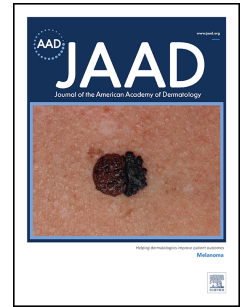


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Hand Dermatitis in Adults Referred for Patch Testing: Analysis of North American Contact Dermatitis Group Data, 2000–2016

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Capsule summary:

- Hand eczema in adults was associated with distinct clinical characteristics, a higher proportions of positive allergic and clinically relevant patch test reactions, with a heterogeneous profile of allergens.
- Patch testing is an important tool in the evaluation of patients with HE.

Abstract

Background: Hand eczema (HE) is a heterogeneous and burdensome disorder.

Objective: To characterize the clinical characteristics, etiologies and allergen relevance in adults with HE referred for patch testing.

Methods: Retrospective analysis (2000–2016) of North American Contact Dermatitis Group data (n=37,113).

Results: Overall, 10,034 were diagnosed with HE, with differences of overlap between allergic contact, irritant contact and atopic dermatitis. Allergic contact HE fluctuated, while atopic HE steadily increased, and irritant HE decreased over time. HE was associated with higher proportions of positive patch tests (67.5% vs. 63.8%; Chi-square, $P<0.0001$). The five most common clinically relevant allergens were methylisothiazolinone, nickel, formaldehyde, quaternium-15 and fragrance mix I. HE was associated with significantly higher odds of positive patch test reactions and clinical relevance in 13 and 16 of the 25 most common allergens, respectively, including preservatives, metals, topical medications, and rubber accelerators.

Limitations: No data on HE phenotype.

Conclusion: HE in adults was associated with higher proportions of positive patch tests, with a heterogeneous profile of allergens. Patch testing remains an important tool in the evaluation of patients with HE.

Introduction

Hand eczema (HE) is a complex and burdensome disorder with heterogeneous morphology and triggers^{1,2}. HE has been shown to be associated with a history of atopic dermatitis (AD)³ and filaggrin (FLG) gene mutations^{4,5}. In addition, HE is commonly caused by allergic (ACD) and/or irritant contact dermatitis (ICD). The European Society of Contact Dermatitis guidelines for HE recommend that patch testing should be performed irrespective of the location and morphology of lesions⁶.

Previous studies examined the profile of the most common and relevant allergens for HE in North America and Europe⁷⁻⁹. However, the use of potential allergens in personal care product and workplace exposures has evolved considerably over the past decade¹⁰⁻¹². Yet, little is known about recent trends in North America with respect to the clinical presentation and role of patch testing in HE. This study sought to determine the clinical characteristics and etiologies of HE in a large North American cohort of adults referred for patch testing, and determine the frequency of positive patch test allergens, and allergen relevance.

Methods

North American Contact Dermatitis Group (NACDG) Database and Data Elements

This retrospective study examined de-identified data from adults (age ≥ 18 years) who were patch tested by the NACDG screening series from 2000–2016. Patch testing was conducted per NACDG standards^{11, 13-15}. Data were entered at a centralized location (Access 2010 and Excel 2019; Microsoft).

Collected data included patient demographics (age, sex, race/ethnicity, occupation), history of atopy (asthma, atopic dermatitis, hay fever), body site(s) of dermatitis (up to 3 coded), and final diagnoses based on clinical history and physical examination (up to 3 coded, 12 diagnoses including ACD, ICD, AD, pompholyx and/or other). Tested allergens varied by two-year cycles; not all allergens were tested during every cycle. At the 48 hour and final readings (72-168 hours after application), patch tests were graded as +/- (weak/doubtful/macular erythema), + (mild), ++ (strong), or +++ (very strong) on the basis of degrees of induration, papules, vesicles and/or spreading. A final determination of presumed “allergic” or “not allergic” was determined by each investigator based on the temporal pattern (crescendo/decrecendo), patch test appearance, and known characteristics of that allergen. For example, a weak/doubtful (macular erythema) reaction to a formaldehyde-releasing agent could be determined to be an allergic/positive reaction in the setting of multiple or stronger reactions to related formaldehyde-releasing allergens.

Current clinical allergen relevance comprised reactions coded as “definite,” (a positive patch and/or use test with a skin contactant verified to contain the allergen and suspected to be the source of the allergen), “probable” (the allergen was verified as present in a known skin contactant of the patient), or “possible” (the patient was exposed to circumstances in which skin

contact with materials likely to contain the allergen was possible)¹⁶. Other relevance categories included “past” or “unknown.” Past relevance is considered if the allergen exposure was in the past but not the present.

This study included previously published data on HE from the 2000–2004 NACDG cycle (n=10,061)⁷. The study was approved by the institutional review board at Northwestern University.

Hand eczema and HE subsets

The two study groups, HE and no HE, were defined based on the presence or absence of hands as one of the 3 coded body site(s) of dermatitis, respectively. Sensitivity analyses were also performed in the patient subset with hands as the primary site of dermatitis, which excluded patients that had HE as a second or third site of dermatitis. The overlap of HE with dermatitis affecting the arms and/or feet was also examined. The following HE subsets were also examined: allergic contact HE (ACHE: hand eczema and a primary diagnosis of ACD), irritant contact HE (ICHE: hand eczema and a primary diagnosis of ICD), atopic HE (AHE: hand eczema and a primary diagnosis of AD) and pompholyx.

