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The European baseline series in 10 European Countries, 2005/2006 – Results of the European Surveillance System on Contact Allergies (ESSCA)

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Background: Continual surveillance based on patch test results has proved useful for the identification of contact allergy.

Objectives: To provide a current view on the spectrum of contact allergy to important sensitizers across Europe.

Patients/Methods: Clinical and patch test data of 19 793 patients patch tested in 2005/2006 in the 31 participating departments from 10 European countries (the European Surveillance System on Contact Allergies' (ESSCA) www.essca-dc.org) were descriptively analysed, aggregated to four European regions.

Results: Nickel sulfate remains the most common allergen with standardized prevalences ranging from 19.7% (central Europe) to 24.4% (southern Europe). While a number of allergens shows limited variation across the four regions, such as *Myroxylon pereirae* (5.3–6.8%), cobalt chloride (6.2–8.8%) or thiuram mix (1.7–2.4%), the differences observed with other allergens may hint on underlying differences in exposures, for example: dichromate 2.4% in the UK (west) versus 4.5–5.9% in the remaining EU regions, methylchloroisothiazolinone/methylisothiazolinone 4.1% in the South versus 2.1–2.7% in the remaining regions.

Conclusions: Notwithstanding residual methodological variation (affecting at least some 'difficult' allergens) tackled by ongoing efforts for standardization, a comparative analysis as presented provides (i) a broad overview on contact allergy frequencies and (ii) interesting starting points for further, in-depth investigation.

Key words: clinical epidemiology; contact allergy; patch testing. © John Wiley & Sons A/S, 2009.

Conflicts of interest: The authors have declared no conflicts

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Past experience has shown that clinical surveillance of contact allergy, i.e. systematic analysis of patch test data, is a prerequisite for the identification and, ultimately, the control of contact allergy epidemics (1). As these often start locally or nationally, continual analysis should not only focus on global trends but also on possible differences between, e.g. European regions to derive valuable starting points for the in-depth investigation of possible unacceptable exposures. On a European level, the 'European Surveillance System on Contact Allergies' (ESSCA; www.essca-dc.org) has proved useful in providing current information on the spectrum of contact allergy across Europe in the countries participating (2, 3). The present analysis of 2005/2006 patch test data aims at providing an update.

Methods

Background information on the objectives and methods of the ESSCA has been reported (2). Briefly, patch test results obtained with the European Baseline Series and selected other allergens also tested in consecutive patients, e.g. in local or national adaptations of the European Baseline Series, were collected along with basic demographic and clinical data. After import from the various patch test software databases, including 'WinAlldat/ESSCA' (4), internal reports were delivered to each centre to be checked for completeness and plausibility. If feedback necessitated amendments, these were made before pooling data for the analyses presented. As a compromise between a global and a very detailed results presentation on the level of single departments, a regional aggregation within Europe was chosen with the 'western' region equivalent to the UK, but otherwise grouping several countries in one region (Table 1).

Routine patch test exposure time was 2 days, except in Kiel, Germany, where it was 1 day. Patch test results were recorded according to international guidelines (5). The standard 'positive outcome' (allergic reaction) of the patch test was defined as a morphologically + to +++ reaction (5) between D3 and D5 after the application of the patch test which was not, upon final evaluation, considered irritant. Descriptive analysis of data followed current guidelines as elaborated by ESSCA (6), in particular employing age- and sex-standardization of sensitization prevalences (7). For data management and descriptive analysis, the statistical software package SASTM (version 9.1, SAS Institute, Cary, NC, USA) was used.

Results

In the 31 participating departments 9695 patients were patch tested in the year 2005 in the course of 9767 consultations, and 10 293 patients were tested in 2006, in the course of 10 366 consultations (Table 1), i.e. a small proportion of patients was seen and patch tested more than once. In these cases, the most current consultation was chosen for analysis. In the following analyses, the 2 years are aggregated. The median number of patients per clinic was 608 in the 2 years. With 240 and 110 patients, respectively, Middlesbrough, UK and Bern, Switzerland contributed the lowest number of patients (in 2006 only). The largest number of patients consulted the departments in Amsterdam, The Netherlands and Leeds, UK (1558 and 1537 patients, respectively). Among the 31 departments, one department is specialized in paediatric dermatology (Padova 'Pediatría', Italy). Because of its restricted age range (all patients less than 18 years old, see Ref. (3)), and in view of the fact that many allergens exhibit a strong association with age, the results of this specialized department are not included in the further analyses presented in this paper but will be reported elsewhere.

