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Anogenital Contact Dermatitis in Spain: A REIDAC Study of Patients Undergoing Patch Testing in 2019–2024

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ABSTRACT

Background: The REIDAC (Spanish Registry for Research in Contact Dermatitis) conducts nationwide epidemiological surveillance of contact dermatitis in Spain. Anogenital involvement within REIDAC has not been previously studied.

Objectives: To describe the most common diagnoses and update relevant allergens in patients with anogenital lesions referred for patch testing.

Methods: We analysed patients who underwent patch testing within REIDAC from 2019 to 2024. Patients were classified into three groups: (G1) exclusively anogenital lesions, (G2) no anogenital involvement and (G3) both anogenital and non-anogenital lesions. Sensitisation and relevance were assessed.

Results: Among 18 291 patients, 116 (0.6%) had exclusively anogenital lesions, 17 576 (96.1%) had no anogenital involvement and 599 (3.3%) had both. G1 patients were more likely to have at least one positive reaction (91.4%), a current relevant reaction (53.4%, diagnosed with allergic contact dermatitis, ACD) and to be polysensitised compared to other groups ($p < 0.001$). 14.5% of anogenital ACD identified cases were not identified by the Spanish baseline series. Fragrances, preservatives, topical anaesthetics and steroids were the leading relevant allergens. Benzisothiazolinone, sodium metabisulfite and propolis emerged as new sensitisers.
Conclusion: ACD was highly prevalent among patients with anogenital lesions referred for patch testing. The threshold for patch testing in these patients may need reconsideration.

1 | Background

Anogenital dermatoses can severely impair quality of life [1–3]. Although their exact prevalence remains unknown, epidemiological data suggest that they might account for around 3.2% of dermatological diagnoses in outpatient clinics [4]. However, underdiagnosis is likely, driven by patient reluctance to seek care due to stigma or embarrassment, uncertainty regarding the appropriate specialist referral, and insufficient training among clinicians [1, 5, 6].

Data from patch testing networks such as the North American Contact Dermatitis Group (NACDG) and the German Information Network of Departments of Dermatology (IVDK) suggest anogenital dermatoses might represent 2.9% of all patch-tested patients [7, 8], with 0.8% being finally diagnosed with allergic contact dermatitis (ACD). In contrast, specialised vulva clinics report much higher rates of clinically relevant reactions, with around 12% receiving a final diagnosis of ACD [9, 10]. Coexisting dermatoses, including irritant contact dermatitis, lichen sclerosus and inverse psoriasis among others, may obscure the diagnosis and contribute to skin barrier dysfunction, increasing the risk of sensitisation [1, 7, 11, 12]. Additionally, limited access to specialised care often leads to self-treatment with multiple over-the-counter products increasing the risk for sensitisation, and this might be amplified by unverified advice found on social media [13].

A recent systematic review on vulvar contact dermatitis highlighted significant methodological limitations [14]. Of the 17 included studies, some included genital and other anogenital contact dermatitis. Most were single-centred, limiting generalizability. Basic demographic data were often missing, and other issues were heterogeneity in the presentation of results, patch testing techniques and inconsistent reporting of relevance.

Given the evolving landscape of allergen exposure driven by shifts in consumer habits and industrial applications, we aimed to update knowledge on relevant allergens in the anogenital region. To the best of our knowledge, this represents the first nationwide epidemiological study in Spain focused on anogenital ACD. We aimed to (1) describe the most frequent diagnoses and relevant allergens in patients presenting with anogenital lesions at contact dermatitis clinics, (2) assess the proportion of patients with anogenital ACD identified by the current Spanish baseline series [15] and (3) identify potentially emergent sensitisers relevant to this anatomical region.

2 | Methods

2.1 | REIDAC Database and Patch Testing Methods

As previously described [15], the Spanish Registry for Research in Dermatitis and Contact Allergy (REIDAC) was launched in 2018 and includes all consecutive patients undergoing patch testing at participating centres, currently comprising 26 contact dermatitis units located in tertiary hospitals across Spain. All patients are tested with the Spanish baseline series. In most hospitals, the Spanish extended series is also applied, incorporating candidate allergens for inclusion in the baseline series [15]. Additional series, based on patient-specific exposures, are also used at the discretion of the evaluating dermatologists.

Participating clinics use either products from AllergEaze (SmartPractice, Calgary, Canada) or from Chemotechnique (Chemotechnique MB, Vellinge, Sweden), depending on local availability. Many also incorporate the TRUE Test (SmartPractice Denmark ApS, Hillerød, Denmark) alongside additional allergens from both providers to complete the Spanish baseline series [15].

Following the recommendations of the European Society of Contact Dermatitis (ESCD) guidelines for patch testing, readings are performed on Days 2 and 4, after a 2-day occlusion time for all allergens. An additional reading is conducted on Day 7, following the guidance of each investigator. This reading is always performed when corticosteroid or drug allergy is considered [16]. Reactions are classified as negative, doubtful, positive (graded +/++/+++) or irritant. For positive reactions, clinical relevance is assessed by participating dermatologists and categorised as current, past, or unknown, based on clinical examination and evaluation of the patient's history of previous exposures [17].

Collected data include demographic and clinical characteristics and patch test results. Patients can receive up to two different diagnoses. Diagnoses are recorded after patch testing and reflect the conditions considered most relevant to the clinical presentation. All patients sign informed consent before patch testing. Data are collected using REDCap electronic data capture tools [18] hosted at the Spanish Healthy Skin Foundation (Fundación Piel Sana, Academia Española de Dermatología y Venereología). Data monitoring is performed to resolve potential discrepancies every 3 months. The REIDAC was approved by the Research Ethics Committee of the Complejo Hospitalario Universitario Insular-Materno Infantil (CEIm-CHUIMI-2017/964).

2.2 | Study Population

For this study, all patients referred for patch testing at participating centres between 1 January 2019 and 31 December 2024, were classified into three groups: G1: patients with exclusively anogenital lesions; G2: patients without anogenital involvement; G3: patients with both anogenital and non-anogenital lesions. Polysensitisation was defined as three or more positive reactions in the Spanish baseline and extended series in the same patient, regardless of chemical relationship [19]. Co-sensitisation was defined as the presence of more than one current relevant reaction in the same patient.

