Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007–2008

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Summary

Background. The pattern of contact sensitization to the supposedly most important allergens assembled in the baseline series differs between countries, presumably at least partly because of exposure differences.

Objectives. To describe the prevalence of contact sensitization to allergens tested in consecutive patients in the years 2007 and 2008, and to discuss possible differences.

Methods. Data from the 39 departments in 11 European countries comprising the European Surveillance System on Contact Allergy network (www.essca-dc.org) in this period have been pooled and analysed according to common standards.

Results. Patch test results with the European baseline series, and country-specific or department-specific additions to it, obtained in 25 181 patients, showed marked international variation. Metals and fragrances are still the most frequent allergens across Europe. Some allergens tested nationally may be useful future additions to the European baseline series, for example methylisothiazolinone, whereas a few long-term components of the European baseline series, namely primin and clioquinol, no longer warrant routine testing.

Conclusions. The present analysis points to 'excess' prevalences of specific contact sensitization in some countries, although interpretation must be cautious if only few, and possibly specialized, centres are representing one country. A comparison as presented may help to target in-depth research into possible causes of 'excess' exposure, and/or consideration of methodological issues, including modifications to the baseline series.

Key words: clinical epidemiology; contact allergy; health reporting; patch testing.

The most important contact allergens are traditionally assembled in a 'baseline series', which is usually applied to every patient who is patch tested as a general screening test. Recommendations regarding a European baseline series are issued by the European Society of Contact Dermatitis (www.escd.org) (1). National contact dermatitis research groups often adopt these recommendations, usually with a number of omissions and additions as deemed appropriate in the specific country. Sometimes, a 'monitor series' is used, that is, a temporary supplement to the baseline series to quickly check whether certain allergens should possibly be included in the baseline series (2). Moreover, single departments may compile supplements to the baseline series to reflect local needs. Hence, some variation of a seemingly standardized diagnostic tool is created, offering the opportunity to evaluate possible changes to national standard batteries or the European baseline series.

In the present article, we summarize and discuss results obtained with the European baseline series and additions – all applied to consecutive patients – collected by the members of the European Surveillance System on Contact Allergy (ESSCA; www.essca-dc.org) network in the years 2007 and 2008.

Methods

The ESSCA network has been described in previous publications (3–5). Briefly, clinical and demographic data, along with patch test results, of all patients patch-tested in the departments participating in the ESSCA are documented electronically in the local departments, with the use of diverse data capture software and, partly, the multilingual software WINALLDAT/ESSCA provided by the ESSCA (4). Patch testing follows international recommendations (6), often refined nationally. It is the responsibility of national contact dermatitis groups, if they exist in a country, to work on the quality control and standardization of patch testing and to issue recommendations regarding specific (additions to the) baseline series. At 2-yearly intervals, data are transferred to the Erlangen data centre. Standardized reports are prepared and supplied to the network partners for a critical review of the analyses. After possible corrections, data are pooled for further analysis, with the use of SAS™ (version 9.2; SAS Institute, Cary, NC, USA) and R (version 2.11.1; http://www.R-project.org) software.

For the present analyses, the maximum patch test reaction between day 3 and day 5 (inclusive) was considered as the outcome, with + to + + + reactions classified as positive, and negative, irritant and doubtful reactions

Table 1. Characteristics of included countries and departments comprising the European Surveillance System on Contact Allergy network

	No. of departments	No. of consultations (cases)	No. (%) tested with baseline series
Austria	1	692	678 (98.0)
Denmark	1	1318	1318 (100)*
Finland	2	760	760 (100)*
Germany	6	3161	2712 (85.8)
Italy	3 (4†)	3052	2938 (96.3)
Lithuania	1	680	680 (100)
The Netherlands	2	2325	2172 (93.4)
Poland	3	936	793 (84.7)
Spain	5	2018	1845 (91.4)
Switzerland	3	2586	2415 (93.4)
United Kingdom	12	9201	9201 (100)*

*Only data of patients tested with baseline series were registered and submitted.
†'Padova Pediatrica' not included in this particular analysis, owing to an entirely paediatric population.

as non-positive. In cases of multiple consultations, with multiple applications of the baseline series within this 2-year period, the strongest patch test reaction per patient was chosen. It should be noted that only the results of the current patch test session were considered in our analysis; that is, patients not tested with a particular allergen, because of known sensitization, are not counted as positive. Depending on the role of a department in the national healthcare framework, the proportion of such 'prediagnosed' patients may be non-negligible, and thus lead to an underestimation of the true sensitization prevalence in these departments. Sensitization frequencies are given directly as age-standardized and sex-standardized prevalences (7), accompanied by a 95% confidence interval (CI). This allows comparisons to be made that are not confounded by age and sex. We have chosen the country as the unit of aggregation of results in this analysis.

Results

Data from 39 departments in 11 European countries are included; for more details, see Table 1. During the 2-year study period (January 2007 to December 2008), 26 729 consultations, yielding 25 512 applications of the baseline series, by 25 181 patients were documented.