The distribution of important demographic variables according to the MOAHLFA index in the four regions is shown in Table 2. While the proportion of male patients is relatively similar, other patient characteristics differ more – most markedly the proportion of patients with occupational dermatitis, diagnosed upon final evaluation (see Discussion). The age distribution showed some differences, with the youngest patients tested in the south (median age 39, inter-quartile range [IQR] 26–56) and the oldest in central Europe (median age 45 years, IQR 32–58), the western (median 43 years, IQR 29–58) and north-eastern (median 42 years, IQR 30–52) regions occupying an intermediate rank.

In 25 of the 31 centres at least 95% of the patients were tested with the European Baseline Series (8), as locally or nationally adapted, in five centres between 90% and 95%. In one centre only (Erlangen, Germany) slightly fewer than 90% of the patients were tested to this series. The proportion of patients with positive reactions to at least one allergen of the European Baseline Series among those tested with this series as used in the respective department displayed considerable variability between centres, but was very similar across regions (Table 1). The patch test results with the European Baseline Series in the 30 departments, aggregated to four regions, are shown in Table 3, the allergens grouped into different classes (fragrances, metals, preservatives, rubber allergens, a few 'diverse' allergens and topical agents). The number of patients

Table 1. Participating ESSCA departments in 2005/2006 with patient numbers

Region	Department	Shorthand	Allergen supplier(s) [#]	Number of patients	Number of consultations [§]	Percentage positive to ESS
	Amersham	UK-01	HT, CH	1038	1061	41.6
	Nottingham	UK-02	HT, CH	926	926	45.2
	Oxford*	UK-04	HT, CH	372	372	42.2
	Sheffield	UK-05	HT, CH	808	808	42.0
	Dundee	UK-07	HT, CH	919	919	35.9
	Leeds	UK-08	HT, CH	1537	1537	36.8
	Aberdeen	UK-09	HT, CH	605	605	62.5
	Bristol	UK-10	HT, CH	613	613	44.5
	Liverpool	UK-11	HT, CH	618	618	49.5
	Middlesbrough*	UK-12	HT, CH	240	240	59.6
	Swansea	UK-30	HT, CH	344	344	44.5
	Cardiff	UK-31	HT, CH	584	584	36.8
West				8604	8627	43.1
	Barcelona	ES-01	HT, CH	751	755	43.5
	Napoli	IT-01	CH	708	708	36.1
	Padova	IT-02	CH	895	895	52.7
	Padova Ped.	IT-03	CH	648	648	30.6
	Pordenone	IT-06	CH	431	431	41.1
South				3240	3240	41.5
	Groningen	NL-01	TT	784	793	41.8
	Amsterdam-VU	NL-02	HT, CH	1558	1582	42.7
	Basel	CH-42	TT, HT	517	535	47.3
	Bern*	CH-56	HT	110	112	56.5
	Graz	AT-25	HT	660	660	50.9
	Dortmund	DE-01	HT	593	602	31.1
	Göttingen	DE-03	HT	258	261	37.1
	Kiel	DE-06	HT	470	472	48.8
	Jena	DE-12	HT	672	696	40.4
	Erlangen	DE-24	HT	683	744	50.1
Central				6305	6457	43.7
	Helsinki	FI-01	HT, CH	296	297	42.1
	Lahti	FI-02	CH	465	465	50.3
	Kaunas	LT-01	HT	242	242	46.3
	Lodz	PL-01	CH	608	608	39.1
Northeast				1611	1612	44.0

[#]HT = Trolab™ (Almirall-Hermal, Reinbek, Germany), CH = Chemotechnique Diagnostics™ (Malmo, Sweden), TT = True test®.

[§]Consultation is the presentation of a patient for patch testing, possibly multiply during a period.

