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Cosmetovigilance for infrequent allergens in Spain using a national online registry: The example of allergic contact dermatitis caused by phenylethyl resorcinol

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Abstract

Background: Monitoring of adverse events induced by cosmetics performed by health authorities, known as cosmetovigilance, has been relied on the collection of case notifications.

Objectives: We aimed to show how a contact dermatitis registry can contribute to the cosmetovigilance of emerging allergens. We used the example of phenylethyl resorcinol, an infrequent allergen with only 6 previous cases reported in Europe and Japan since 2013.

Methods: A systematic search in the Spanish Registry of Contact Dermatitis and Cutaneous Allergy (REIDAC) database was performed to identify patients with positive patch test to phenylethyl resorcinol or cosmetics that contains it between June 2018 and January 2023. We collected the main clinical features of these patients and compared them with those of patients recorded in the registry with similar epidemiological features.

Results: Thirteen patients with positive patch test to phenylethyl resorcinol were identified. All the patients were women with a mean age of 42 years (range 32–59) and their lesions were mainly in the face.

Conclusion: Assessing the importance of infrequent allergens based solely on a case series is difficult. Multicentre registries facilitate the collection of cases and provide appropriate background information for new allergens.

KEYWORDS
allergens, cosmetovigilance, phenylethyl resorcinol

1 | INTRODUCTION

In Europe, monitoring of the adverse effects of cosmetics, known as cosmetovigilance,[1] depends on case notifications from manufacturers, consumers, pharmacists, physicians, and other health professionals to the public health authorities. The undesirable effects that should be reported must occur under normal or reasonably foreseeable conditions of use.[2–5] Today, cosmetovigilance is recognized globally as a concept of public health, to address the safety of cosmetic products.[6] In Spain cosmetovigilance is conducted by the Spanish Agency for

Members of REIDAC collaborators are present in Appendix.

Medicines and Health Products (AEMPS), in compliance with the most recent European legislation for cosmetics.[7] In 2021, the AEMPS started a collaboration with the Spanish Registry of Research in Contact Dermatitis and Cutaneous Allergy (REIDAC) with a nominative grant (budget heading 26.301.313A.48607) to support the registry.[8] In exchange the REIDAC issues an annual epidemiological surveillance report on substances requested by the AEMPS, and promptly communicates any severe adverse effects resulting from cosmetics. Additionally, they report any information that may involve a new risk or a change in frequency and severity of a known risk, including new or infrequent allergens. One of these allergens is phenylethyl resorcinol (PER) [4-(1-phenylethyl)-1,-3-benzenediol] (CAS no 85-27-8) a potent skin-lightening agent derived from *Pinus sylvestris*[9] that was considered effective and safe during its premarketing development.[10–12] It is widely used in sunscreens, hair-lightening products, and skin care cosmetics,[10] but only six cases of allergic contact dermatitis has been previously reported in the literature.[9,13,14]

This study aimed to demonstrate the usefulness of an online contact dermatitis registry in identifying infrequent allergens in cosmetics. We have selected PER as an example to depict the purpose and applicability of this registry. We have outlined the clinical characteristics of patients allergic to PER and compared the main allergens with present relevance in patients as recorded in the registry with similar epidemiological and clinical features to those allergic to PER to provide a proper background information to this allergen.

2 | METHODS

The REIDAC is a research project of the Spanish Group for Research in Contact Dermatitis and Skin Allergy (Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea) that collects results of patch tests performed in 20 contact dermatitis clinics in different Spanish public hospitals. The methodology and objectives of the register have been previously described.[15]

REIDAC uses the REDCap web application (http://www.project-redcap.org/ RRID:SCR_003445) to record patient data. REDCap allows patient data to be uploaded to the centralized national registry at the time of testing. It also provides free-text items that can be used to identify and classify new allergens that are not included in the commercially available series.[16] To find the patients allergic to PER, the free-text items were downloaded to a Microsoft Excel (RRID: SCR_016137) spreadsheet and searched using the key words 'feniletil resorcinol' and 'phenylethyl resorcinol'. We also searched for the trademarks 'Pigmentclar' and 'Foto Ultra Active Unify' previously related to contact dermatitis caused by PER.[13,14]

Further, we searched the registry for patients with clinical characteristics similar to those of patients allergic to PER and the main allergens that were relevant to them.