The demographic and clinical characteristics according to the MOAHLFAP index (8) in the countries are shown in Table 2. With the exception of Lithuania, the proportion of male patients is in a fairly narrow range of 32–40%, whereas other characteristics differ more, in particular age or face dermatitis, mostly indicative of cosmetic contact allergy. Characteristics seem to vary more between departments within one country than between countries, as judged by averages.

The practice of patch testing across Europe with the European baseline series is evident from Table 1 (regarding the proportion of patients tested with the European baseline series) and from Table 3 (regarding the scope of allergens). In some cases, allergens recommended for the European baseline series (1) had not been included in certain countries, for example clioquinol. Some allergens were not tested as recommended; for example, the mercapto mix (1% pet.) without mercaptobenzothiazole (MBT) was used by most departments instead of the mercapto mix including MBT (2% pet.). The two corticosteroid screening agents, tixocortol pivalate and budesonide, were tested at 1% and 0.1%, respectively, in several countries, instead of at the recommended concentrations of 0.1% and 0.01%.

Regarding the results, for the sake of compactness the number of patients tested with the European baseline series is given only once, in the first row, even though some deviations from this number may have occurred – these are noted only if the number of patients tested with an allergen is <90% of this overall number. The number and crude percentage of positive reactions are not shown; only the age-standardized and sex-standardized proportions are given (for reasons of space limitation). The use of standardized prevalences is justified by the considerable differences in the age structure, if sex is not regarded, of patch-tested patients in our clinical sample. Sensitization prevalences in the countries are, to some extent, influenced by the background of departments in those countries where few centres participate. For instance, the background of an interest in occupational dermatitis introduces a bias for Finland, with the Finnish Institute of Occupational Health as one of two departments, and for Poland, with the Nofer Institute as one of three departments (Table 2). For just one allergen, sensitization prevalence varies by a factor of 2, namely, *p*-phenylenediamine. For all other allergens, including those for which an occupational background is not prominent, for example nickel, cobalt, neomycin sulfate, and the fragrance screening allergens, considerable, and often significant (if 95% CIs do not overlap), differences between sensitization frequencies are seen on comparison of different countries.

The proportions of patients who reacted to at least one of the preservatives included in the European baseline series (Table 3) were 5.0% for the UK, 5.6% for Switzerland, 6–8% for most countries, 9.5% for Finland, 9.9% for Austria, and 12.9% for Lithuania. Cross-tabulation of results with formaldehyde versus

Table 2. MOAHLFAP index (8) of patients patch-tested in 11 European countries: average % (range; where appropriate)

	M	O	A	H	L	F	A	P
Austria	34	16	17	24	9	14	66	54
Denmark	33	24	19	43	3	23	63	40
Finland	38 (32–48)	39* (26–61)	27 (22–30)	51 (38–72)	3 (1–5)	15 (14–15)	61 (55–65)	50 (43–54)
Germany	39 (35–49)	22 (14–29)	16 (10–23)	31 (22–37)	8 (6–12)	17 (9–25)	70 (62–78)	43 (32–49)
Italy	34 (31–37)	10 (6–15)	10 (5–15)	27 (26–31)	9 (7–11)	17 (15–19)	51 (49–54)	46 (42–53)
Lithuania	26	21	17	32	9	34	62	47
The Netherlands	36 (36–36)	22 (21–24)	27 (25–30)	24 (21–30)	5 (4–5)	21 (17–26)	56 (53–58)	47 (40–52)
Poland	32 (30–36)	28 (24–29)	18 (8–24)	40 (34–43)	4 (2–7)	15 (13–19)	48 (16–67)	45 n(31–76)
Spain	35 (31–40)	16 (5–57)	11 (7–27)	26 (17–66)	9 (1–12)	14 (4–24)	64 (45–76)	49 (48–51)
Switzerland	40 (38–44)	17 (16–19)	17 (10–27)	31 (21–37)	7 (5–8)	17 (15–20)	62 (60–63)	48 (42–54)
United Kingdom	33 (27–39)	11 (8–18)	†	30 (24–43)	7 (5–9)	28 (22–31)	57 (51–64)	43 (33–60)

M, male; O, occupational; A, age ≥ 40 years; H, hand; L, leg; F, face; A, atopic dermatitis; P, percentage of patients positive to at least one allergen of the baseline series.
*Comprising predominant and exclusive occupational causation.
†Atopy in general recorded, that is, also comprising history of allergic rhinitis and asthma.

diazolidinyl urea in 9950 (imidazolidinyl urea in 11 531) patients tested with both respective allergens identified a proportion of 53% (58%) patients positive to these formaldehyde-releasers without a concomitant positive reaction to formaldehyde.