2.3 | Statistical Analysis

For the purposes of this study, patients with repeated positive reactions to the same allergen were counted only once. To enhance feasibility, allergen grouping was applied. Different concentrations of the same allergen (e.g., linalool hydroperoxides at 0.1% or 0.3% in petrolatum) were conceptually grouped for reporting purposes. If a patient showed positive reactions to more than one concentration of the same allergen, these were recorded as a single positive response and, where applicable, as a clinically relevant reaction. Reactions considered irritant or doubtful were excluded from the analysis.

Data on positive reactions and those with current clinical relevance were extracted both overall and by groups. Patients with positive reactions deemed currently relevant were diagnosed with allergic contact dermatitis (ACD).

Hypothesis tests were conducted using the chi-squared test to assess differences in proportions, with Fisher's exact test when expected cell counts were fewer than five. The Mann–Whitney *U* test was used for quantitative variables that did not follow a normal distribution. To account for multiple comparisons and minimise false-positive findings, a conservative significance threshold was set at $p < 0.001$. Statistical analyses were performed using STATA 17.0 (College Station, TX: StataCorp LLC).

3 | Results

3.1 | Demographic and Clinical Characteristics

Between January 2019 and December 2024, a total of 18 291 patients underwent patch testing at participating centres. Of these, 116 (0.6%) had exclusively anogenital lesions, 17 576 (96.1%) had no anogenital involvement and 599 (3.3%) had both anogenital and non-anogenital skin lesions. The demographic, clinical and MOAHLFA characteristics for each group are summarised in Table 1.

Patients with anogenital involvement only (G1) had a longer duration of symptoms at the time of patch testing compared to those without anogenital involvement (median: G1: 24 vs. G2: 12 months, $p < 0.01$). They were also more likely to have at least one positive reaction to the Spanish baseline series compared to patients without anogenital involvement and compared to those with both anogenital and non-anogenital lesions (G1: 91.4% vs. G2: 47% and G3: 34.6%, $p < 0.001$). Moreover, they were also more likely to be polysensitised (46.6% vs. 24.8% and 20.5%, respectively, $p < 0.001$, Table 1).

3.2 | Most Frequent Allergens in the G1 Group

Among the 116 patients from G1, 226 positive reactions were detected, 131 of them deemed of current relevance. These occurred in 62 patients (53.4% of G1), who were diagnosed with ACD. Table 2 presents the most frequently identified allergens in the G1 group compared to other patient groups. Certain topical anaesthetics (Caine mix), steroids (tixocortol pivalate) and preservatives (benzisothiazolinone) were more likely to be identified as the cause of reactions with current relevance in G1 than in G2 ($p < 0.001$, Table 2). Similar differences were observed when comparing G1 patients to G3 (Table 2).

Although fragrances accounted for the highest number of current relevant reactions (Table 3), the leading contributor to the diagnosis of anogenital ACD was the preservatives/stabilisers group, responsible for 36 relevant reactions in 24 cases (38.7% of G1 patients with ACD). Fragrances followed closely, causing 45 relevant reactions in 21 patients (33.9%), and topical anaesthetics ranked third, causing 18 reactions in 12 patients (19.4%). When considering individual allergens irrespective of category, the most frequent with current relevance were Caine mix (11 patients), fragrance mix I (9), methylisothiazolinone (8), fragrance mix II (8), and Myroxylon pereirae (balsam of Peru) together with benzisothiazolinone (7 each; Table 2).

3.3 | Performance of Baseline and Extended Spanish Series in Detecting Allergens With Current Clinical Relevance in the Anogenital Region

Among the 62 patients with exclusively anogenital lesions (G1) and ACD, a total of 131 positive reactions with current relevance were recorded. In 53 of these patients (85.5%), at least one relevant allergen was identified through the baseline series. The remaining nine patients were identified through other allergens: five via the extended series, particularly with benzisothiazolinone (associated with 10.9% of relevant reactions among those tested—see Table 2), sodium metabisulfite (4.5%), propolis (3.1%), clobetasol-17-propionate (3%) and either methyldibromo glutaronitrile or hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral, 1%). The other four were diagnosed based on single relevant reactions to allergens not included in either series—namely, tetracaine, povidone iodine, chlorhexidine digluconate and diltiazem hydrochloride.

3.4 | Final Diagnoses in Patients With Anogenital Lesions Only

Among the 116 patients with exclusively anogenital skin lesions, 62 (53.4%) were diagnosed with ACD (Table 4), of whom 44 (71.0%) were women. Of these 62 patients, 36 (58.1%) were co-sensitised, and 18 (29.0%) had three or more positive reactions deemed currently relevant (Table S1).

TABLE 1 | Demographic, MOAHLFA and clinical characteristics of patch-tested patients in REIDAC, categorised by anatomical location of skin lesions (total $N = 18\,291$).