Data Analysis

The frequency and proportions of HE, and dermatitis affecting hands, arms and/or feet were estimated. Among HE patients, the frequency and proportion of patients diagnosed with ACD, ICD and/or AD were estimated. Venn-diagrams were created to present the overlap of the three sites of dermatitis, and three diagnoses in HE patients. Trends in HE and HE subsets over time were assessed by Cochran-Armitage Trend Test.

Summary statistics were estimated for the age, race/ethnicity (white/black/Hispanic/Asian/other), sex (male/female), occupation (employed/unemployed) and history of eczema, asthma or hay fever (yes/no) for the overall cohort, and those with or without any HE, primary HE, ACHE, ICHE and AHE. Multivariable logistic regression models were constructed to examine the associations of all these factors (independent variables) with HE or HE subsets (binary dependent variables). Adjusted odds ratio (aOR) and 95% confidence intervals (CI) were estimated.

The proportion and number of positive allergic patch tests were compared between those with vs. without HE using Chi-square and t tests, respectively. The frequency and proportion of positive allergic patch test and relevant allergic patch test reactions were estimated for those with any HE and primary HE compared to other patch tested patients without documented HE, and sorted in descending order of most common positive reactions. Multivariable logistic regression models were constructed to determine whether allergic patch test (yes vs. no) or relevant allergic patch test reactions (definite/probable/possible vs. none; excluding past relevance) to the 25 most common allergens were associated with any or primary HE (yes/no), while adjusting for age, race/ethnicity, sex and employment. aOR and 95% CI were estimated.

Significance-prevalence index number (SPIN) is a weighted calculation that for each allergen incorporates a composite measure of clinical relevance combined with prevalence to determine “hot” allergens¹⁷. SPIN was calculated at each year by: (proportion of population allergic) * (1*percentage with definite relevance + 0.66*percentage with probable relevance + 0.33*percentage with possible relevance) * 100. Mean SPIN was calculated for adults with HE.

All statistical analyses were performed in SAS v9.4.3 (SAS Institute, Cary, NC).

Complete case-analysis was performed. Post-hoc correction for multiple dependent tests was

176 performed by minimizing the false discovery rate with the approach of Benjamini and
177 Hochberg¹⁸ and corrected P values are presented. Two-sided corrected P-values less than or
178 equal to 0.05 were considered significant. Uncorrected 95% CI are presented.

Results

Population characteristics

The cohort consisted of 37,113 adults, including 12,102 (32.6%) males, 31,945 (86.6%) whites, with 8,342 (22.6%) having AD, 5,503 (14.9%) asthma and 10,809 (29.2%) hay fever, and 26,781 (72.6%) age 40 years or more (Table 1), with 24,443 (65.9%) allergic reactions. Overall, 8,632 (24.2%) and 10,034 (27.1%) had hands coded as the primary or any of up to 3 site(s) of dermatitis, respectively.

HE compared to no HE was associated with higher proportions of dermatitis affecting the feet (14.2% vs. 4.2%) and arms (20.4% vs. 13.7%), but lower proportions of all other sites (data not shown; $P < 0.0001$ for all).

The overlap of dermatitis affecting the hands, arms and/or feet was examined. A higher proportion of patients had dermatitis only affecting the hands (18.1% of adults who were patch tested) than the arms (9.6%) or feet (2.5%), i.e. no HE; 3.5% and 5.2% also had dermatitis of the feet or arms, respectively (Figure 1A).

The majority of patients were diagnosed with ACD (59.4%), followed by ICD (29.1%), AD (15.4%) and pompholyx (2.5%). The overlap of the three most common diagnoses (ACD, ICD and AD) was examined: 40.6%, 13.6%, and 5.6% were diagnosed as having ACD, ICD, or AD alone; 12.2% and 6.6% were diagnosed as having concomitant ICD or AD with ACD, respectively (Figure 1B).

Associations of HE and HE subsets

Overall, the proportion of patients referred for patch testing with HE appeared to decreased from 2003-2004 to 2011-2012, and increased again in 2015-2016 (Supplemental

Figure 1A). This pattern was observed for primary HE and primary allergic contact HE. In contrast, the proportion of patients diagnosed as pompholyx increased in 2003-2004, then decreased until 2015-2016. Whereas, the proportion of primary atopic HE steadily increased, while primary irritant HE decreased over time. All HE subsets were most common at age 18-30 years, and steadily decreased with older age (Supplemental Figure 1B).

In multivariable logistic regression models, being employed, having a history of eczema were associated with increased odds of any HE or primary HE (Table 1). Whereas, ages 31-40, 41-50, 51-60 and ≥ 70 years, female sex, and non-white race/ethnicity were inversely associated with HE. Similar results were observed for allergic contact HE, irritant contact HE and atopic AHE (Supplemental Table 1).

Positive patch test reactions in adults with HE

Higher proportions of positive allergic reactions were observed in adults with HE (68.6%) and primary HE (67.8%) compared to those without HE (64.9%; Chi square, $P < 0.0001$ for both). Moreover, a higher mean $\pm$ SD number of positive allergic reactions were observed in adults with HE (2.2 ± 2.5) and primary HE (2.1 ± 2.5) compared to those without HE (1.8 ± 2.2 ; t test, $P < 0.0001$ for both).