Table 4 lists a number of allergens that have been tested in addition to the European baseline series, that is, in consecutive patients, so that sensitization prevalences are comparable to those obtained with the original European baseline series (Table 3), in more than two countries. The two formaldehyde-releasers diazolidinyl urea and imidazolidinyl urea are relatively rare allergens, with a sensitization prevalence of up to 1%, except for Finland, where a higher prevalence is noted. 2-Bromo-2-nitropropane-1,3-diol [bronopol (INN)], which has been tested at both 0.5% pet. and 0.25% pet., is a slightly more frequent allergen. Comments on other allergens are given in the discussion.

Discussion

Continual analysis of prevalences of sensitization to the most important allergens–in terms of frequency of sensitization in patients patch-tested, as provided by these current results from the ESSCA–is important for a number of reasons: (i) detection of temporal trends or geographical differences (which could indicate exposure changes or differences needing to be investigated or prompting intervention, as appropriate); (ii) as a contribution to standardized, comparative international health reporting; and (iii) as a quality control measure regarding the diagnostic usefulness of the battery of screening allergens used. However, despite all efforts at standardization, methodological variation must also be discussed as a potential source of variation between countries and even between departments within one country. In the following discussion, we will address these aspects, as appropriate, in subsections defined by categories of allergens.

Metals

Nickel is still the by far most common allergen, although there is a greater than two-fold variation between countries. The low frequency observed in Denmark is probably attributable to the longstanding nickel regulation established there, which has shown a marked beneficial effect before (9). Conversely, persistently high prevalences in other countries may indicate later implementation of the regulation, different fashion habits, or insufficient control of exposure (10–12). The partial beneficial effect of the EU nickel regulation has recently been reviewed (11); the very recent tightening of a 'tolerance factor' for the measurement of nickel release according to EN 1811 (13) is expected to contribute to a further reduction in nickel exposure and sensitization in the future. However, beyond nickel, a very high frequency of cobalt contact sensitization is observed, at >5% in all included countries, and particularly high prevalences are seen in countries where occupational dermatology departments have an impact, namely Finland and Poland, but also in Graz, Austria and in Switzerland. This is in line with the observation of cobalt being the second most common allergen in the first ESSCA analysis, covering the years 2002 and 2003 (14). Often, exposure to cobalt remains unclear in patients with cobalt sensitization; the question of whether individual 'metal contacts' could possibly cause allergic contact dermatitis can, in the future, be addressed by the use of a recently available

Table 3. Results obtained with the European baseline series in 11 European countries, 2007–2008, as age-standardized and sex-standardized percentage positive with accompanying 95% confidence intervals in parentheses