Variable	Anogenital only (G1), *N* (column %)	No anogenital involvement (G2), *N* (column %)	*p* value[a] G1 vs. G2	Anogenital and non-anogenital (G3), *N* (column %)	*p* value[a] G1 vs. G3
Patients	116 (100)	17 576 (100)	—	599 (100)	—
Age (median, SD)	49.5 (17.8)	48.1 (18.3)	0.51	51.0 (19)	0.35
Symptoms' duration in months (median, Q1–Q3)	24.0 (12–48)	12.0 (6–36)	< 0.01	16.5 (9–48)	0.36
Sex (M): men	25 (21.6)	5178 (29.5)	0.06	231 (38.6)	< 0.001
Occupational (O): yes	0 (0)	1692 (10)	< 0.001	12 (2.1)	0.12
Atopic dermatitis (A)	3 (2.6)	3343 (19.3)	< 0.001	81 (13.6)	< 0.01
Hands (H): yes	0 (0)	5721 (32.6)	< 0.001	37 (6.2)	< 0.01
Legs (L): yes	0 (0)	880 (5)	0.01	8 (1.3)	0.21
Face (F): yes	0 (0)	4447 (25.3)	< 0.001	44 (7.3)	< 0.01
Age (A) > 40 years	78 (67.8)	11 792 (67.2)	0.88	432 (72.2)	0.34
Asthma	5 (4.3)	1921 (11.1)	0.02	71 (11.9)	0.016
Rhino conjunctivitis	17 (14.9)	3940 (22.7)	0.047	131 (22.2)	0.08
At least 1 positive reaction (baseline series)	106 (91.4)	8261 (47)	< 0.001	207 (34.6)	< 0.001
At least 1 positive reaction (baseline + extended series + others)	114 (98.3)	9030 (51.4)	< 0.001	239 (39.9)	< 0.001
Diagnosis (grouped)					
Allergic contact dermatitis	62 (53.4)	6356 (36.2)	< 0.001	155 (25.9)	< 0.001
Irritant contact dermatitis	22 (19)	4672 (26.6)		176 (29.4)	
Other	32 (27.6)	6548 (37.3)		268 (44.7)	
Polysensitisation (3 or more positive reactions (baseline + extended series)): yes	54 (46.6)	4357 (24.8)	< 0.001	123 (20.5)	< 0.001
Main occupation					
Health care worker	8 (7.1)	1391 (8.2)	0.41	40 (6.9)	0.52
Administrative	13 (11.6)	2009 (11.8)		70 (12.1)	
Housewife/ househusband	15 (13.4)	1480 (8.7)		49 (8.5)	
Student	8 (7.1)	1768 (10.4)		57 (9.8)	
Retired	23 (20.5)	2965 (17.4)		146 (25.2)	
Other	45 (40.2)	7453 (43.7)		217 (37.5)	
Predominant anatomical location, first diagnosis					
Anogenital	116 (100)	0 (0)	—	406 (67.8)	—
Head and neck	0 (0)	5376 (30.6)		57 (9.5)	
Lips/oral mucosa	0 (0)	905 (5.1)		13 (2.2)	

(Continues)

TABLE 1 | (Continued)

Variable	Anogenital only (G1), *N* (column %)	No anogenital involvement (G2), *N* (column %)	*p* value[a] G1 vs. G2	Anogenital and non-anogenital (G3), *N* (column %)	*p* value[a] G1 vs. G3
Hands	0 (0)	5721 (32.6)		37 (6.2)	
Limbs (excludes hands)	0 (0)	2749 (15.8)		26 (4.3)	
Trunk	0 (0)	2798 (15.9)		60 (10)	

[a]Results of hypothesis testing: chi-squared test (Fisher's exact test in case $N < 5$ in one of the cells), for differences in proportions and Mann–Whitney *U* test for quantitative non-normally distributed variables.

4 | Discussion

4.1 | Most Frequent Diagnoses in Patients With Anogenital Lesions

Of the 18 291 patch-tested patients in the REIDAC, only 116 cases (0.8%) exhibited lesions confined solely to the anogenital region (G1). ACD was the most frequent diagnosis both in women and men within this group. Irritant contact dermatitis followed in frequency (Table 4). Our findings are consistent with prior results from the NACDG [7], which reported at least one relevant reaction in 50.6% of G1 patients patch-tested between 2004 and 2014, and with those reported by Foley et al. in a unicentric Irish cohort of patients with anogenital symptoms (67.2%), who also described significant diagnostic delays [20]. The prevalence found in our study exceeds that of the German IVDK registry, where ACD was diagnosed in 29.8% of similar patients [21].

G1 patients were not only more likely to be diagnosed with ACD than those in other groups ($p < 0.001$), but also more likely to be polysensitised, with 46.6% showing positive reactions to three or more allergens compared to 24.8% and 20.5% in G2 and G3, respectively ($p < 0.001$). These figures are not directly comparable to other studies. The IVDK reported 45% of patients with reactions to more than one allergen but used a less stringent definition of polysensitisation. When considering reactions of current clinical relevance, co-sensitisation remained high: 58.1% of patients with anogenital ACD had more than one current relevant reaction. These results support reconsidering the current threshold for patch testing in patients with anogenital lesions in Spain, as many cases of anogenital ACD are likely being underdiagnosed, and those that are diagnosed often experience substantial delays (Table 1).

4.2 | Most Frequent Relevant Allergens in Anogenital Area, Diagnostic Yield of Baseline Series and Emergent Allergens

Among ACD G1 patients, the most common allergens were fragrances, preservatives/stabilisers, topical anaesthetics and topical corticosteroids. Despite fragrances leading the number of current relevant reactions overall and in women (Table 3), the largest contributor group to the diagnosis of anogenital ACD was the preservatives/stabilisers group, responsible for 24 cases (38.7%), 20 of which (83.3%) were identified using the Spanish baseline series. The remaining four were missed by the Spanish baseline series and detected only through the extended series: two with sodium metabisulfite, one with benzisothiazolinone and one with either benzisothiazolinone or propolis. Notably, all of these allergens are among the most recent incorporations in the European baseline series and are included in the current Spanish extended series [22, 23].

Importantly, benzisothiazolinone—a synthetic biocide with antimicrobial properties not previously highlighted as a relevant allergen in the anogenital area [7, 14, 21, 24]—emerged as one of the most frequent allergens among women in our cohort (Table 3). While unexpected, this finding aligns with recent data from the European Environmental Contact Dermatitis Research Group, indicating that benzisothiazolinone has surpassed methylisothiazolinone in the number of contact allergy cases across Europe—despite not being allowed for use in cosmetic products [25, 26]. Within our cohort, benzisothiazolinone was significantly more likely to elicit both a positive reaction and a current relevant reaction in G1 compared to other groups ($p < 0.001$ for both comparisons). Cross-reactivity with other thiazolinones is unlikely [27], as it could only have accounted for two of the seven cases with current relevance and would not explain the overall findings. Although rinse-off cosmetics and medical disinfectants were initially recorded as suspected sources, this could reflect misclassification. Some patients may have used detergents or household products for genital hygiene [28, 29], which may have been incorrectly categorised as rinse-off cosmetics. The exact source of benzisothiazolinone could not be confirmed. Trace levels of benzisothiazolinone may also be present in products despite regulatory restrictions, with exposure from imported goods not subject to European regulations. Additionally, hand-washing underwear may lead to indirect exposure through residual benzisothiazolinone left in the fabric [30]. A recent case report documented resolution of generalised intractable dermatitis following the removal of benzisothiazolinone-containing laundry detergents, supporting its clinical relevance [31]. This aligns with earlier findings from a study conducted in the United Kingdom, showing a significant rise in benzisothiazolinone sensitisation over recent years, likely linked to increased use in household products [32]. We hypothesise that overwashing practices may contribute to these reactions by compromising the skin barrier, facilitating both irritant reactions and subsequent sensitisation. For instance, although vaginal douching is not, to our knowledge, a traditional practice in Spain, immigration has increased significantly over the past decade [33], and a recent systematic review reported that between 29% and 92% of women worldwide engage in this practice [34], suggesting it may be more common than previously assumed. The use of multiple and varied over-the-counter products for perineal hygiene among

