis to bisabolol and phytonadione epoxide found in a moisturizing and strengyhening facial cream. *Contact Dermatitis*. 2024;91:174-176. doi:10.1111/cod.14575
20. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis*. 2015;73(4):195-221.
21. Scientific Committee on Consumer Safety (SCCS). Request for a scientific opinion: Vitamin K1 Oxide (EC No 247-022-9; CAS No 25486-55-9) Submission I. Accessed April 6, 2024. https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_q_049.pdf

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