The top ten NACDG allergens for positive allergic reactions in adult HE patients included nickel sulfate hexahydrate (17.9%), methylisothiazolinone (17.0%), formaldehyde 2% (12.3%), quaternium-15 (11.3%), formaldehyde 1% (10.7%), thimerosal (10.2%), fragrance mix I (10.0%), gold sodium thiosulfate (9.3%), neomycin sulfate (9.3%) and bacitracin (8.9%) (Table 2). Similar results were observed for primary HE (Supplemental Table 2).

Additionally, 2,222 (22.2%) adult HE patients had positive reactions to ≥ 1 non-NACDG screening allergen; 348 (3.5%) had reactions only to non-NACDG allergens, whereas 1874 (18.7%) had reactions to both NACDG and non-NACDG allergens.

HE was associated with significantly higher odds of positive patch test reactions in 13 of the 25 most common allergens, including methylisothiazolinone, formaldehyde 1% and 2%, quaternium-15, bacitracin, cobalt, carba mix, thiuram mix, methylchloroisothiazolinone/methylisothiazolinone, methyldibromoglutaronitrile/ phenoxyethanol, potassium dichromate, diphenylguanidine, 2-hydroxyethyl methacrylate (Table 2). Similarly, primary HE was associated with 14 of the top 25 allergens, including all of the abovementioned allergens, as well as diazolidinyl urea (Supplemental Table 2).

Allergen relevance in adults with HE

Among adults with HE, the five allergens with highest proportion of current relevance (definite, probable and possible) were methylisothiazolinone, nickel sulfate hexahydrate, formaldehyde, quaternium-15 and fragrance mix I (Table 3). HE was associated with higher odds of relevance in 16 of the top 25 most relevant allergens, but lower odds of relevance in 2 allergens.

In adults with HE, the allergens with highest mean SPIN across all testing cycles, included methylisothiazolinone, nickel, methylchloroisothiazolinone/methylisothiazolinone, quaternium-15, formaldehyde, fragrance mix I, and balsam of Peru (Figure 2).

Discussion

This study had several important findings. Adult HE patients had a high proportion of positive patch test reactions, with both statistically and clinically significantly more reactions compared to adults without HE. These results are consistent with previous studies that found high rates of positive patch tests in HE patients referred for patch testing^{7, 8, 19}. HE was associated with higher odds of positive patch tests and relevant allergic reactions to a variety of different allergens, including preservatives, metals, topical medications, and rubber accelerators. The top 5 NACDG currently-relevant allergens included methlisothiazolinone, nickel, formaldehyde, quaternium-15 and fragrance mix I in adults.

The profile of most common allergens in HE appears to have shifted over time. Previous analysis of data from the NACDG database between 1994 and 2004 found the 5 most common relevant allergens (in adults and children) with HE to be quaternium-15, formaldehyde, nickel, fragrance mix I, and thiuram mix⁷. While these allergens continue to be relevant, methylisothiazolinone has emerged as one of the most commonly relevant allergens in adult HE, consistent with the ongoing “epidemic” of methylisothiazolinone contact allergy²⁰. Methylisothiazolinone had the highest HE-specific SPIN of all allergens tested, indicating both high prevalence and relevance. Formaldehyde and formaldehyde releasers were more commonly positive and relevant in HE. Previous studies found myriad potential sources of formaldehyde and releasers in HE, including occupational dermatitis^{21, 22}, gloves²³, skin cleansers²⁴, and even cigarettes²⁵. Carba mix and thiuram mix were both common and significantly increased in HE, which is relevant for guidance on glove alternatives. Other common rubber sources include tires, tubes, footwear, hoses, belting, gaskets, packing, and sealing devices²⁶. While nickel allergic reactions were not significantly more common in HE patients, nickel was still the most common

positive allergic reaction in HE patients and had a high proportion of relevance and SPIN score. Common sources of nickel exposure to the hands include electronic devices and protective cases, coins, pots and pans, musical instruments, tools and jewelry²⁷. Dietary intake of nickel has been reported as a less common cause of HE²⁸. It is noteworthy that some allergens were common in HE patients, but were not more likely to be positive or relevant in HE, e.g. gold. This is consistent with previous studies that found high proportions of positive reactions to gold, but mixed results regarding its relevance to the underlying dermatitis^{29, 30}.

These results have important clinical ramifications. First, they highlight the importance of patch testing in HE patients. The ESCD guidelines recommend that patch testing be performed in chronic HE irrespective of the location or morphology of lesions⁶. Second, some of the most common and relevant allergens in HE would be missed by Thin-Layer Rapid Use Epicutaneous (T.R.U.E.)© test, including benzalkonium chloride, iodopropynyl butylcarbamate, and lanolin. Thus, use of an expanded patch test series should be encouraged over a T.R.U.E. test in the workup of HE patients. Third, approximately 1 in 5 adults with HE had a positive reaction to one or more allergens not present on the NACDG screening series. These results underscore the importance of testing HE patients to supplemental allergens in both children and adults, including patient's own products, workplace materials and/or other suspected allergens. Finally, there was considerable overlap between ACD and ICD on the hands, consistent with previous studies. Thus, even HE patients with relevant positive allergic reactions and a diagnosis of ACD should be counseled about irritant avoidance to address overlapping ICD.