TABLE 2 | Patch test results with the Spanish baseline and extended series in patients with exclusive anogenital involvement, compared to those without anogenital involvement and those with both anogenital and non-anogenital lesions (REIDAC, 2019–2024).

	Group 1: anogenital only			Group 2: non-anogenital			Group 3: anogenital and non-anogenital			*p* value Group 1 vs. Group 2 (CR)[a]	*p* value Group 1 vs. Group 3 (CR)[a]
	N° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)		
Allergens from the Spanish baseline series											
Caine mix 7% pet, 10% pet	116	12 (10.3)	11 (9.5)	17 519	173 (1)	25 (0.1)	593	13 (2.2)	6 (1.0)	< 0.001	< 0.001
Fragrance mix I 8% pet	116	10 (8.6)	9 (7.8)	17 522	735 (4.2)	460 (2.6)	593	20 (3.4)	7 (1.2)	< 0.01	< 0.001
Methylisothiazolinone 0.2% aq	110	10 (9.1)	8 (7.3)	15 706	1026 (6.5)	779 (5.0)	548	39 (7.1)	27 (4.9)	0.27	0.35
Fragrance mix II 14% pet	109	9 (8.3)	8 (7.3)	15 708	470 (3.0)	308 (2.0)	546	14 (2.6)	5 (0.9)	< 0.01	< 0.001
Myroxylon pereirae (balsam of Peru) 25% pet	116	7 (6)	7 (6.0)	17 522	573 (3.3)	259 (1.5)	593	15 (2.5)	7 (1.2)	< 0.01	< 0.01
Linalool hydroperoxides 0.5% pet, 1% pet	72	7 (9.7)	5 (6.9)	12 979	743 (5.7)	483 (3.7)	463	25 (5.4)	14 (3.0)	0.20	0.16
Methylchloroisothiazolinone/ methylisothiazolinone 0.02% aq	116	6 (5.2)	4 (3.4)	17 542	1044 (6)	748 (4.3)	596	24 (4.0)	16 (2.7)	1	0.55
Formaldehyde 2% aq	116	4 (3.4)	4 (3.4)	17 540	415 (2.4)	216 (1.2)	597	8 (1.3)	4 (0.7)	0.06	0.03
Textile dye mix 6.6% pet	68	5 (7.4)	3 (4.4)	11 571	382 (3.3)	141 (1.2)	420	9 (2.1)	3 (0.7)	0.05	0.04
Tixocortol-21-pivalate 0.1% pet	73	5 (5.5)	3 (4.1)	17 519	581 (4.5)	370 (2.8)	463	20 (4.3)	11 (2.4)	< 0.001	0.03
Limonene hydroperoxide 0.2% pet, 0.3% pet	116	5 (4.3)	3 (2.6)	13 002	49 (0.3)	21 (0.1)	594	3 (0.5)	2 (0.3)	0.47	0.42
Budesonide 0.01% pet	116	3 (2.6)	3 (2.6)	17 521	112 (0.6)	51 (0.3)	594	13 (2.2)	5 (0.8)	< 0.01	0.13
Nickel sulphate hexahydrate 5% pet	116	59 (50.9)	3 (2.6)	17 528	4100 (23.4)	1015 (5.8)	593	69 (11.6)	12 (2.0)	0.16	0.72
Quaternium-15 1% pet	116	9 (7.8)	2 (1.7)	17 530	651 (3.7)	383 (2.2)	593	14 (2.4)	3 (0.5)	0.10	0.07
p-phenylenediamine 1% pet	116	2 (1.7)	2 (1.7)	17 522	138 (0.8)	80 (0.5)	594	1 (0.2)	1 (0.2)	1	0.19
Neomycin sulphate 20% pet	116	3 (2.6)	1 (0.9)	17 518	273 (1.6)	196 (1.1)	593	2 (0.3)	1 (0.2)	0.20	0.59
N-isopropyl-n′-phenyl-p-phenylenediamine(IPPD) 0.1% pet	116	2 (1.7)	1 (0.9)	17 524	136 (0.8)	33 (0.2)	593	10 (1.7)	4 (0.7)	0.33	0.30
Thiuram mix 1% pet	116	1 (0.9)	1 (0.9)	17 519	142 (0.8)	60 (0.3)	593	5 (0.8)	1 (0.2)	1	0.30

(Continues)

TABLE 2 | (Continued)