	Austria	Denmark	Finland	Germany	Italy	Lithuania	The Netherlands	Poland	Spain	Switzerland	United Kingdom
Number of patients	678	1318	760	2694	2938	680	2168	789	1845	2402	8909
Nickel sulfate 5%	25.2 (22.0–28.5)	11.9 (9.9–13.9)	21.3 (18.3–24.4)	16.8 (15.2–18.5)	27.4 (25.8–29.0)	18.0 (15.2–20.8)	14.9 (13.4–16.4)	24.3 (21.3–27.2)	26.5 (24.5–28.5)	22.0 (20.3–23.7)	18.6 (17.8–19.4)
Cobalt chloride 1%	13.6 (10.9–16.4)	4.8 (3.3–6.2)	9.5 (7.3–11.7)	6.3 (5.2–7.4)	6.0 (5.1–6.9)	5.6 (3.7–7.5)	5.3 (4.4–6.3)	12.2 (9.8–14.6)	7.5 (6.3–8.8)	9.9 (8.6–11.1)	5.9 (5.4–6.4)
Potassium dichromate 0.5%	9.5 (7.1–11.9)	1.7 (0.8–2.6)	4.2 (2.8–5.7)	6.1 (5.1–7.1)	4.6 (3.8–5.3)	4.7 (2.9–6.4)	2.9 (2.2–3.7)	6.9 (5.0–8.7)	6.0 (4.9–7.1)	7.1 (6.1–8.2)	2.3 (1.9–2.6)
Fragrance mix I 8.0%	10.4 (8.0–12.7)	6.0 (4.3–7.7)	6.1 (4.4–7.7)	6.4 (5.4–7.3)	4.2 (3.5–4.9)	3.7 (2.3–5.2)	7.3 (6.2–8.4)	6.1 (4.5–7.6)	4.9 (4.0–5.9)	7.7 (6.6–8.7)	7.2 (6.7–7.7)
Myroxylon pereirae (Balsam of Peru) 25%	10.6 (8.3–12.9)	3.0 (1.9–4.2)	6.9 (5.2–8.7)	7.6 (6.6–8.6)	1.6 (1.1–2.0)	8.3 (6.2–10.4)	4.2 (3.4–5.1)	5.0 (3.6–6.5)	5.0 (4.1–6.0)	7.6 (6.6–8.7)	5.2 (4.8–5.7)
Fragrance mix II 14%	7.9 (5.5–10.3)	3.0 (1.8–4.2)	3.6 (2.1–4.7)	4.3 (3.5–5.2)	—	2.6 (1.4–3.9)	6.4 (5.3–7.4)	2.5 (1.5–3.5)	1.9 (1.3–2.5)	5.5 (4.5–6.4)	3.2 (2.8–3.5)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0%	2.9 (1.6–4.2)	1.8 (0.9–2.8)	2.0 (0.8–3.2) in 479	2.2 (1.6–2.8)	0.8 (0.4–1.2)	1.0 (0.2–1.8)	—	0 (0–1.4) in 256	1.1 (0.6–1.7) in 1639	2.2 (1.5–2.8)	1.3 (1.0–1.5)
Paraben mix 16%*	2.2 (1.0–3.4)	0.1 (0–0.3)	0.4 (0–0.9)	1.0 (0.6–1.4)	0.7 (0.3–1.1) in 1674	3.4 (1.9–5.0)	0.6 (0.2–1.1) in 1259	1.2 (0.4–1.9)	0.7 (0.3–1.1)	1.2 (0.8–1.7)	0.6 (0.4–0.7)
Formaldehyde 1.0%†	1.8 (0.7–2.9)	1.4 (0.7–2.2)	5.9 (4.2–7.7)	1.4 (1.0–1.9)	1.9 (1.4–2.4)	3.3 (1.8–4.7)	1.3 (0.8–0.18)	3.6 (2.3–4.9)	2.5 (1.7–3.2)	0.7 (0.3–1.0)	1.2 (0.9–1.4)
Quaternium-15 1.0%	—	1.0 (0.3–1.8)	3.2 (1.9–4.6)	—	0.1 (0–0.3) in 1676	1.3 (0.4–2.1)	1.2 (0.7–1.7)	1.8 (0.8–2.8)	1.2 (0.6–1.7)	—	1.6 (1.3–1.8)
Methylchloroisothiazolinone/ methylisothiazolinone (3:1) 0.01%†	3.4 (2.0–4.8)	3.1 (1.7–4.4)	2.7 (1.5–3.9)	1.8 (1.2–2.3)	4.2 (3.5–4.9)	1.9 (0.9–3.0)	2.4 (1.5–3.3)	1.2 (0.4–2.0)	2.9 (2.1–3.8)	1.6 (1.0–2.1)	1.9 (1.6–2.1)
Methyldibromo glutaronitrile (MDBGN) 0.2%	4.1 (0.7–7.5) in 115	—	—	2.1 (1.0–3.1) in 573	§	—	1.7 (0.7–2.6) in 731	—	—	1.7 (0.7–2.8) in 481	—
MDBGN 0.3%	2.7 (1.4–4.1) in 438	—	1.7 (0.7–2.7)	3.2 (2.4–3.9) in 2080	0.3 (0–0.7) in 1220	5.7 (3.9–7.6)	3.8 (2.8–4.8) in 1259	—	1.0 (0.4–1.6) in 963	2.7 (1.9–3.4)	0.8 (0.6–1.0)
MDBGN 0.5%	—	3.1 (1.7–4.4)	—	—	0 (0–0.4) in 984	—	—	2.4 (1.4–3.4)	1.2 (0.4–2.0) in 821	—	—
Neomycin sulfate 20%	—	1.1 (0.5–1.7)	3.3 (2.0–4.5)	—	1.6 (1.1–2.0)	0.8 (0.2–1.4)	0.2 (0–0.4)	3.3 (2.1–4.4)	1.4 (0.8–1.9)	—	1.4 (1.2–1.7)
Benzocaine 5%	—	0.6 (0–1.3)	‡	—	0.6 (0.3–0.8)	2.5 (1.3–3.7)	—	1.0 (0.4-1.6)	1.6 (0.9–2.2) in 1412	0.6 (0–1.2) in 520	‡
Clioquinol 5%	—	0.4 (0–0.8)	—	—	—	0.5 (0–1.0)	0.1 (0–0.3) in 1259	0.3 (0–0.7)	0.2 (0–0.5) in 1012	—	—
Budesonide 0.01%	—	0.9 (0.2–1.7)	0.7 (0–1.4) in 479	—	0.8 (0.2–1.4) in 984	—	0.6 (0.2–1.0) in 1259	1.6 (0.7–2.6)	1.5 (0.6–2.4) in 821	—	—
Budesonide 0.1%	—	—	0.4 (0–1.1) in 281	—	—	0.6 (0–1.1)	0.2 (0–0.6) in 787	—	0.6 (0.2–1.0) in 1056	1.8 (0.7–2.9) in 520	0.4 (0.2–0.5)
Tixocortol pivalate 0.1%	—	0.7 (0.1–1.2)	0.7 (0.1–1.3)	—	0.2 (0–0.5) in 984	—	0.4 (0.2–0.7)	1.0 (0.3–1.7)	0.6 (0.1–1.1) in 821	0.8 (0.1–1.5) in 657	—
Tixocortol pivalate 1%	—	—	—	—	—	—	—	—	0.3 (0–0.7) in 721	0.6 (0.1–1.0) in 886	1.2 (0.9–1.4)
Thiuram mix 1.0%	2.0 (0.9–3.1)	2.3 (1.1–3.5)	2.5 (1.3–3.6)	2.7 (2.0–3.4)	0.9 (0.5–1.2)	0.6 (0.1–1.1)	1.4 (0.9–1.9)	2.2 (1.1–3.2)	2.0 (1.3–2.7)	2.3 (1.7–2.9)	2.2 (1.9–2.5)
Mercaptobenzothiazole (MBT) 2.0%	1.3 (0.3–2.2)	0.9 (0.1–1.7)	0.8 (0.1–1.5)	0.7 (0.3–1.0)	0.4 (0.2–0.7)	0.2 (0–0.5)	0.9 (0.5–1.3)	1.3 (0.4–2.1)	0.6 (0.2–1.0)	1.4 (0.9–2.0)	0.7 (0.5–0.8)