All patients were tested using the Spanish baseline series, and additional series were used if the involvement of other allergens was suspected. The True Test® (SmartPractice Denmark ApS, Hillerød, Denmark) and additional allergens supplied by Chemotechnique (Vellinge, Sweden) to complete the Spanish baseline series, were tested on Finn chambers AQUA (SmartPractique, Phoenix, USA) at Hospital Universitario de Guadalajara and Hospital Universitario de Toledo. At Hospital Morales Meseguer and Hospital Universitario de Araba the Spanish baseline series was supplied by Chemotechnique and was tested on Finn Chambers AQUA. Occlusion time and readings, on D2 and D4, were conducted following the guidelines of the ESCD. For the patients tested in Hospital Morales Meseguer, the 2% and 5% concentrations of PER in PET were used. The raw material was supplied by Fagrón Ibérica (Terrassa, Spain) to the pharmacy of the hospital. Ten controls were tested for each concentration with negative results. At the other centres PER was supplied by the manufacturers of the cosmetics associated with the reactions (Table 1). Although the concentration used for patch testing was not specified for six of our patients (cases 6, 8, 9, 10, 11 and 12), in their work, Pastor-Nieto et al.[13] contacted the manufacturer and confirmed that the concentrations of the provided ingredients were equivalent to the concentrations used in the original product which stated that PER concentration was <0.5%, and the vehicle used was PET. A similar concentration of 0.5% in an aqua/ethanol mixture (50/50) was provided by the manufacturer of Anthelios Age Correct (La Roche-Possay, L'Oréal, Clichy, France) for patch testing case 13. For case 7, PER 2% PET was submitted by the manufacturer of the cosmetic after a request by the dermatologist.

The REIDAC study protocol was approved by the ethics committee of Complejo Hospitalario Universitario Insular Materno Infantil de las Palmas de Gran Canaria as the promoter, as well as each centre involved. The study adhered to the principles of the Declaration of Helsinki and local and European regulations. All patients with data in the registry signed a written consent form to allow the use of their data.

3 | RESULTS

From June 2018 to January 2023, the data of 11 541 patients were included in the REIDAC database. Of these patients, 1714 were tested with their own products, and 779 showed positive results. Eleven patients with positive patch test to PER were found in the registry; other two patients not included in the registry were included after request to the members of the Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea. One patient from Hospital Universitario de Guadalajara and another from Hospital Universitario de Toledo were tested in March 2023. Five other patients had positive patch test to own products containing PER (two with Pigmentclar Eye Serum, two with Foto Ultra Isdin Active Unify and one with Anthelios Age Correct). However, patch testing with the components submitted by the manufacturer were negative and were not included in the study. The main clinical characteristics of the allergic patients are presented in Table 1. All 13 patients were women, with a mean age of 42 years (range 32–59 years). Eight of them had melasma and the Fitzpatrick skin phototype III was predominant. All 13 patients had lesions on their faces (Figure 1), which were mainly around eyelids (nine), around lips (seven) and forehead (four). Another common location was the neck

TABLE 1 Clinical characteristics of patients with contact allergy to PER.