	Group 1: anogenital only			Group 2: non-anogenital			Group 3: anogenital and non-anogenital			*p* value Group 1 vs. Group 2 (CR)[a]	*p* value Group 1 vs. Group 3 (CR)[a]
	N° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)		
Cobalt (II) chloride hexahydrate 1% pet	116	6 (5.2)	0 (0)	17 519	828 (4.7)	224 (1.3)	593	11 (1.9)	2 (0.3)	0.41	1
Potassium dichromate 0.5% pet	116	4 (3.4)	0 (0)	17 525	584 (3.3)	269 (1.5)	593	6 (1.0)	2 (0.3)	0.43	1
Lanolin alcohol 30% pet	116	1 (0.9)	0 (0)	17 519	116 (0.7)	62 (0.4)	593	4 (0.7)	4 (0.7)	1	1
p-tert-butylphenol formaldehyde resin 1% pet	116	1 (0.9)	0 (0)	17 522	251 (1.4)	58 (0.3)	593	12 (2.0)	3 (0.5)	1	1
Epoxy resin (Bisphenol A) 1% pet	116	1 (0.9)	0 (0)	17 522	164 (0.9)	66 (0.4)	593	5 (0.8)	0 (0)	1	NA
Carba mix 3% pet	116	1 (0.9)	0 (0)	17 452	331 (1.9)	190 (1.1)	586	8 (1.4)	2 (0.3)	0.64	1
Mercapto mix 2% pet	116	1 (0.9)	0 (0)	17 520	62 (0.4)	36 (0.2)	593	1 (0.2)	0 (0)	1	NA
2-Mercaptobenzothiazole 2% pet	116	1 (0.9)	0 (0)	17 452	63 (0.4)	41 (0.2)	593	2 (0.3)	0 (0)	1	NA
2-hydroxyethyl methacrylate (HEMA) 2% pet	68	2 (2.9)	1 (1.5)	11 994	673 (6)	511 (4.3)	425	11 (2.6)	7 (1.6)	0.37	1
Colophony 20% pet	116	0 (0)	0 (0)	17 522	232 (1.3)	103 (0.6)	594	9 (1.5)	3 (0.5)	1	1
Paraben mix 16% pet	116	0 (0)	0 (0)	17 524	67 (0.4)	30 (0.2)	594	5 (0.8)	3 (0.5)	1	1
Diazolidinyl urea 2% pet	116	0 (0)	0 (0)	17 528	73 (0.4)	42 (0.2)	596	3 (0.5)	1 (0.2)	1	1
Imidazolidinyl urea 2% pet	116	0 (0)	0 (0)	17 529	66 (0.4)	35 (0.2)	596	2 (0.3)	1 (0.2)	1	1
Allergens from the Spanish extended series 2024[b]											
Benzisothiazolinone 0.1% pet	64	9 (14.1)	7 (10.9)	11 627	501 (4.3)	215 (1.8)	422	25 (5.9)	8 (1.9)	<0.001	0.001
Sodium metabisulfite 1% pet	66	4 (6.1)	3 (4.5)	12 278	259 (2.1)	65 (0.5)	436	10 (2.3)	4 (0.9)	<0.01	0.05
Propolis 10% pet	64	8 (12.5)	2 (3.1)	11 636	509 (4.4)	142 (1.2)	425	22 (5.2)	6 (1.4)	0.19	0.28
Clobetasol-17-propionate 1% pet[c]	33	1 (3)	1 (3)	5078	39 (0.8)	25 (0.5)	219	5 (2.3)	2 (0.9)	0.16	0.34
Methyldibromo glutaronitrile (MBDGN) 0.5% pet	113	2 (1.8)	1 (0.9)	16 803	453 (2.7)	41 (0.2)	580	20 (3.4)	0 (0)	0.25	0.16
Hydroxymethylpentylcyclohexene-carbaldehyde (lyral) 5% pet	105	1 (1)	1 (1)	15 475	124 (0.8)	70 (0.5)	539	4 (0.7)	1 (0.2)	0.38	0.30
Sesquiterpene lactone mix 0.1% pet	76	0 (0)	0 (0)	12 239	31 (0.3)	13 (0.1)	427	0 (0)	0 (0)	1	NA

(Continues)

TABLE 2 | (Continued)

	Group 1: anogenital only			Group 2: non-anogenital			Group 3: anogenital and non-anogenital				
	N° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*N*° tested	Positive reactions, *N* (%)	Current relevance, *N* (%)	*p* value Group 1 vs. Group 2 (CR)[a]	*p* value Group 1 vs. Group 3 (CR)[a]
2-bromo-2-nitropropane-1,3-diol (Bronopol) 0.5% pet	38	0 (0)	0 (0)	7320	47 (0.6)	20 (0.3)	274	0 (0)	0 (0)	1	NA
Compositae mix ii 5% pet	18	0 (0)	0 (0)	2606	19 (0.7)	13 (0.5)	103	1 (1)	0 (0)	1	NA
Octylisothiazolinone 0.1% pet	39	0 (0)	0 (0)	7399	73 (1)	31 (0.4)	278	5 (1.8)	2 (0.7)	1	1
Decyl glucoside 5% pet	39	0 (0)	0 (0)	7401	37 (0.5)	19 (0.3)	278	1 (0.4)	1 (0.4)	1	1
Sorbitan sesquioleate 20% pet	21	0 (0)	0 (0)	3149	20 (0.6)	10 (0.3)	122	0 (0)	0 (0)	1	NA
Sorbitan monooleate (span 80) 5% pet	21	0 (0)	0 (0)	3062	9 (0.3)	3 (0.1)	116	0 (0)	0 (0)	1	NA

[a]CR: current relevance. Results of hypothesis testing: chi-squared test for differences in proportions (Fisher's exact test in case $N < 5$ in one of the cells), comparing results of current relevance.
[b]Extended series: excludes allergens already present in the baseline series at different concentrations or vehicles (see Methods section).
[c]Clobetasol-17-propionate was in the previous extended series but is displayed here due to results with current relevance in G1 and G3.

menopausal women also appears to be high [29]. Social media may further influence these practices [13]. Finally, although clinical relevance was assessed by experienced dermatologists and the observed differences between groups regarding benzisothiazolinone were statistically significant ($p < 0.001$), benzisothiazolinone is known to occasionally elicit doubtful reactions in patch testing. Therefore, some degree of misclassification—while highly unlikely—cannot be entirely ruled out [27]. Further research is needed to better understand the recent increase in sensitisations to benzisothiazolinone in Europe, particularly in Spain.