Table 3. Continued.

	Austria	Denmark	Finland	Germany	Italy	Lithuania	The Netherlands	Poland	Spain	Switzerland	United Kingdom
Mercapto mix (without MBT) 1%	1.0 (0.2–1.8)	0.8 (0–1.6)	0 (0–0.5)	0.6 (0.3–1.0)	—	0.3 (0–0.7)	—	—	0.3 (0–0.7) in 963	1.1 (0.6–1.5)	0.5 (0–1.2) in 443
Mercapto mix (with MBT) 2.0%	—	(–)	—	—	0.4 (0–1.0) in 691	—	0.9 (0.5–1.3)	0.3 (0–0.7)	1.0 (0.4–1.7) in 821	—	0.5 (0.3–0.6) in 7597
N-Isopropyl-*N*-phenyl-4-phenylenediamine 0.1%	0.6 (0–1.1)	0.6 (0–1.3)	—	0.9 (0.5–1.3)	0.4 (0.1–0.6) in 2204	0.2 (0–0.5)	1.1 (0.5–1.6) in 1259	1.8 (0.9–2.8)	0.7 (0.3–1.1) in 1412	0.6 (0.3–1.0)	0.4 (0.3–0.5)
p-Phenylenediamine base 1.0%	—	3.2 (1.7–4.7)	2.6 (1.5–3.7)	—	3.9 (3.2–4.6)	5.2 (3.5–7.0)	2.7 (1.7–3.6)	5.1 (3.3–6.9) in 592	3.9 (3.0–4.8)	4.9 (3.8–5.9) in 1769	4.0 (3.6–4.4)
Lanolin (wool) alcohols 30%	2.5 (1.4–3.5)	0.5 (0–1.0)	0.4 (0–0.9)	2.9 (2.2–3.6)	1.0 (0.6–1.3)	1.8 (0.8–2.8)	0.5 (0–0.9) in 870	1.3 (0.5–2.2)	0.6 (0.2–1.0)	1.8 (1.2–2.3)	1.1 (0.9–1.3)
Epoxy resin 1.0%	3.0 (1.6–4.5)	0.5 (0–1.1)	3.0 (1.8–4.2)	1.8 (1.3–2.4)	0.6 (0.3–0.9)	1.6 (0.6–2.6)	1.1 (0.7–1.6)	1.5 (0.6–2.4)	0.6 (0.2–0.9)	1.8 (1.2–2.3)	0.8 (0.7–1.0)
p-tert-Butylphenol formaldehyde resin 1.0%	0.5 (0–0.9)	1.1 (0.5–1.7)	0.8 (0.1–1.4)	0.8 (0.4–1.2)	1.6 (1.2–2.1)	0.7 (0.1–1.3)	1.2 (0.7–1.6)	0.6 (0.1–1.1)	0.8 (0.3–1.2)	0.8 (0.4–1.2)	0.7 (0.5–0.8)
Sesquiterpene lactone mix 0.1%	—	0.9 (0.4–1.4)	0 (0–1.3)	0.8 (0–2.3) in 427	0.2 (0–0.5) in 984	0.5 (0–1.0)	0.5 (0.2–0.8)	0.8 (0.2–1.4)	0.1 (0–0.3)	—	0.8 (0.6–1.0)
Primin 0.01%	—	0.2 (0–0.5)	0 (0–0.5)	—	0.6 (0.2–0.9) in 1674	0.6 (0.1–1.1)	0.2 (0–0.5) in 1259	0.5 (0–0.9)	0.2 (0–0.4)	—	0.3 (0.2–0.4)
Colophonium (colophony) 20%	6.1 (4.2–8.0)	2.6 (1.4–3.8)	4.5 (2.9–6.0)	4.3 (3.5–5.1)	1.5 (1.0–1.9)	4.8 (3.3–6.4)	2.6 (1.9–3.3)	1.6 (0.7–2.5)	1.8 (1.1–2.5)	2.8 (2.1–3.4)	2.7 (2.4–3.1)