Case number	Centre	Sex	Age	Atopy	Location	Melasma or solar lentigos	Phototype	Positive product and intensity of patch test	Patch test with PER vehicle, concentration, and intensity of patch test reaction	Other positive patch tests
1	Morales Meseguer	Woman	34	No	Face (forehead, around lips and eyelids)	No	III	Foto Ultra 100 Isdin Active Unify (+)	2% PET (+)	None
2	Morales Meseguer	Woman	37	No	Face (around eyelids)	No	III	Foto Ultra 100 Isdin Active Unify (+)	2% PET (++)	Fragrance mix II
3	Morales Meseguer	Woman	38	Yes (asthma)	Face (forehead)	Yes	IV	Foto Ultra 100 Isdin Active Unify (++)	2% PET (++)	Nickel sulphate, colophonium
4	Morales Meseguer	Woman	46	Yes (atopic dermatitis)	Face (around eyelids and forehead)	Yes	V	Pigmentclar UV 30 (+)	5% PET(+)	2-Hydroxyethyl methacrylate
5	Morales Meseguer	Woman	40	Yes (allergic rhinitis)	Face (around eyelids and lips)	No	III	Foto Ultra 100 Isdin Active Unify (+)	5% PET (++)	Cobalt chloride
6	Hospital Universitario Araba	Woman	43	No	Face	Yes	III	Foto Ultra 100 Isdin Active Unify (+++)	Unknown, supplied by the manufacturer* (+++)	None
7	Hospital Universitario de Guadalajara	Woman	59	No	Face (around eyelids and lips), neck, hands, and neckline	No	II	Foto Ultra 100 Isdin Active Unify (+++)	2% PET (+++)	Nickel sulphate, fragrance mix I, fragrance mix II, Colophonium, textile dye mix, lauryl glucoside
8	Hospital Universitario de Toledo	Woman	37	No	Face (cheeks, around eyelids and lips) and neck	Yes	III	Foto Ultra 100 Isdin Active Unify (+)	Unknown supplied by the manufacturer* (+)	None
9	Hospital Universitario de Toledo	Woman	41	No	Face (around eyelids and forehead)	Yes	II	Foto Ultra 100 Isdin Active Unify (++)	Unknown supplied by the manufacturer* (+)	Propolis, sodium metabisulfite, textile dye mix, hydroperoxides of limonene
10	Hospital Universitario de Toledo	Woman	56	No	Face and neck	Yes	III	Foto Ultra 100 Isdin Active Unify (++)	Unknown supplied by the manufacturer* (+)	Myroxylon pereirae resin, fragrance mix I, hydroperoxides of linalool
11	Hospital Universitario de Toledo	Woman	32	No	Face (around eyelids and lips)	Yes	III	Foto Ultra 100 Isdin Active Unify (++)	Unknown supplied by the manufacturer* (+)	None
12	Hospital Universitario de Toledo	Woman	43	No	Face (forehead, around eyelids and lips) and neck	Yes	III	Foto Ultra 100 Isdin Active Unify (+)	Unknown supplied by the manufacturer* (++)	p-tert-Butyl catechol
13	Hospital Universitario de Toledo	Woman	38	No	Face (around lips) and neck	Yes	II	Anthelios Age Correct (++)	0.5% 50%water/50%alcohol (++)	None

Note: (+) weak reaction, (++) intense reaction, (+++) extreme reaction.
Abbreviations: PER, phenylethyl resorcinol; PET, petrolatum.
*Probably <0.5%.