Associations of HE

HE was more common in patients who were male, young adults, and employed. HE has consistently been found in population-based studies to be more common in females^{31, 32}. The observed male-predilection may be related to increased occupational exposures, as males are more likely to work in the manufacturing and metalworking industries³³. Previous studies also found higher rates of other occupational dermatoses^{34, 35} and HE subtypes associated with increased manual labor, e.g. hyperkeratotic HE³⁶, in males. Future studies will specifically examine the associations of occupational HE. HE was less likely to occur with older age, in females, black, Asian and other patients, but not in Hispanics. These demographic differences may be due to differences of occupation, culture, and/or access to care; however, these factors were not examined.

Temporal trends of HE

Different temporal trends were observed across HE subsets. While the proportion diagnosed in the NACDG database with ACHE fluctuated, AHE increased, and ICHE decreased diagnosed over time. Of note, the NACDG database is not a population-based study and cannot estimate disease prevalence per se. However, the observed trends may reflect evolving population-trends of HE in North America. There has also been a steady decline in manufacturing jobs in the United States³⁷, which may be accompanied by lower rates of occupational HE. As such, the proportion of ACD may be increasing as a cause of HE over time.

Limitations

The NACDG database does not distinguish between specific HE phenotypes (e.g., hyperkeratotic vs. vesicular, unilateral vs. bilateral). Names of non-NACDG allergens are not

recorded (only sources of those allergens). Data on HE onset, longitudinal course and treatment history were not collected. Finally, long-term follow-up data are lacking, precluding assessment of whether patients improved with allergen or irritant avoidance.

Conclusions

HE is associated with heterogeneous clinical presentation, and multiple classes of allergens. ACD was the most common diagnosis in adults with HE who were referred for patch testing. HE was associated with a heterogeneous profile of allergic reactions and relevant allergens. Patch testing remains an important tool in the evaluation of patients with HE.

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Figure Legends

Figure 1. Overlap of dermatitis sites and diagnosis. Venn diagram of overlap between (A) dermatitis of the hands, feet and/or arms, in the NACDG database and (B) allergic contact dermatitis (ACD), irritant contact dermatitis (ICD) and atopic dermatitis (AD) among adults patients with hand eczema in the NACDG database.

Figure 2. Temporal and age trends of hand eczema and hand eczema subsets. Prevalences of any hand eczema (black solid line), primary hand eczema (black dotted line), primary allergic contact hand eczema (red), primary irritant contact hand eczema (green) and primary atopic hand eczema (blue) were estimated for (A) each two-year cycle and (B) different age groups.

Figure 3. Allergens with highest significance-prevalence index number (SPIN) in adults with hand eczema. SPIN was calculated at each 2 year cycle by: $(\text{proportion of population allergic}) * (1 * \text{percentage with definite relevance} + 0.66 * \text{percentage with probable relevance} + 0.33 * \text{percentage with possible relevance}) * 100$.

Table 1. Association of hand eczema with demographics and atopic history.