Sodium metabisulfite, a preservative with antioxidant and antimicrobial activity, is commonly used in rinse-off cosmetics and occasionally in topical dermatologic products such as corticosteroids, antibiotic formulations, and over-the-counter hemorrhoidal creams containing topical anaesthetics. REIDAC's data from 2019 to 2022 [35] showed positive reactions to sodium metabisulfite in 2.1% of patients overall, with current relevance in only 0.5%—as observed in G2—compared to 6.1% and 4.5%, respectively, in G1. Given the relatively low number of G1 patients in the registry, the anogenital region may represent a previously underrecognized ('hidden') site of sensitisation to metabisulfites. These findings are consistent with a previous report from an Irish cohort, where sodium metabisulfite was identified as a relevant contact allergen in vulval and perianal dermatitis [20]. In rare instances, sodium metabisulfite may cause perianal contact dermatitis following ingestion or as a manifestation of systemic allergic contact dermatitis. Although these conditions are not systematically recorded in REIDAC, they can be reported in free-text fields, and to the best of our knowledge, no such cases were documented during the study period. These trends may reflect recent shifts in allergen exposure. Notably, sulphites have gained increasing attention and may be responsible for more cases of contact allergy than previously recognised, having been named 'Allergen of the Year' in 2024 [36].

Propolis sensitisation in the anogenital region was more frequent in our cohort (3%) than in earlier NACDG studies (1% between 2005 and 2016, 0% between 1994 and 2004) [7, 24] and was not detected by the IVDK (2004–2008) or the systematic review on vulvar contact dermatitis [8, 14]. However, recent IVDK data (2007–2018)—though not specifying body site involvement—reported a growing trend in sensitisation to this allergen [37]. One proposed explanation is a shift from Chinese to Brazilian propolis by manufacturers [38], but more research is needed. While propolis is not included in the Spanish baseline series, its inclusion in the extended series enabled its detection in our cohort. Still, its overall impact could be underrecognized. For instance, among only five women in G1 with lichen sclerosus and suspected contact dermatitis, four underwent testing with a corticosteroid series, but only one was tested for propolis, and none for beeswax—which is not commercially available for patch testing. None were diagnosed with ACD. This is noteworthy because propolis may pose a greater sensitisation risk in the anogenital area than other commonly suspected corticosteroid excipients, such as propylene glycol (Table 4). In Spain, beeswax is used in both cream and ointment formulations of first-line corticosteroid treatments for lichen sclerosus and in genital moisturizers [39]. Although beeswax and propolis are distinct bee-derived substances, they are closely linked: beeswax is present in propolis, and propolis frequently contaminates beeswax

TABLE 3 | Clinically relevant allergens in the anogenital region in G1 patients with ACD, grouped by category and stratified by sex (REIDAC, 2019–2024).

Group of allergens and number of current relevant reactions per category (NCR)	Women ($N=44$)	Men ($N=18$)	p value[a]	All patients ($N=62$)
Fragrances (NCR = 45)	NCR = 38, in $N=16$	NCR = 7, in $N=5$		$N=21$
Fragrance mix I 8% pet	7/44 (15.9)	2/18 (11.1)	1	9/62 (14.5)
Fragrance mix II 14% pet	6/41 (14.6)	2/17 (11.8)	1	8/58 (13.8)
***Myroxylon pereirae* (balsam of Peru) 25% pet**	5/44 (11.4)	2/18 (11.1)	1	7/62 (11.3)
Linalool hydroperoxides 0.5% pet, 1% pet	5/30 (16.7)	0/10 (0)	0.31	5/40 (12.5)
Limonene hydroperoxides 0.2% pet, 0.3% pet	2/31 (6.5)	1/10 (10)	1	3/41 (7.3)
Isoeugenol 1% pet, 2% pet	2/10 (20)	0	NA	2/10 (20)
Cinnamic alcohol 1% pet, 2% pet	2/12 (16.7)	0	NA	2/12 (16.7)
Citral 2% pet	1/11 (9.1)	0	NA	1/11 (9.1)
Geraniol 1% pet, 2% pet	1/11 (9.1)	0	NA	1/11 (9.1)
Oil of cloves- 2% pet	1/5 (20)	0	NA	1/5 (20)
Hydroxy-methylpentylcyclohexene-carbaldehyde (lyral) 5% pet	1/39 (2.6)	0/16 (0)	1	1/55 (1.8)
Eugenol 1% pet, 2% pet	1/12 (8.3)	0	NA	1/12 (8.3)
Amyl cinnamic alcohol 1% pet, 5% pet	1/11 (9.1)	0	NA	1/11 (9.1)
Cinnamic aldehyde 1% pet	1/5 (20)	0	NA	1/5 (20)
Oil of lemongrass 2% pet	1/5 (20)	0	NA	1/5 (20)
Hydroxycitronellal 1% pet, 2% pet	1/11 (9.1)	0	NA	1/11 (9.1)
Preservatives and stabilisers (NCR = 36)	NCR = 28, in $N=17$	NCR = 8, in $N=7$		$N=24$
Methylisothiazolinone 0.2% aq	5/41 (12.5)	3/17 (17.6)	0.68	8/58 (14)
Benzisothiazolinone 0.1% pet	7/27 (25.9)	0/9 (0)	0.16	7/36 (19.4)
Formaldehyde 2% aq	3/44 (6.8)	1/18 (5.6)	1	4/62 (6.5)
Methylchloroisothiazolinone/ Methylisothiazolinone 0.02% aq	2/44 (4.5)	2/18 (11.1)	0.57	4/62 (6.5)
Sodium metabisulfite 1% pet	3/28 (10.7)	0/9 (0)	0.56	3/37 (8.1)
Propolis 10% pet	2/27 (7.4)	0/9 (0)	1	2/36 (5.6)
Quaternium-15 1% pet	1/44 (2.3)	1/18 (5.6)	0.50	2/62 (3.3)
Gallate mix 2% pet	0/11 (0)	1/3 (33.3)	0.21	1/14 (7.1)
DMDM hydantoin 1% pet	1/2 (50)	0/2 (0)	1	1/4 (25)
Ethylenediamine dihydrochloride 1% pet	1/35 (2.9)	0/17 (0)	1	1/52 (1.9)
Oleamidopropyl dimethylamine 0.1% eth	1/2 (50)	0		1/2 (50)
Methyldibromo glutaronitrile (MBDGN) 0.5% pet	1/42 (2.4)	0/18 (0)	1	1/50 (2)
Dimethylaminopropylamine (DMAPA) 1% aq	1/2 (50)	0	NA	1/2 (50)
Topical anaesthetics (NCR = 18)	NCR = 11, in $N=7$	NCR = 7, in $N=5$		$N=12$
Caine mix 7% pet, 10% pet	6/44 (13.6)	5/18 (27.8)	0.27	11/62 (17.7)