Number of patients tested in cases of > 10% divergence from the overall number of baseline tests.
*Paraben mix 15% (5 × 3%) tested in 1221 patients in Italy (0.4%; 95% CI 0.1–0.7%) and in 870 patients in The Netherlands (0.1%; 95% CI 0–0.3%).
†All allergens in pet., except where indicated otherwise: water.
‡Caine mix III (10% pet.) has been used in the United Kingdom, yielding 1.2% of positive reactions (95% CI 0.9–1.4%), and in Finland (1.6%, 95% CI 0.7–2.6%).
§MDBGN + phenoxyethanol 1:4 1.5% tested in 1674 Italian patients, with 3.2% (95% CI 2.4–4.0%) positive reactions.

Table 4. Additional results with allergens regionally or nationally added to the European baseline series in 11 European countries, 2007–2008, as age-standardized and sex-standardized % positive with accompanying 95% confidence intervals in parentheses

	Austria	Denmark	Finland	Germany	Italy	Lithuania	The Netherlands	Poland	Spain	Switzerland	United Kingdom
Number of patients	678	1318	760	2694	2938	680	2168	789	1845	2402	8909
Methylisothiazolinone 0.05%*,†	—	—	—	—	—	—	2.6 (0.6–4.5) in 245	—	—	—	—
Diazolidinyl urea 2%	—	0.9 (0.4–1.5)	1.8 (0.8–2.7)	—	—	0.9 (0–2.7) in 112	0.7 (0.3–1.1) in 1393	1.1 (0.1–2.1) in 478	0.8 (0.2–1.4) in 815	—	0.8 (0.6–1.0)
Imidazolidinyl urea 2%	—	0.5 (0.2–1.0)	1.3 (0.5–2.1)	—	0.6 (0.1–1.1) in 984	1.0 (0–2.5) in 160	0.4 (0.1–0.8) in 1393	0.7 (0–1.5) in 478	1.0 (0.4–1.7) in 815	—	0.6 (0.4–0.7)
2-Bromo-2-nitropropane-1,3-diol 0.5%‡	1.7 (0.6–2.7) in 553	0.5 (0.2–1.1)	—	1.3 (0.9–1.8)	—	0 (0–2.3) in 158	—	—	—	1.4 (1.0–1.9)	1.1 (0.7–1.6) in 5037
Iodopropynyl butylcarbamate 0.2%	—	0.7 (0.3–1.3)	0.6 (0.1–1.2)	—	—	0 (0–2.5) in 146	1.7 (1.0–2.4) in 1337	0 (0–0.8) in 478	—	—	—
Bufexamac 5%	1.8 (0.8–2.8)	—	—	1.1 (0.6–1.6)	—	—	—	—	—	0.9 (0.5–1.3)	—
Zinc diethyldithiocarbamate 1%	0.7 (0.1–1.3)	—	0.3 (0–0.8) in 281	0.8 (0.4–1.2)	—	—	—	—	—	1.0 (0.6–1.4)	—
Cetearyl alcohol 20%	0.9 (0.3–1.5)	—	—	0.8 (0.4–1.2)	—	0.9 (0–1.8) in 229	—	—	—	1.0 (0.6–1.4)	0.4 (0.2–0.5)
Oil of turpentine 10%	2.1 (1.0–3.2)	—	1.7 (0.7–2.7)	1.8 (1.3–2.3)	—	0.6 (0–1.7) in 113	—	—	—	1.1 (0.7–1.6)	—
Propolis 10%	4.0 (2.6–5.4)	—	—	2.2 (1.6–2.8)	1.5 (0.8–2.3) in 984	2.3 (0.4–4.3) in 223	—	—	0.7 (0–1.4) in 372	3.8 (3.0–4.5)	1.4 (1.1–1.8) in 4997
Disperse Blue 124/106 mix 1%	—	—	0.5 (0.1–1.0)	—	1.6 (0.8–2.5) in 984	—	—	—	—	—	0.4 (0.3–0.6)
Compositae mix 6%§	—	—	—	—	0.9 (0.3–1.5) in 984	—	0.8 (0.1–1.4) in 731	—	—	—	—

*All allergens in pet., except where indicated otherwise: water.

†Methylisothiazolinone additionally tested in 281 Finnish patients at 0.03% (aqua), yielding 1.1% (95% CI 0–2.3%) positive reactions, and at 0.1% (aqua), yielding 1.7% (95% CI 0.1–3.2%) positive reactions. In 1280 Danish patients, 1.4% (95% CI 0.8–2.2%) positive reactions were observed to 0.2% (aqua).

‡2-Bromo-2-nitropropane-1,3-diol additionally tested at 0.25% in 281 Finnish patients (0.8% positive; 95% CI 0–1.9%).