Variable	Overall (n=37,113)	Hand eczema							
		Hand Involvement Coded as any of up to 3 Anatomic Sites (n=10034)				Hand involvement Coded as the Primary Anatomical Site (n=8632)			
		No	Yes	Adjusted OR (95% CI)	P*	No	Yes	Adjusted OR (95% CI)	P*
		Freq (%)	Freq (%)			Freq (%)	Freq (%)		
<i>Age (yr)</i>									
18-30	4935 (13.3%)	3163 (64.1%)	1769 (35.9%)	1.000 [ref]	–	3163 (67.2%)	1541 (32.8%)	1.000 [ref]	–
31-40	6110 (16.5%)	4044 (66.2%)	2064 (33.8%)	0.823 (0.754-0.897)	<0.0001	4044 (69.3%)	1793 (30.7%)	0.828 (0.760-0.902)	<0.0001
41-50	8043 (21.7%)	5638 (70.1%)	2403 (29.9%)	0.676 (0.622-0.735)	<0.0001	5638 (73.0%)	2082 (27.0%)	0.678 (0.624-0.736)	<0.0001
51-60	8546 (23.0%)	6162 (72.2%)	2379 (27.9%)	0.625 (0.575-0.679)	<0.0001	6162 (74.9%)	2062 (25.1%)	0.637 (0.587-0.692)	<0.0001
61-70	5785 (15.6%)	4718 (81.6%)	1064 (18.4%)	0.420 (0.379-0.465)	<0.0001	4718 (84.3%)	879 (15.7%)	0.426 (0.385-0.471)	<0.0001
≥70	3694 (10.0%)	3335 (90.4%)	355 (9.6%)	0.215 (0.185-0.250)	<0.0001	3335 (92.4%)	275 (7.6%)	0.221 (0.191-0.256)	<0.0001
<i>Sex</i>									
Female	25007 (67.4%)	19122 (76.5%)	5871 (23.5%)	0.525 (0.497-0.554)	<0.0001	19122 (79.6%)	4892 (20.4%)	0.521 (0.494-0.549)	<0.0001
Male	12102 (32.6%)	7936 (65.6%)	4161 (34.4%)	1.000 [ref]	–	7936 (68.0%)	3738 (32.0%)	1.000 [ref]	–
<i>Race/ethnicity</i>									
White	31945 (86.6%)	23197 (72.7%)	8730 (27.3%)	1.000 [ref]	–	23197 (75.5%)	7528 (24.5%)	1.000 [ref]	–
Black	1835 (5.0%)	1384 (75.4%)	451 (24.6%)	0.799 (0.706-0.906)	0.0007	1384 (78.4%)	381 (21.6%)	0.794 (0.702-0.899)	0.0005
Hispanic	693 (1.9%)	487 (70.3%)	206 (25.4%)	1.077 (0.898-1.292)	0.5088	487 (73.1%)	179 (26.9%)	1.051 (0.877-1.261)	0.6442
Asian	1802 (4.9%)	1343 (74.5%)	459 (25.5%)	0.798 (0.707-0.901)	0.0005	1343 (77.5%)	390 (22.5%)	0.800 (0.710-0.903)	0.0005
Other	615 (1.7%)	464 (75.6%)	150 (24.4%)	0.706 (0.570-0.874)	0.0016	464 (69.6%)	118 (20.3%)	0.703 (0.569-0.869)	0.0018
<i>Occupation</i>									
Unemployed	12839 (35.8%)	10682 (83.3%)	2148 (16.7%)	1.000 [ref]	–	10682 (86.1%)	1720 (13.9%)	1.000 [ref]	–
Employed	23011 (64.2%)	15404 (67.0%)	7602 (33.0%)	1.916 (1.793-2.046)	<0.0001	15404 (69.8%)	6672 (30.2%)	1.916 (1.800-2.046)	<0.0001
<i>Atopic disease</i>									
<i>Atopic dermatitis</i>									
No	28621 (77.4%)	21216 (74.2%)	7389 (25.8%)	1.000 [ref]	–	21216 (76.7%)	6451 (23.3%)	1.000 [ref]	–
Yes	8342 (22.6%)	5725 (68.7%)	2614 (31.4%)	1.166 (1.092-1.244)	<0.0001	5725 (72.7%)	2154 (27.3%)	1.182 (1.108-1.260)	<0.0001
<i>Asthma</i>									
No	31506 (85.1%)	23044 (73.2%)	8447 (26.8%)	1.000 [ref]	–	23044 (76.0%)	7293 (24.0%)	1.000 [ref]	–
Yes	5503 (14.9%)	3939 (71.6%)	1560 (28.4%)	0.976 (0.903-1.054)	0.6064	3939 (75.0%)	1316 (25.0%)	0.977 (0.905-1.055)	0.6189
<i>Hay fever</i>									
No	26195 (70.8%)	19245 (73.5%)	6936 (26.5%)	1.000 [ref]	–	19245 (76.1%)	6034 (23.9%)	1.000 [ref]	–
Yes	10809 (29.2%)	7731 (71.6%)	3073 (28.4%)	0.966 (0.908-1.027)	0.3371	7,731 (75.0%)	2577 (25.0%)	0.970 (0.913-1.032)	0.4154

Missing values were encountered in 28 (0.07%) for age, 8 (0.02%) for sex, 240 (0.6%) for race/ethnicity, 1288 (3.3%) for occupation, 160 (0.4%) for history of atopic dermatitis, 111 (0.03%) for history of asthma and 115 (0.3%) for history of hay fever.

* Corrected p-values are presented.

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Table 2. Most common positive allergic reactions in adult patients with a primary or secondary site for hand eczema.