*2006 only.

tested varies within regions, because of different compositions of the local standard series in the departments aggregated, or because allergens have been withdrawn or added to the series during the study period, such as hydroxyisohexyl 3-cyclohexene carboxaldehyde (e.g. Lyrall®) or the fragrance mix II. Regarding methyl dibromo glutaronitrile, a subset of 'central' patients had initially (also) been tested with 0.2% in petrolatum, yielding 3.0% [95% confidence interval (CI): 2.3–3.7%] standardized positive reactions.

The temporary addition of allergens to a Baseline series (locally or in a contact allergy network) can give clues on its potential to become a permanent part of the Baseline series. Among those allergens tested in consecutive patients in more than one region, 2-bromo-2-nitropropane-1,3-diol (bronopol) yielded 1.1% and 1.2% positive reactions in the 'West' (tested 0.25% pet.) and the 'Central' region

(tested 0.5% in pet.), respectively appears to be a candidate for inclusion.

Discussion

The present descriptive analysis of contact allergy prevalences in patients patch tested for suspected allergic contact dermatitis throughout many, albeit not all, European countries differs from the preceding report, which contrasted global contact allergy prevalences (and MOAHLFA characteristics) with local minima and maxima (3): In an attempt to reduce the impact of inter-departmental variation in patient characteristics and the potential for variation in interpretation of positive reactions several centres have now been aggregated to regions. This reduced the amount of variation and yielded a more stable picture. As a trade-off, local clustering of contact allergy to specific allergens cannot be recognized. However, supplementary centre-wise reports from

Table 2. MOAHLFA percentages in the four regions (average percentage and range)

		West (n = 8604)	South (n = 2590)	Central (n = 6310)	Northeast (n = 1611)
2005/2006					
Male	M	32.9 (UK-11: 28.6 – UK-31: 34.9)	33.8 (ES-01: 29.6 – IT-06: 36.9)	37.5 (AT-25: 31.8 – DE-01: 48.1)	32.8 (LT-01: 20.7 – FI-01: 49.0)
Occupational dermatitis	O	11.5 (UK-01: 4.1 – UK-30: 17.4)	4.4 (IT-02,06: 3.0 – ES-01: 13.7)	18.8 (DE-06: 9.4 – NL-01: 26.2)	37.0 (FI-02: 30.5 – FI-01: 55.1)
Atopic dermatitis	A	§	11.8 (IT-02: 6.9 – IT-01: 17.2)	23.4 (DE-06: 7.2 – NL-01: 39.0)	25.1 (PL-01: 21.4 – FI-02: 31.0)
Primary site: Hand	H	29.1 (UK-01: 20.0 – UK-30: 48.0)	25.6 (ES-01: 14.5 – IT-06: 33.0)	26.1 (AT-25: 14.2 – CH-56: 42.7)	46.2 (LT-01: 23.6 – FI-01: 74.3)
Primary site: Leg	L	7.6 (UK-12: 3.3 – UK-04: 11.3)	8.1 (IT-01: 5.1 - IT-02: 11.0)	8.4 (NL-01: 4.9 – DE-06: 17.5)	2.7 (FI-01: 1.4 – LT-01: 4.6)
Primary site: Face	F	24.9 (UK-09: 15.7 – UK-02: 31.9)	15.9 (IT-01: 12.4 – IT-06: 22.0)	16.0 (CH-56: 8.2 – NL-01: 22.8)	18.7 (FI-01: 13.2 – LT-01: 38.4)
Age, above 40	A	57.3 (UK-31: 51.5 – UK-12: 63.3)	49.1 (IT-01: 40.7 – ES-01: 65.6)	61.2 (NL-01: 49.1 – DE-06: 74.0)	55.9 (LT-01: 52.1 – FI-02: 57.9)

§The historical data particularly on atopic dermatitis has not been recorded by the British Contact Dermatitis Society (only atopy in general) (Amersham, UK: 4.1%).

Departments with missing data (10% for sex and age; 20% for all other categories) were excluded from the analysis of the respective item. Additionally 'partial' occupational contribution was noted in Lahti, Finland (19.8%); Groningen, The Netherlands (9.5%); Amsterdam, The Netherlands (8.3%); Barcelona, Spain (0.9%) and Kaunas, Lithuania (0.8%).

Only past atopic dermatitis was considered.

In departments with more than 20% missing data for primary site, the first site to the first final diagnosis was considered equivalent for this analysis.