(Continues)

TABLE 3 | (Continued)

Group of allergens and number of current relevant reactions per category (NCR)	Women ($N=44$)	Men ($N=18$)	p value[a]	All patients ($N=62$)
Tetracaine-HCl 1% pet, 5% pet	2/5 (40)	1/2 (50)	1	3/7 (42.9)
Benzocaine 5% pet	1/5 (20)	1/2 (50)	1	2/7 (28.6)
Articaine-HCl 1% pet	1/5 (20)	0/2 (0)	1	1/7 (14.3)
Cinchocaine-HCl 5% pet	1/5 (20)	0/2 (0)	1	1/7 (14.3)
Corticosteroids (NCR = 11)	NCR = 3, in $N=3$	NCR = 8, in $N=4$		$N=7$
Tixocortol-21-pivalate 0.1% pet	2/44 (4.5)	1/18 (5.6)	1	3/62 (4.8)
Budesonide 0.01% pet	1/44 (2.3)	2/18 (11.1)	0.20	3/62 (4.8)
Hydrocortisone-17-butyrate 0.1% pet, 1% pet	0/19 (0)	1/14 (7.1)	0.42	1/33 (3)
Clobetasol-17-propionate 1% pet	0/10 (0)	1/5 (20)	0.33	1/15 (6.7)
Prednicarbate 1% eth	0/1 (0)	1/2 (50)	1	1/3 (33.3)
Methylprednisolone aceponate 0.1% eth, 1% pet	0/2 (0)	1/2 (50)	1	1/4 (25)
Fluticasone propionate 0.1% aq	0/1 (0)	1/2 (50)	1	1/3 (33.3)
Antiseptics and other medications (NCR = 5)	NCR = 3, in $N=3$	NCR = 2, in $N=2$		$N=5$
Povidone iodine 10% aq	1/1 (100)	1/2 (50)	1	2/3 (66.7)
Neomycin sulphate 20% pet	1/44 (2.3)	0/18 (0)	1	1/62 (1.6)
Chlorhexidine digluconate 0.5% aq	0/3 (0)	1/2 (50)	0.40	1/5 (20)
Diltiazem hydrochloride 10% pet	1/1 (100)	0	NA	1/1 (100)
Dyes (NCR = 5)	NCR = 5, in $N=4$	NCR = 0		$N=4$
p-Phenylenediamine 1% pet	2/44 (4.7)	0/18 (0)	1	2/62 (3.2)
Textile dye mix 6.6% pet	3/27 (11.1)	0/10 (0)	0.55	3/37 (8.1)
Metals (NCR = 3)	NCR = 3, in $N=3$	NCR = 0		$N=3$
Nickel sulphate hexahydrate 5% pet	3/44 (6.8)	0/18 (0)	0.55	3/62 (4.8)
Rubber chemicals (NCR = 3)	NCR = 3, in $N=2$	NCR = 0		$N=2$
N-isopropyl-n'-phenyl-p-phenylenediamine (IPPD) 0.1% pet	1/44 (2.3)	0/18 (0)	1	1/62 (1.6)
Thiuram mix 1% pet	2/44 (4.5)	0/18 (0)	1	2/62 (3.2)
Vehicles (NCR = 1)	NCR = 1, in $N=1$	NCR = 0		$N=1$
Propylene glycol 30% aq	1/8 (12.5)	0/3 (0)	1	1/11 (9.1)
Adhesives (NCR = 3)	NCR = 3, in $N=1$	NCR = 0		$N=1$
2-hydroxyethyl methacrylate (HEMA) 2% pet	1/28 (3.6)	0/10 (0)	1	1/38 (2.6)
2-hydroxyethyl acrylate 0.1% pet	1/1 (100)	0	NA	1/1 (100)
2-hydroxypropyl-methacrylate 2% pet	1/1 (100)	0	NA	1/1 (100)

Note: In bold, allergens with current relevances in over 5% of patch-tested patients.
Abbreviations: *N*, number of patients; NCR, number of current relevant reactions.
[a]Results of hypothesis testing with Fisher's exact test, comparing the proportion of clinically relevant reactions per patch-tested patient between women and men with anogenital ACD. Percentages (indicated in brackets for each allergen) represent the number of relevant reactions divided by the number of patch-tested patients in each group.

[40]. Beeswax used in pharmaceutical formulations should be 'purified' [41], but labelling lacks clarity, and the consistency of such purification appears poorly documented. Co-sensitisation may be higher than previously thought, yet remains poorly understood [41–44]. Further research is needed to clarify the roles of propolis and beeswax in contact sensitisation among women with chronic inflammatory vulvar dermatoses requiring long-term topical treatments.

TABLE 4 | Final diagnoses overall and stratified by sex, among patients with anogenital lesions only (G1, total $N = 116$).

Diagnosis	*N* of diagnoses in women = 97, *N* (%)	*N* of diagnoses in men = 25 (%), *N* (%)	Total *N* of diagnoses in G1 = 124, *N* (%)
Allergic contact dermatitis	44 (48.4)	18 (72)	62 (53.4)
Irritant contact dermatitis	18 (19.8)	6 (24)	24 (20.7)
Pruritus sine materia	6 (6.6)	2 (8)	8 (6.9)
Vulvodynia	6 (6.6)	0 (0)	6 (5.2)
Lichen sclerosus	5 (5.5)	0 (0)	5 (4.3)
Seborrheic dermatitis	3 (3.3)	1 (4)	4 (3.4)
Psoriasis	2 (2.2)	0 (0)	2 (1.7)
Atopic dermatitis	1 (1.1)	0 (0)	1 (0.9)
Xerodermic eczema	1 (1.1)	0 (0)	1 (0.9)
Lichen planus	1 (1.1)	0 (0)	1 (0.9)
Patch test after surgery	1 (1.1)	0 (0)	1 (0.9)
Others	9 (9.9)	0 (0)	9 (7.8)

Note: Percentages are calculated over the number of patients in each category: 91 women, 25 men (Total $N = 116$ patients in G1). Percentages do not necessarily add 100% due to two diagnoses being allowed per patient.