Allergen	No hand eczema			Primary/secondary hand eczema			Adjusted OR (95% CI)	P-value
	No. of pts tested	Allergic reaction, n (%)	Rank order	No. of pts tested	Allergic reaction, n (%)	Rank order		
Nickel sulfate hexahydrate, 2.5% pet.	26976	4845 (18%)	1	9986	1784 (17.9%)	1	1.016 (0.953-1.083)	0.6797
Methylisothiazolinone, 0.2% aq. (2000 ppm)	7509	820 (10.9%)	3	2586	440 (17.0%)	2	1.756 (1.541-2.001)	<0.0001
Formaldehyde, 2.0% aq.	3904	285 (7.3%)	9	1411	174 (12.3%)	3	1.968 (1.597-2.426)	<0.0001
Quaternium 15, 2.0% pet.	27038	1604 (5.9%)	13	10020	1134 (11.3%)	4	2.237 (2.054-2.436)	<0.0001
Formaldehyde, 1.0% aq.	27041	1700 (6.3%)	11	10022	1071 (10.7%)	5	1.96 (1.798-2.136)	<0.0001
Thimerosal 0.1% pet.	3372	333 (9.9%)	4	1354	138 (10.2%)	6	0.987 (0.792-1.232)	0.9163
Fragrance mix I, 8.0% pet.	27014	2970 (11%)	2	10024	1003 (10.0%)	7	1.058 (0.977-1.146)	0.2187
Sodium gold thiosulfate, 0.5% pet.	6803	654 (9.6%)	6	2861	265 (9.3%)	8	1.082 (0.92-1.273)	0.4185
Neomycin sulfate, 20.0% pet.	27021	2589 (9.6%)	6	10008	920 (9.2%)	9	1.079 (0.992-1.173)	0.1072
Bacitracin, 20.0% pet.	27021	2073 (7.7%)	8	10020	892 (8.9%)	10	1.279 (1.173-1.396)	<0.0001
Myroxylon Pereirae Resin (Balsam of Peru), 25.0% pet.	27048	2662 (9.8%)	5	10028	857 (8.5%)	11	0.956 (0.877-1.042)	0.3810
Cobalt (ii) chloride hexahydrate, 1.0% pet.	27022	1846 (6.8%)	10	10014	831 (8.3%)	12	1.179 (1.078-1.289)	0.0005
Carba mix, 3.0% pet.	27046	987 (3.6%)	18	10020	726 (7.2%)	13	2.039 (1.836-2.265)	<0.0001
Thiuram mix, 1.0% pet.	27039	668 (2.5%)	30	10021	711 (7.1%)	14	3.225 (2.875-3.617)	<0.0001
Methylchloroisothiazolinone /methylisothiazolinone, 0.02% aq.=200ppm	27005	890 (3.3%)	20	10016	644 (6.4%)	15	2.145 (1.921-2.395)	<0.0001
Methyldibromoglutaronitrile/Phenoxyethanol,(Euxyl K 400), 2.0% pet.	27015	1289 (4.8%)	15	10023	517 (5.2%)	16	1.183 (1.058-1.323)	0.0050
4-phenylenediamine, 1.0% pet.	27005	1628 (6%)	12	10008	512 (5.1%)	17	0.901 (0.81-1.003)	0.0810
Fragrance mix II, 14.0% pet.	17193	876 (5.1%)	14	5880	279 (4.7%)	18	1.002 (0.868-1.158)	0.9730
Potassium dichromate, 0.25% pet.	27053	717 (2.7%)	28	10023	458 (4.6%)	19	1.553 (1.366-1.766)	<0.0001
Diphenylguanidine, 1% pet.	7511	214 (2.8%)	27	2587	115 (4.4%)	20	1.542 (1.209-1.967)	0.0008
2-Hydroxyethyl methacrylate, 2.0% pet.	17180	381 (2.2%)	36	5880	228 (3.9%)	21	2.156 (1.808-2.571)	<0.0001
Benzalkonium Chloride, 0.1% aq.	3364	153 (4.5%)	16	1354	53 (3.9%)	21	0.861 (0.613-1.209)	0.4672
Propylene glycol, 100%	7512	251 (3.3%)	20	2587	99 (3.8%)	23	1.158 (0.906-1.481)	0.3132
Iodopropynyl butylcarbamate, 0.5% pet.	20196	831 (4.1%)	17	7154	237 (3.3%)	24	0.98 (0.838-1.145)	0.8396
Lanolin alcohol (Amerchol L101), 50% pet.	27045	814 (3%)	24	10024	328 (3.3%)	24	1.057 (0.922-1.211)	0.5088

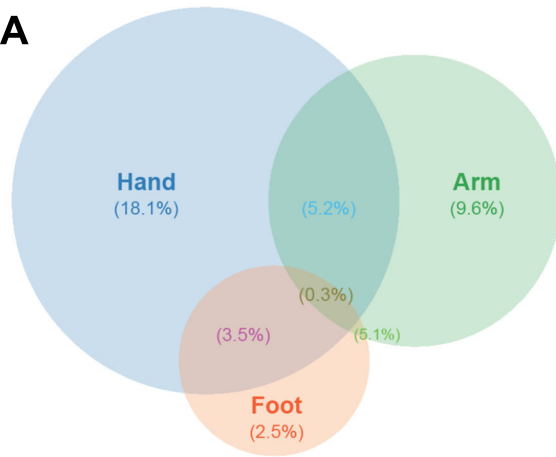
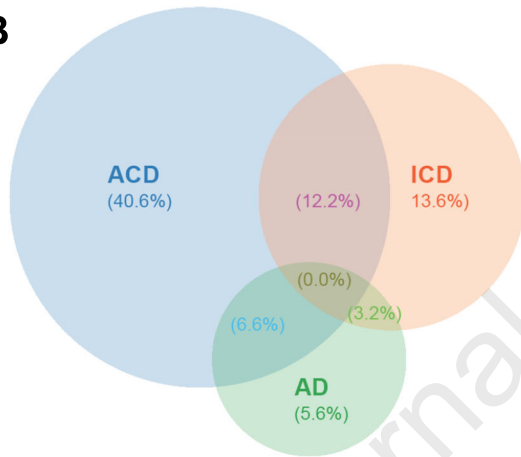
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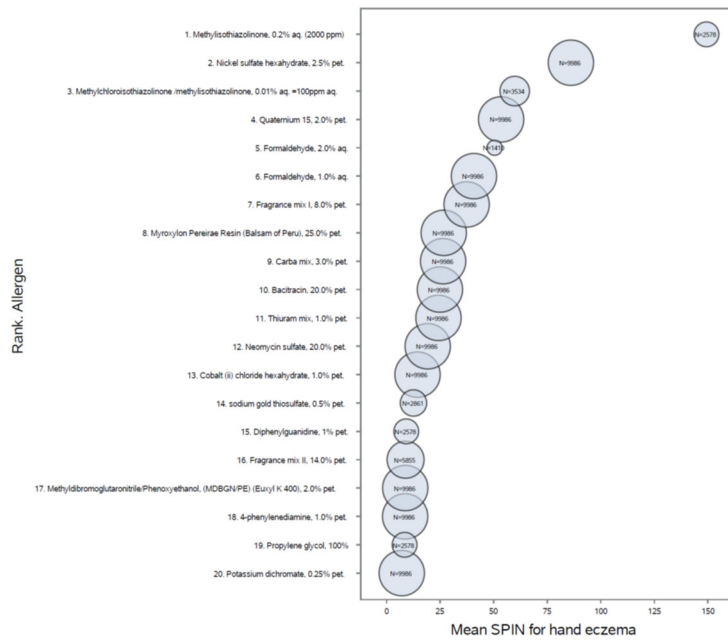
Table 3. Most common relevant allergens in adults with hand eczema.