§Compositae mix additionally tested at 2.5% in 3414 patients in the UK (0.9% positive; 95% CI 0.6–1.3%), at 3% in 281 Finnish patients (0.4% positive; 95% CI 0–1.1%), and at 5% in another 479 Finnish patients (0.5% positive; 95% CI 0–1.1%).

spot test for cobalt (15). It has been speculated that cobalt has replaced nickel in cheap jewellery (16), which may contribute to the observed high sensitization frequency. Regarding chromium, the third metal included in the European baseline series, no clear geographical pattern can be observed. Following the EU-wide regulation of the content of hexavalent chromium in cement[1], a similar decrease in the incidence of occupational chromium sensitization caused by cement exposure, as seen decades before in Scandinavia, has recently been observed, for instance, in Germany (17). At present, chromium exposure via leather seems to be gaining importance as a cause of sensitization (18). False-positive patch test reactions to metal salts are not entirely uncommon, according to the work of Fischer and Rystedt (19), and may thus, to some extent, bias the sensitization prevalences upwards, especially for cobalt and chromium.

Fragrances

The prevalence of sensitization to fragrance mix (FM) I is lowest in the southern countries (Italy and Spain) and Lithuania, and highest in western and central Europe. This pattern is not paralleled by sensitization to *Myroxylon pereirae* resin (balsam of Peru), which, in a few countries, even exceeds that to FM I. The newer FM II is also an important screening allergen, although nowhere exceeding FM I. It has been stressed that only extracts or distillates of *M. pereirae* are used in perfumery (20); however, exposure to these, or to some of the single constituents, is apparently so intense or frequent that this oldest of fragrance contact allergy screening allergens is still important. Hydroxyisohexyl 3-cyclohexene carboxaldehyde, the most important single substance from FM II, is a relatively frequent allergen and is justifiably part of the European baseline series (1).

Preservatives (biocides)

Parabens are not frequent allergens and, considering the vast amount of exposure, are associated with a low risk of sensitization (21). Interestingly, sensitization prevalence is highest in the two eastern countries and Austria (the Austrian centre having high sensitization prevalences throughout, possibly because of a highly selected group of patients; see also the highest P measure in Table 2). Prevalences of sensitization to formaldehyde vary greatly, and are highest in Finland and Poland, most likely because of the occupational background of the two respective departments, with a number of cases with occupational exposure to formaldehyde. Quaternium-15 has a sensitization prevalence of 1% (or well above), with more limited variation. Exposure to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) 3:1, a well-known contact sensitizer, has been partially regulated, the maximum concentration in cosmetic products being 15 ppm (22). However, sensitization prevalences remain quite stable at 1–4%, and slightly above. The question also remains of whether the recent increased use of MI (permitted at up to 100 ppm in cosmetics (23), but otherwise unregulated) (24) is possibly contributing to a persisting problem with MCI/MI (25). One of the successors of MCI/MI is methyldibromo glutaronitrile (MDBGN). This has turned out to be an important contact sensitizer in humans, as shown by a remarkable epidemic of contact sensitization across Europe soon after its use expanded massively. In keeping with this, figures are high for MDBGN, which has been tested at 0.2–0.5% (Table 3). However, following the banning of MDBGN, first in leave-on and later also in rinse-off products, prevalences are expected to fall, and have indeed begun to do so according to some recent national surveillance data (26, 27).

A number of other preservatives have been tested in consecutive patients, in addition to, or as part of, adapted baseline series (Table 4). Approximately 1% of patients were found to be sensitized to diazolidinyl urea and imidazolidinyl urea, respectively, with the highest proportions being observed in Finland. Thus, these are 'borderline candidates' for possible inclusion in a baseline series (in those countries where they are not yet included). Interestingly, and in contrast to previous results (27, 28), more than half of the patients sensitized to the above formaldehyde-releasers did not show concomitant sensitization to formaldehyde. The prevalence of sensitization to 2-bromo-2-nitropropane-1,3-diol is quite clearly above 1% in four countries, but not in Lithuania. The small size of the Lithuanian subsample does not rule out the existence of a relevant sensitization frequency there (upper 95% confidence limit: 2.3%). The significance of iodopropynyl butylcarbamate, in contrast, has yet to be settled.

Topical drugs

Neomycin sulfate has been part of various baseline series for a long time. However, according to the prevalences seen in different countries, its importance may differ according to whether it is available by prescription only or 'over the counter'. In central Europe, exposure and sensitization prevalence have been continuously decreasing (29), prompting the German Contact Dermatitis Group to remove it from the German baseline series.