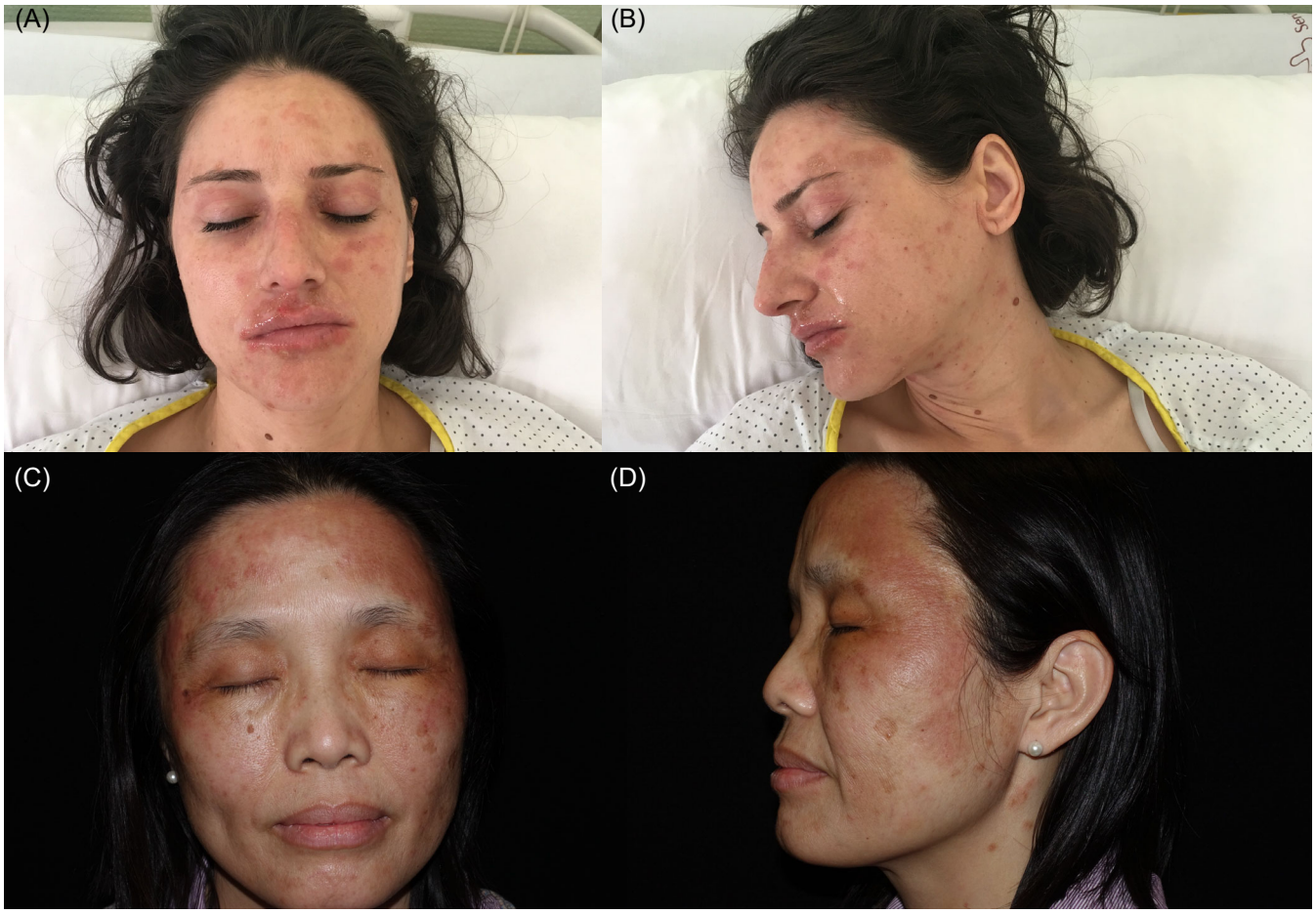

FIGURE 1 Patient 1 (A, B) and 4 (C, D).

(five). Only one patient had lesions in a location other than the face or neck. Only one patient had atopic dermatitis, one had asthma and another one had allergic rhinitis.

To compare the prevalence of contact allergy to PER with the prevalence of other allergens with present relevance found in patients with similar epidemiologic features recorded in the registry, we selected women aged between 20 and 60 years, who presented with facial lesions with or without neck involvement. Those with lesions in other locations were excluded. During the same period, we identified 1160 patients of which 269 had 576 positive patch tests with present relevance (Table 2).

4 | DISCUSSION

In this study, we observed a higher incidence of contact dermatitis caused by PER than that reported in previously published articles.[9,13,14] A literature review showed that between 2013 and 2021, only six cases of contact dermatitis caused by PER have been documented. These cases were in Japan and across Europe. However, we found 13 patients reported between 2018 and 2023 from a single country. The main cosmetic implicated in our patients; 11 out of 13, was Foto Ultra Isdin Active Unify (Isdin, Barcelona,Spain), a sunscreen used for patients with different types of facial pigmentations, that was previously described as a cause of contact dermatitis in two Spanish patients by Pastor-Nieto et al.[13] Another cosmetic with PER, that has been previously linked to contact dermatitis, was Pigmentclar UV SPF 30 (La Roche-Possay, L'Oréal, Clichy, France), a lightening cream implicated in one of the three cases described by Mairlot et al.[14] PER is chemically related to other resorcinol derivates like 4-n-butylresorcinol (BR) or 4-hexylresorcinol (HR) but cross-reactions between them has not been tested.[13] BR has been recently implicated in a case of contact dermatitis after using a night cream for skin hyperpigmentation[17] and HR was described in 1982 as the cause of hand contact dermatitis in a technician working in a tobacco factory.[18] In this case resorcinol 2% PET was patch tested with negative results. The use of these two compounds in skin-lightening products is widespread, Martinez-Pastor et al.[13] reported that BR was present in 19.4% (7 out 36) of skin-lightening products from different dermocosmetic brands in Spain, whereas PER was present in 11% (4 out 36) and HR in 5.6% (2 out 36). Nevertheless, the risk of contact dermatitis with BR or HR seems low, as very few cases of contact dermatitis have been reported. An active search for cases such as

TABLE 2 Patch test with present relevance found in patients with lesions in face with or without involvement of the neck.