Allergen	Rank order of allergen relevance in hand eczema	Hand eczema	Relevance of allergens - freq. (%)					Adjusted OR (95% CI)*	P-value
			Not relevant allergen	Definite	Probable	Possible	Past		
Methylisothiazolinone, 0.2% aq. (2000 ppm)	1	No	6684 (89.7%)	58 (0.8%)	380 (5.1%)	314 (4.2%)	17 (0.2%)	1.00 [ref]	-
		Yes	2143 (83.8%)	30 (1.2%)	225 (8.8%)	147 (5.7%)	11 (0.4%)	1.743 (1.522-1.996)	<0.0001
Nickel sulfate hexahydrate, 2.5% pet.	2	No	22225 (84.3%)	75 (0.3%)	809 (3.1%)	1710 (6.5%)	1535 (5.8%)	1.00 [ref]	-
		Yes	8217 (84%)	38 (0.4%)	331 (3.4%)	659 (6.7%)	539 (5.5%)	1.092 (1.006-1.185)	0.0516
Formaldehyde, 2.0% aq.	3	No	3601 (94%)	3 (0.1%)	76 (2%)	148 (3.9%)	4 (0.1%)	1.00 [ref]	-
		Yes	1232 (89.5%)	2 (0.1%)	31 (2.3%)	106 (7.7%)	5 (0.4%)	1.986 (1.574-2.507)	<0.0001
Quaternium-15, 2.0% pet.	4	No	25425 (94.5%)	42 (0.2%)	480 (1.8%)	901 (3.3%)	59 (0.2%)	1.00 [ref]	-
		Yes	8873 (89.7%)	32 (0.3%)	294 (3%)	648 (6.5%)	48 (0.5%)	2.157 (1.97-2.363)	<0.0001
Formaldehyde, 1.0% aq.	5	No	25309 (94.5%)	15 (0.1%)	480 (1.8%)	935 (3.5%)	41 (0.2%)	1.00 [ref]	-
		Yes	8923 (90.6%)	16 (0.2%)	222 (2.3%)	657 (6.7%)	26 (0.3%)	1.972 (1.796-2.166)	<0.0001
Fragrance mix I, 8.0% pet.	6	No	23973 (89.8%)	70 (0.3%)	888 (3.3%)	1642 (6.1%)	126 (0.5%)	1.00 [ref]	-
		Yes	8989 (91%)	14 (0.1%)	235 (2.4%)	598 (6.1%)	41 (0.4%)	1.023 (0.938-1.115)	0.6619
Myroxylon Pereirae Resin (Balsam of Peru), 25.0% pet.	7	No	24323 (91%)	37 (0.1%)	803 (3%)	1476 (5.5%)	92 (0.3%)	1.00 [ref]	-
		Yes	9140 (92.5%)	9 (0.1%)	192 (1.9%)	516 (5.2%)	29 (0.3%)	0.927 (0.844-1.017)	0.1447
Carba mix, 3.0% pet.	8	No	26017 (97%)	22 (0.1%)	228 (0.9%)	464 (1.7%)	76 (0.3%)	1.00 [ref]	-
		Yes	9275 (93%)	82 (0.8%)	255 (2.6%)	325 (3.3%)	34 (0.3%)	2.552 (2.273-2.866)	<0.0001
Thiuram mix, 1.0% pet.	9	No	26360 (98%)	29 (0.1%)	162 (0.6%)	261 (1%)	85 (0.3%)	1.00 [ref]	-
		Yes	9301 (93.1%)	71 (0.7%)	255 (2.6%)	312 (3.1%)	54 (0.5%)	4.149 (3.642-4.726)	<0.0001
Methylchloroisothiazolinone /methylisothiazolinone, 0.02% aq. =200ppm	10	No	26107 (96.9%)	68 (0.3%)	375 (1.4%)	351 (1.3%)	30 (0.1%)	1.00 [ref]	-
		Yes	9366 (93.9%)	45 (0.5%)	294 (2.9%)	243 (2.4%)	26 (0.3%)	2.181 (1.942-2.449)	<0.0001
Bacitracin, 20.0% pet.	11	No	24984 (93.8%)	121 (0.5%)	380 (1.4%)	286 (1.1%)	859 (3.2%)	1.00 [ref]	-
		Yes	9139 (92.6%)	73 (0.7%)	228 (2.3%)	149 (1.5%)	278 (2.8%)	1.691 (1.493-1.915)	<0.0001
Cobalt (ii) chloride hexahydrate, 1.0% pet.	13	No	25190 (95.1%)	12 (0%)	133 (0.5%)	667 (2.5%)	473 (1.8%)	1.00 [ref]	-
		Yes	9169 (93.7%)	10 (0.1%)	95 (1%)	303 (3.1%)	207 (2.1%)	1.287 (1.133-1.462)	0.0001
Fragrance mix II, 14.0% pet.	13	No	16283 (95.1%)	22 (0.1%)	352 (2.1%)	437 (2.6%)	25 (0.1%)	1.00 [ref]	-
		Yes	5596 (95.7%)	5 (0.1%)	73 (1.2%)	167 (2.9%)	9 (0.2%)	0.955 (0.82-1.112)	0.6189