[1] **DIRECTIVE 2003/53/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 June 2003** http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:178:0024:0027:en:PDF

However, in other countries, it may be well warranted to test this aminoglycoside routinely. Similar considerations are valid for benzocaine (or caine mix III, as tested by the British Society for Cutaneous Allergy), which seems to be a worthwhile part of the baseline series in some countries. In contrast, clioquinol is a rare allergen; in fact, the upper 95% confidence limit is ≤1% in those countries still testing it. Thus, clioquinol significantly fails to meet the conventional criterion for inclusion in the baseline series (30). For several years, budesonide and tixocortol pivalate (the latter as a marker for hydrocortisone contact allergy) have been part of the recommended European baseline series. The sensitization prevalences observed in this analysis give borderline justification for this. Bufexamac (Table 4) was part of the baseline series in some countries where it was used; however, thanks to a recent revocation of marketing authorization by the European Medicines Agency (31), based on a negative assessment of the balance of effectiveness (not proven) and adverse effects (contact sensitization: well proven!), contact allergy to bufexamac should become a thing of the past.

Rubber additives

The pattern of nationally aggregated prevalences of sensitization to thiuram mix is peculiar, as in eight countries this lies in a narrow range between 2.0 and 2.7%, whereas in Italy, Lithuania and The Netherlands, it is considerably lower. Neither this pattern, nor the reverse, is reflected in the prevalence of sensitization to mercaptobenzothiazole or mercapto mix. Thus, our morbidity data cannot provide a simple explanation in terms of more exposure to benzothiazoles and less exposure to thiurams/dithiocarbamates. This issue should be addressed by appropriate field studies. In some countries, 'black rubber mixes' are partly used instead of *N*-isopropyl-*N′*-phenyl-*p*-phenylenediamine (IPPD). IPPD itself is an uncommon allergen, with sensitization prevalences ranging from well below 1% to ~1%. Sometimes, a 'carba mix' is tested in baseline series; in other cases, zinc diethyldithiocarbamate is tested as one representative of this class of vulcanizing agents. This is not a frequent allergen; however, cross-reactivity to the antigenically closely related thiurams/thiuram mix is very prominent (32).

Miscellaneous agents

p-Phenylenediamine is an important contact allergen (33), sensitization being related to hair dye exposure, which may be occupational in ~50% of cases (34). Lanolin (wool alcohols) is a controversial allergen. In the present analysis, ≥1% positive patch test reactions were noted in most of the countries; however, the clinical relevance, particularly of weak positive reactions, is often difficult to establish or verify by the use of patch tests or repeated open application tests. Cetearyl (cetostearyl) alcohol, in contrast, evoked positive patch test reactions in ≤1% of cases, and is thus a borderline component of baseline series. Epoxy resins [bisphenol A diglycidyl ether (BADGE)] are predominantly occupational allergens, with increasing importance, for instance in the building trade (17). However, the BADGE type used in the European baseline series detects most, but not all, cases of sensitization to epoxy system components. *p*-tert-Butylphenol formaldehyde resin is a glue that is mostly used for shoes, and is thus one of the most important 'shoe allergens', with a relatively low general sensitization prevalence. The sesquiterpene lactone mix elicited positive patch test reactions in <1% of cases in those countries testing it; the frequencies of sensitization to different Compositae mixes aimed at also covering allergens beyond the three most important sesquiterpene lactones included in the sesquiterpene lactone mix were in a similar range. Primin has repeatedly been found to be an unimportant allergen, except possibly in special regional situations (3, 5, 14); its exclusion from the European baseline series should be discussed (35). Oil of turpentine is sometimes regarded as a 'historical' allergen, as its main use as a solvent for paints and related products has mostly been abandoned, except in 'alternative' or 'natural' types of product. However, it is a fairly important sensitizer in those countries where it is tested routinely. The temporal trend previously paralleled that of FM I, suggesting that it may be a marker of sensitization to (oxidized) terpenes used in perfumery (36). Propolis is used, with strong regional differences, in 'alternative' or 'natural' topical products, foodstuffs, or folk remedies of various kinds. This natural mixture contains a number of sensitizing substances. The use of propolis in the baseline series has been recommended (37). Disperse Blue 106/124 was labelled as 'allergen of the year' in 2000. However, at present, prominent prevalence on screening testing is noted only in Italy, whereas Finland and the UK the prevalence is low. Colophonium (colophony) is a complex mixture of over 100 compounds derived from Pinaceae, with a highly variable content, moreover, spontaneous oxidation and industrial processing of colophony may result in the formation of new sensitizers. Contact sensitization to colophonium tested in the European baseline series is not uncommon; sources of exposure include occupational (cutting fluids, wood from conifers, and adhesives) and non-occupational (adhesives and cosmetics) products.

Conclusion

The pooled analysis of European patch test data shows international variation in sensitization prevalences. This is most likely attributable to differences in exposure, at least to a certain extent. A number of allergens have been identified that are not deemed to be a necessary part of a European baseline series (e.g. primin and clioquinol), whereas other allergens with some importance in the countries testing them routinely may warrant consideration for inclusion in the European baseline series (particularly MI, and possibly oil of turpentine). Continued surveillance is needed to monitor developing allergens across Europe.

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