Allergen	Number of positive test	%	CI(95%)
Nickel sulphate	52	9.03	(6.95–11.65)
Methylisothiazolinone	35	6.08	(4.40–8.33)
Fragrance mix I	34	5.90	(4.25–8.14)
Methylchloroisothiazolinone/methylisothiazolinone	32	5.56	(3.96–7.74)
Hydroperoxide of limonene	30	5.21	(3.67–7.34)
Hydroperoxide of linalool	29	5.03	(3.53–7.14)
Paraphenylendiamine	28	4.86	(3.38–6.94)
Fragrance mix II	22	3.82	(2.54–5.72)
Hydroperoxides of linalool 0.5%	21	3.65	(2.40–5.51)
Hydroperoxides of limonene 0.2%	14	2.43	(1.45–4.04)
Formaldehyde	14	2.43	(1.45–4.04)
Myroxylon pereirae resin	12	2.08	(1.20–3.61)
Others	253	43.92	(39.92–48)
Total	576	100	

Note: % percentage of positive tests regarding the total of patch test with present relevance (576). CI(95%) 95% Confidence Interval.

the one we have carried out in this paper may change this perception.

The concentration submitted by the manufacturers in most of our cases was 0.5%, they may consider that this is the best concentration, as it is the closest to that found in the products. However, it should be noted that in our series there were five patients with a positive patch to their own products containing PER, but with negative results for patch tests done with the components provided by the manufacturer. That was the main reason for using higher concentrations in the cases attended in Hospital Morales Meseguer and case 7. Many sensitizers may need higher individual test concentrations than their use concentration present in cosmetics, sometimes up to 10–20 times, as has been demonstrated for methylisothiazolinone or polyhexamethylene biguanide.[19,20] Three of the five patients with negative tests with the components provided by the manufacturer were tested with PER 5% PET with negative results, so we cannot exclude than higher concentrations were necessary for these patients, although another possible explanation may be that another allergen may have been involved.

The patients had relatively homogeneous clinical characteristics. All were women, most of them had dark skin; 10 had Fitzpatrick skin phototype III or higher, and nine were affected by melasma or solar lentigos. Dark-skinned people are prone to hyperpigmentation[21] and logically the use of skin lightening products is higher in these patients, which explains why most cases have been described in countries with high skin phototypes such as Japan and Spain.[13] The localisation of the lesions, mainly around the lips and eyelids, was probably related to the thinner skin in these areas and the cream application pattern. Only one patient, patient 7, had lesions in addition to the face and neck; this patient was allergic to other substances that can cause dermatitis in regions besides the face. Atopy does not seem to be a significant factor in our patients.

The main relevant allergen of the patients recorded in the registry with clinical features similar to those allergic to PER was nickel sulphate; the other allergens were components found in cosmetics. In this subgroup of patients, PER was as frequent as other allergens present in the baseline series (13 positive test out 576, 2.26%), including Myroxylon pereirae resin and formaldehyde. However, we are comparing target testing with PER with consecutive testing with the baseline series. This is a limitation, given that allergens tested in a targeted way will always reveal higher figures because the pre-test probability is higher.[22] For most test series, results of 'target' testing will always be higher than those of 'consecutive' testing, and a simple comparison is not easy.

AEMPS was previously notified of a severe adverse event for only one of our cases (patient 3) because the patient visited the emergency department twice due to skin lesions. Other patients would have remained unreported if an active search had not been performed. In the European Union, current legislation on cosmetics[7] states that a 'serious undesirable effect' refers to any effect that results in temporary or permanent functional incapacity, disability, hospitalization, congenital anomalies, or an immediate vital risk or death. This definition may be too restrictive and limit the number of reports, as most cosmetic reactions are self-limited and do not result in hospitalization or death. However, given that contact allergy is permanent and may disturb the quality of life of the patients, most of our cases should be notified as a permanent disability.

There have been different approaches to cosmetovigilance. The term cosmetovigilance was first used in 1997 by Vigan to refer to postmarket surveillance carried out by the industry,[23] however a previous cosmetic control system had been introduced in 1989 in Sweden by the Medical Products Agency.[2] This system included a voluntary adverse reaction reporting system that could be used by consumers or physicians. In 2000, the French Health Products Safety Agency instituted a cosmetology commission and established the Working Group on the Safety of Use of Cosmetic Products in 2002.[1] The mission of this working group was to set the foundations for a

national cosmetovigilance system. At this time, the progress of cosmetovigilance in other European countries was limited. In a survey in Europe published in 2006,[3] only two out of fourteen countries, which were Sweden and Germany, had formal reporting systems; and five (Italy, Malta, Estonia, Lithuania and Portugal) used informal systems. This year the Council of Europe's Committee of Ministers adopted a resolution 'ResAP(2006)1' on a vigilance system for undesirable effects of cosmetic products ('cosmetovigilance') in Europe to protect public health.[24]

In 2013, the new European regulations about cosmetics came into effect. Articles 22 and 23 require member states to provide surveillance authorities with the necessary powers, to monitor their functioning every 4 years and make these results available to the public.