Diphenylguanidine, 1% pet.	15	No	7281 (98.1%)	2 (0%)	25 (0.3%)	99 (1.3%)	18 (0.2%)	1.00 [ref]	-
		Yes	2464 (96%)	15 (0.6%)	24 (0.9%)	59 (2.3%)	4 (0.2%)	2.274 (1.712-3.019)	<0.0001
Methyldibromoglutaronitrile/Phenoxyethanol, (Euxyl K 400), 2.0% pet.	15	No	25647 (96.3%)	23 (0.1%)	311 (1.2%)	594 (2.2%)	62 (0.2%)	1.00 [ref]	-
		Yes	9460 (96%)	17 (0.2%)	95 (1%)	256 (2.6%)	24 (0.2%)	1.149 (1.007-1.311)	0.0562
Propylene glycol, 100%	16	No	7249 (96.9%)	16 (0.2%)	132 (1.8%)	77 (1%)	4 (0.1%)	1.00 [ref]	-
		Yes	2480 (96.3%)	6 (0.2%)	54 (2.1%)	35 (1.4%)	0 (0%)	1.253 (0.972-1.614)	0.1127
Neomycin sulfate, 20.0% pet.	17	No	24464 (92.4%)	87 (0.3%)	320 (1.2%)	284 (1.1%)	1311 (5%)	1.00 [ref]	-
		Yes	9092 (92.4%)	53 (0.5%)	159 (1.6%)	145 (1.5%)	391 (4%)	1.547 (1.348-1.774)	<0.0001
Sodium gold thiosulfate, 0.5% pet.	18	No	6116 (95%)	4 (0.1%)	79 (1.2%)	176 (2.7%)	61 (0.9%)	1.00 [ref]	-
		Yes	2588 (95.9%)	3 (0.1%)	21 (0.8%)	65 (2.4%)	22 (0.8%)	0.923 (0.705-1.208)	0.6199
Potassium dichromate, 0.25% pet.	19	No	26279 (98.5%)	12 (0%)	92 (0.3%)	227 (0.9%)	72 (0.3%)	1.00 [ref]	-
		Yes	9547 (96.5%)	20 (0.2%)	110 (1.1%)	176 (1.8%)	44 (0.4%)	2.057 (1.738-2.436)	<0.0001
4-phenylenediamine, 1.0% pet.	21	No	25361 (94.9%)	55 (0.2%)	659 (2.5%)	343 (1.3%)	309 (1.2%)	1.00 [ref]	-
		Yes	9484 (96%)	29 (0.3%)	151 (1.5%)	97 (1%)	120 (1.2%)	0.734 (0.638-0.845)	<0.0001
Lanolin alcohol (Amerchol L101), 50% pet.	21	No	26212 (97.3%)	43 (0.2%)	306 (1.1%)	362 (1.3%)	28 (0.1%)	1.00 [ref]	-
		Yes	9680 (97%)	22 (0.2%)	113 (1.1%)	149 (1.5%)	11 (0.1%)	1.048 (0.906-1.213)	0.6064
Diazolidinyl urea (Germall II), 1.0% pet.	23	No	26370 (97.7%)	35 (0.1%)	196 (0.7%)	357 (1.3%)	21 (0.1%)	1.00 [ref]	-
		Yes	9717 (97.2%)	20 (0.2%)	83 (0.8%)	175 (1.7%)	7 (0.1%)	1.468 (1.257-1.714)	<0.0001
Iodopropynyl butylcarbamate, 0.5% pet.	23	No	19261 (96.3%)	20 (0.1%)	287 (1.4%)	407 (2%)	14 (0.1%)	1.00 [ref]	-
		Yes	6884 (97.2%)	10 (0.1%)	64 (0.9%)	119 (1.7%)	8 (0.1%)	0.907 (0.764-1.076)	0.3327
2-Hydroxyethyl methacrylate, 2.0% pet.	24	No	16800 (98.3%)	7 (0%)	86 (0.5%)	98 (0.6%)	92 (0.5%)	1.00 [ref]	-
		Yes	5650 (96.5%)	7 (0.1%)	90 (1.5%)	59 (1%)	45 (0.8%)	2.95 (2.353-3.697)	<0.0001
Propylene glycol, 30.0% aq.	25	No	26137 (97.2%)	106 (0.4%)	321 (1.2%)	322 (1.2%)	11 (0%)	1.00 [ref]	-
		Yes	9742 (97.6%)	31 (0.3%)	108 (1.1%)	95 (1%)	5 (0.1%)	0.792 (0.679-0.925)	0.0050

* Multivariable logistic regression models were constructed with specific allergen relevance (definite/probable/possible vs. not relevant; excluding past or unknown relevance) as the dependent variable and hand eczema (yes vs. no) as the independent variable, and age (continuous), race/ethnicity (white, non-Hispanic/black/Hispanic/Asian/other), sex and employment.

A**B**



Capsule summary:

- Hand eczema in adults was associated with distinct clinical characteristics, a higher proportions of positive allergic and clinically relevant patch test reactions, with a heterogeneous profile of allergens.
- Patch testing is an important tool in the evaluation of patients with HE.