See Table 1 for departments aggregated to the regions. Padova 'Pediatria', Italy not included.

the contributing national contact dermatitis groups can compensate for this (e.g. Ref. (9)).

Still, focussing first on the patient characteristics according to the MOAHLFA index, remarkable differences persisted. As mentioned above, the specialization of two of four 'north-eastern' departments in occupational dermatology [Finnish Institute of Occupational Health (FIOH), Helsinki, Finland and Nofer Institute, Lodz, Poland] has a strong impact on the MOAHLFA index, with a very high proportion of occupational dermatitis (2004 average: 14.3%) and hand dermatitis (2004 average: 32.9%), see Table 2. In the UK patients with facial dermatitis are over-represented compared with the remaining regions, while the proportion of patients with dermatitis affecting the leg and hand and male patients is very similar. The proportion of patients aged 40 and above is high among the 'central' European patients, mostly due to the German patients (10). As many allergens exhibit an age gradient – positive, e.g., the fragrance mix (11, 12), or negative, as in case of nickel (13) – an age distribution differing across space (as here) or over time may confound comparisons. Hence, the contact allergy prevalences have been standardized for age and sex in this analysis, following pertinent guidelines (6).

The European Baseline Series is continually being adapted by a working group of the European Society of Contact Dermatitis (ESCD). During the study period, the latest addition had been methyl dibromo glutaronitrile, recommended to be tested at 0.5% in pet. (14). While this allergen had indeed been

included by most ESSCA participants, the most common test concentration was 0.3%. About 3 years later, the fragrance mix II (14% pet.) and hydroxyisohexyl 3-cyclohexene carboxaldehyde (5% pet.) have been included in the recommendation (8). As these allergens, in particular hydroxyisohexyl 3-cyclohexene carboxaldehyde, have been tested by several groups starting in 2005 or 2006 (earlier in some centres) already, the present analysis is able to confirm the necessity to include these important fragrance allergens in the European Baseline Series in terms of a high contact allergy prevalence. With respect to the metal allergens the regionally aggregated prevalences of contact allergy to nickel appear remarkably similar, and to average out between-centre differences (even within regions) previously noted (3). In contrast, patch test results with cobalt and particularly with chromate diverge more, with the contact allergy prevalence to chromate being significantly lower in the UK ('western' region) than in each of the other three regions. This observation may warrant further investigation.

Some allergens such as *p*-phenylenediamine, *Myroxylon pereirae* resin, thiuram mix or budesonide yielded very similar contact allergy frequencies, which may illustrate fairly homogenous exposure across Europe. In case of other allergens outliers are observed:

- Contact allergy to lanolin (wool alcohol) is significantly more common in 'central' Europe than in the remaining regions – be it due residual

Table 3. Test results with the European Baseline Series (EBS) (8) in the four regions