Fragrances were the second most frequent allergen group, responsible for 45 current relevant reactions in 21 patients (33.9% of patients with anogenital ACD). All sensitisations were identified with the baseline series, specifically through fragrance mix I, fragrance mix II, *Myroxylon pereirae* (balsam of Peru)—all longstanding components—and the hydroperoxides of limonene and linalool, added in the 2022 update [45]. While fragrance mixes and balsam of Peru have long been recognised as relevant allergens in the anogenital area [11, 14, 20, 21, 24], oxidised terpenes such as limonene and linalool hydroperoxides appear to be emerging sensitisers. Notably, neither the NACDG nor the IVDK identified reactions to these compounds, and only one study included in the systematic review reported sensitisation to limonene. In contrast, the present study found linalool hydroperoxide to be currently relevant in 5 out of 40 (12.5%) patch-tested G1 patients (all women), and limonene in 3 out of 41 patients (7.3%), suggesting increasing clinical significance. Both hydroperoxides are in the Spanish baseline series, have been under consideration for inclusion in the European baseline series, and are currently part of the European extended series [23].

Topical anaesthetic-related ACD, a well-established cause of anogenital ACD and a leading contributor to iatrogenic cases in this region [12], was identified in 12 patients (19.4%), all but one identified with the Caine mix. The remaining patient reacted to tetracaine despite testing negative to the mix. Caine-related ACD was relatively more frequent in men and was primarily associated with the use of topical anaesthetic creams, which should always be considered in patients with anogenital lesions. This fact is especially relevant given the frequent promotion, including in advertising, of topical preparations for haemorrhoid-related or genital pain and/or itching that contain topical anaesthetics.

ACD to corticosteroids was observed in seven patients—six identified via the baseline series, and one sensitised to clobetasol-17-propionate. Corticosteroids are also a well-established cause of iatrogenic allergens in the anogenital area [12]. This possibility should always be considered when a patient with an anogenital dermatosis fails to respond to standard treatments, and it is worth reminding that diagnosis requires delayed patch test readings.

Other suspected sources of allergens included textiles (dyes), sanitary pads (acrylates), piercings and zippers (nickel sulphate) and condoms (black rubber and thiuram mix). Although methyldibromo glutaronitrile has been banned in cosmetic products, it was considered of current relevance in one patient. Exposure may still occur through non-cosmetic products, but the specific source could not be identified during clinical assessment, which represents a limitation.

4.3 | Strengths and Limitations

This multicentric REIDAC study was conducted across Spanish contact dermatitis units in 26 tertiary hospitals in Spain and includes a large, recent cohort of consecutive patients, making it broadly representative of individuals seeking care within the Spanish healthcare system. Standardised procedures and quality control through data monitoring were implemented across REIDAC units. Additionally, we applied a conservative significance threshold to minimise false-positive findings.

Although standardised procedures were followed, including adherence to ESCD guidelines for patch test interpretation, multicentre studies may carry variability in how reactions and their relevance are assessed, due to potential differences in clinical judgement among contact dermatologists. In particular, the assessment of relevance represents the most important limitation. Current relevance was determined based on clinical judgement, which may introduce subjectivity and is a key reason why some studies focus solely on positive reactions. However, relevance

assessments also add value, as they reflect the clinical expertise of experienced contact dermatitis specialists. For transparency, all positive reactions are presented in Table 2. Other limitations include the lack of differentiation between perianal and genital dermatitis, and the exclusive focus on patients with anogenital lesions, which may have led to an underestimation of the overall burden of anogenital ACD. Additionally, for feasibility purposes and in line with our objectives, we grouped allergens tested at different concentrations. Finally, only two diagnoses are recorded per patient, based on clinical assessment after patch testing, which may have resulted in underreporting of coexisting dermatoses.

5 | Conclusions

ACD was highly prevalent among patients with anogenital lesions referred for patch testing, indicating that the threshold for patch testing in this population may need reconsideration. Polysensitisation was common, and in 85.5% of all anogenital ACD cases, at least one allergen of current clinical relevance was identified with the Spanish baseline series. Benzisothiazolinone, sodium metabisulfite, propolis and hydroperoxides of limonene and linalool emerged as sensitisers in the anogenital region and should be considered when evaluating patients with suspected anogenital contact dermatitis.

Author Contributions

Mercè Grau-Pérez: conceptualization, methodology, data curation, writing – original draft, visualization and project administration. **Pedro Mercader-García:** investigation, writing – review and editing, methodology and project administration. **Ana María Giménez-Arnau:** investigation and writing – review and editing. **Tatiana Sanz-Sánchez:** investigation, writing – review and editing and project administration. **Violeta Zaragoza Ninet, Susana Córdoba Guijarro, Francisco Javier Miquel Miquel, Juan Francisco Silvestre Salvador, Ricardo González-Pérez, Inmaculada Ruíz González, Esther Serra Baldrich, Francisco Javier Ortiz de Frutos, Mercedes Rodríguez Serna, Carmen Paredes Suárez, Francisco José Navarro Triviño, Pablo Chicharro, Marta Andreu, José Juan Pereyra Rodríguez, Paloma Sánchez-Pedreño Guillén, Enrique Gómez de la Fuente, Marta Elosua-González, Mónica Munera-Campos, and Fátima Tous Romero:** investigation and writing – review and editing. **José Manuel Carrascosa:** investigation, writing – review and editing and project administration. **María Elena Gatica Ortega, María Antonia Pastor Nieto:** investigation. **Araceli Sánchez Gilo:** investigation, writing – review and editing and resources. **Gemma Melé-Ninot:** investigation, resources and writing – review and editing. **Miguel Ángel Descalzo:** methodology, formal analysis and writing – review and editing. **Leopoldo Borrego:** methodology, data curation, investigation, funding acquisition, writing – review and editing, supervision and project administration.

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Ethics Statement

The REIDAC was approved by the Research Ethics Committee of the Complejo Hospitalario Universitario Insular-Materno Infantil (CEIm-CHUIMI-2017/964).

Consent

Written informed consent was obtained from all participants prior to their inclusion in the study.

Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Allergens causing current relevant reactions in G1 patients diagnosed with anogenital ACD (REIDAC, 2020–2024).