Cosmetovigilance is considered a passive monitoring system[25] in contrast with the active surveillance carried out by contact dermatitis registries.[16,25] These registries perform epidemiologic surveillance of contact dermatitis through continuous collection and analysis of patch test results from several contact dermatitis clinics. Time trends and regional differences can be monitored to reveal information on the need for further research or preventive actions to the regulatory authorities.[25,26] However, these registries work with standardized series, as those present in baseline series or other commercial allergen series.[16] Therefore, it takes time to identify new allergens, include them in the registry software and study their time trends. Furthermore, these registries may exclude adverse events other than contact dermatitis, such as anaphylaxis or seizures.[1] Another disadvantage of contact dermatitis registries is that allergens may be present in products other than cosmetics, and an increase in their prevalence is not always related to cosmetic products.[1]

On the other hand, cosmetovigilance systems are limited by underreporting.[2,3,27] Adverse effects may not be reported because of self-diagnosis and self-medication, which are common interventions for mild-to-moderate reactions such as those associated with cosmetics.[5] To prevent underreporting the National Institute for Public Health and the Environment in The Netherlands set up a pilot project to report undesirable effects attributed to cosmetic products using a website and a public awareness campaign to encourage consumers to report undesirable effects.[4] More than 1600 reports were received from 2009 to 2011, and these were from consumers, general practitioners, and dermatologists involved in the study of cosmetic adverse events. However, patch tests with the European baseline series were only performed for 156 of the cases, which form a minority. This may be another drawback of cosmetovigilance systems, as the quality of reports made by consumers is often worse than those made by health professionals, especially those made by dermatologists.

The first proposal of a centralized cosmetovigilance system based on case reports from the members of a scientific group was made by Revidal-GERDA in 2000.[28] This system collected data from locally distributed databases ad hoc on demand for a study project.[29] However, in our opinion, our approach of searching dermatitis registries with a centralized data centre has advantages in terms of ongoing feedback[29] and ease to detect potential allergens.

The analysis of patch test data with patients' own products in contact dermatitis registries[30] has several limitations. Test results are difficult to standardize because of the different concentrations and vehicles used. Furthermore, the names of the products are entered as free text, and subsequent searches can be challenging if there are typing mistakes. We searched for active ingredients, written in English and Spanish, and cosmetic trademarks previously related to contact dermatitis with PER; therefore, products of other brands with PER may have been missed.

Another limitation of our study is the selection bias, as 11 of the patients were registered from only two centres. This may be attributed to the underreporting of patch tests with patient's own products in our registry. In a previous study of IVDK on patch testing with patients' own products,[30] 19 321 out of 47 561 (40.77%) patients were tested with their own products, whereas in our series only 1714 out of 11 541 (14.85%) were tested. Another possible explanation for the selection bias is that the clinical characteristics of the patients were relatively specific: middle-aged women with melasma, darker skin and lesions around the lips and eyelids, and it is easier to suspect the cause and ask about the use of products containing PER once the clinical pattern is recognized by the dermatologist.

An additional limitation to our work is the lack of standardization of patch tests. Further research on this topic should attempt to perform patches with serial concentrations of the allergen in order to establish the most appropriate concentration for patch testing.

5 | CONCLUSIONS

In conclusion, contact dermatitis registries may facilitate cosmetovigilance through the continuous collection of patch-test data in a controlled network, allowing the identification of allergens that could be underrated in case notifications. Furthermore, we can provide an appropriate background for these new allergens by using data collected from patients included in the registry. Direct communication of information from contact dermatitis registries to the health authorities will facilitate implementation of control measures.

AUTHOR CONTRIBUTIONS

Pedro Mercader-García: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; project administration; funding acquisition; visualization. **Maria-Elena Gatica-Ortega:** Investigation; writing – review and editing; project administration; funding acquisition. **Ricardo González-Pérez:** Investigation; writing – review and editing; project administration; funding acquisition. **Maria Antonia Pastor-Nieto:** Funding acquisition; investigation; project administration; writing – review and editing. **Andrés Carrillo:** Writing – review and editing; supervision; methodology. **Leopoldo Borrego:** Conceptualization; funding acquisition; investigation; project administration; resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Pedro Mercader-García reports lectures and advisory boards from Sanofi, Leo Pharma, Lilly and Abvvie, outside the submitted work. Other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX A: REIDAC COLLABORATORS

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