	Western			Southern			Central			Northeast							
	%	nr(t)	nr(p)	%p	95% CI	nr(t)	nr(p)	%p	95% CI	nr(t)	nr(p)	%p	95% CI				
Fragrance mix I	8.0	8539	614	6.8	(6.3–7.3)	2666	128	4.8	(3.9–5.5)	5733	464	7.7	(7.0–8.4)	1604	94	5.7	(4.6–6.8)
Fragrance mix II	14	782	19	2.5	(1.4–3.7)	333	5	1.8	(0.1–3.5)	3742	208	5.5	(4.7–6.2)	545	23	4.0	(2.4–5.7)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrat TM)	5.0	4787	89	1.8	(1.4–2.2)	1675	8	0.5	(0.2–0.9)	4310	113	2.7	(2.2–3.2)	1018	12	1.2	(0.5–1.9)
<i>Myroxylon perirae</i>	25	8537	488	5.4	(4.9–5.8)	2666	143	5.4	(4.5–6.2)	5733	422	6.8	(6.2–7.5)	1603	103	6.2	(5.0–7.3)
Nickel sulfate	5.0	8468	1752	20.8	(19.9–21.6)	2666	660	24.5	(22.9–26.1)	5708	1056	19.7	(18.7–20.8)	1585	348	22.4	(20.4–24.4)
Cobalt(II) chloride	1.0	8498	522	6.2	(5.7–6.7)	2616	178	6.8	(5.8–7.8)	5730	398	7.2	(6.5–7.9)	1596	137	8.8	(7.4–10.2)
Potassium dichromate	0.5	8537	211	2.4	(2.1–2.7)	2666	119	4.5	(3.7–5.3)	5737	347	5.9	(5.3–6.5)	1606	86	5.3	(4.2–6.4)
Colophonium	20	8529	333	3.8	(3.4–4.2)	2666	45	1.7	(1.2–2.2)	5738	244	4.1	(3.6–4.7)	1604	50	3.0	(2.1–3.8)
p-Phenylenediamine	1.0	8535	313	3.6	(3.2–4.0)	2665	113	4.2	(3.4–4.9)	2995	123	4.0	(3.3–4.7)	1601	69	4.2	(3.2–5.2)
Lanolin alcohol	30	8543	125	1.4	(1.2–1.7)	1920	25	1.3	(0.8–1.8)	4360	113	2.5	(2.0–3.0)	1601	21	1.3	(0.7–1.8)
Methyl dibromo glutaronitrile + 2-phenoxyethanol	1.0		333	0.9	(0.0–2.0)	333	3	0.9	(0.0–2.0)	909	38	4.0	(2.7–5.2)				
Methyl dibromo glutaronitrile	0.3	8549	109	1.2	(1.0–1.4)	929	1	0.1	(0.0–0.3)	4118	255	5.6	(4.9–6.3)	903	14	1.5	(0.7–2.2)
Methylchloro- isothiazolinone/Met- hylisothiazolinone*	0.01	7504	159	2.1	(1.8–2.4)	2397	99	4.1	(3.3–4.9)	5735	157	2.7	(2.3–3.1)	1605	33	2.1	(1.4–2.8)
Formaldehyde*	1.0	8541	179	2.0	(1.7–2.3)	2626	110	4.2	(3.5–5.0)	5733	100	1.8	(1.4–2.1)	1603	61	3.7	(2.8–4.6)
Quaternium-15	1.0	8550	158	1.8	(1.5–2.1)	1054	9	0.8	(0.3–1.4)	2854	22	0.8	(0.5–1.2)	1604	31	1.9	(1.2–2.6)
Paraben mix	16	8552	60	0.7	(0.5–0.9)	2057	17	0.8	(0.4–1.2)	5739	88	1.5	(1.2–1.8)	849	21	2.3	(1.3–3.3)
Thiuram mix	1.0	8540	199	2.2	(1.9–2.6)	2595	42	1.6	(1.1–2.1)	5739	141	2.4	(2.0–2.8)	1604	39	2.3	(1.6–3.0)
2-Mercaptoben- zothiazole	2.0	8546	84	1.0	(0.8–1.2)	2665	14	0.5	(0.3–0.8)	5742	52	0.9	(0.6–1.1)	1606	9	0.6	(0.2–1.0)
Mercapto mix	2.0	8535	60	0.7	(0.5–0.9)	921	4	0.4	(0.01–0.9)	950	11	1.2	(0.5–1.8)	607	3	0.5	(0.0–1.1)

Table 3. (Continued)

	Western				Southern				Central				Northeast				
	%	nr(t)	nr(p)	%p	95% CI	nr(t)	nr(p)	%p	95% CI	nr(t)	nr(p)	%p	95% CI	nr(t)	nr(p)	%p	95% CI
Mercapto mix (only CBS, MBTS, MOR)	1.0					473	0	0.0		3414	31	1.0	(0.6–1.4)	998	4	0.4	(0.01–0.8)
<i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylene diamine (IPPD)	0.1	8528	27	0.3	(0.2–0.5)	2666	24	0.9	(0.5–1.2)	4790	51	1.1	(0.8–1.4)	849	5	0.7	(0.1–1.3)
Epoxy resin	1.0	8544	81	0.9	(0.7–1.1)	2665	23	0.9	(0.5–1.2)	5741	118	2.0	(1.7–2.4)	1603	24	1.6	(0.9–2.2)
4- <i>tert</i> -butylphenol	1.0	8551	55	0.6	(0.5–0.8)	1942	26	1.4	(0.8–1.9)	5740	72	1.3	(1.0–1.6)	1606	12	0.8	(0.3–1.3)
formaldehyde resin																	
Sesquiterpene	0.1	8547	100	1.1	(0.9–1.3)	1904	10	0.5	(0.2–0.8)	2610	19	0.7	(0.4–1.0)	1144	9	0.8	(0.3–1.3)
lactone mix																	
Primin	0.01	8552	23	0.2	(0.1–0.3)	1987	22	1.1	(0.6–1.5)	1904	9	0.5	(0.2–0.8)	1606	3	0.2	(0.0–0.3)
Neomycin sulfate	20	8544	170	1.9	(1.6–2.2)	2666	39	1.4	(1.0–1.9)	3239	39	1.1	(0.8–1.5)	1598	64	3.8	(2.9–4.7)
Benzocaine	5.0					2665	28	1.0	(0.7–1.4)	890	13	1.3	(0.6–2.1)	849	10	1.3	(0.5–2.1)
Clitiquinol	5.0					1574	3	0.2	(0.0–0.4)	1377	1	0.1	(0.0–0.2)	1490	8	0.5	(0.2–0.9)
Budesonide [§]	0.01	8547	56	0.6	(0.5–0.8)	1302	9	0.7	(0.3–1.2)	1376	10	0.7	(0.3–1.1)	1512	9	0.6	(0.2–0.9)
Tixocortol-21-pivalate [§]	0.1	6211	85	1.3	(1.1–1.6)	1311	1	0.1	(0.0–0.3)	2083	18	0.9	(0.5–1.2)	1364	24	1.7	(1.0–2.4)

[§]Budesonide tested 0.1% and tixocortol-21-pivalate 1% by the UK departments ('western').

Methylidibromo glutaronitrile 0.5% in pet. had not been tested in the period.

Allergens were tested in pet., except where otherwise indicated (*water).

nr(t): number tested; nr(p): number positive; %p: percent positive (standardized for age and sex); 95% CI: accompanying 95% confidence interval. IT-03 not included.

confounding by higher age, or differing specific reading standards (which may, of course, explain some amount of variation in case of other allergens as well).

- The prevalence of contact allergy to methyl-dibromo glutaronitrile (tested 0.3%) showed marked variation across Europe, but also nationally (9) which seems hard to explain, assuming that the main exposure via leave-on and rinse-off cosmetics is fairly homogenous due to a European market of these products. However, methyl-dibromo glutaronitrile can probably be regarded a declining allergen (15).
- Methylchloroisothiazolinone/methylisothiazolinone has achieved a relatively stable contact allergy prevalence of around 2%, notwithstanding some between-centre variation (3, 9) or decreases noted in some parts of Europe (16). However, in the ‘south’ contact allergy to this preservative is still significantly more common, which may warrant investigation of possible sensitizing exposures.
- Neomycin sulfate is still (slightly) above 1% positive patch test reactions in consecutively tested patients and thus qualifies as part of the European Baseline Series. However, at least in Germany, it is not available as over-the-counter drug, prescriptions decrease and, accordingly, contact allergy prevalence decreases (17).
- In contrast to budesonide, contact allergy frequencies to tixocortol-21-pivalate varied significantly as has also been found in previous studies (reviewed in Ref. (18)). It has been pointed out that the corticosteroids should best be read at D7 of the test, so with the presently employed reading frame (D3–D5) some false-negative results may be expected (18). Moreover, the issue of the ideal test concentration does not seem to be settled: regarding tixocortol-21-pivalate, the British Contact Dermatitis Society recommends (19) and uses 1% instead of 0.1%.

It has been stated that the contact allergy prevalence in consecutively tested patients should normally exceed 0.5–1% for an allergen to be eligible for inclusion in the Baseline series (20). From this background and other considerations as well, clioquinol could be removed from this [also (3, 16)], while other, overall rare, sensitizers are at least regionally more important, such as primin or *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD).

Conclusion

The 2005/2006 results provide an up-to-date view on the prevalence of contact allergy to allergens of the (European) Baseline Series across Europe. Methodological differences may contribute to between-centre, possibly also to between-country, variation. Hence, methods to standardize application and reading, and to monitor the reproducibility of reading and interpretation of patch test results within national and international contributors to contact dermatitis databases should be (further) developed. Still, the comparison potentially offers starting points for the in-depth investigation of possible causes of contact allergy in those areas particularly affected.

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