

The European standard series in 9 European countries, 2002/2003 – First results of the European Surveillance System on Contact Allergies

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Since January 2001, the European Surveillance System on Contact Allergies (ESSCA), supported by European Union funding (contract QLK4-CT-2001-00343), has started to collect patch-test data. This comprises a standardized clinical history and the patch-test results using the European standard series, from 17 centres in 9 European countries listed above. In 2002 and 2003, 10 511 patients' test results have been pooled and analysed. The anamnestic data partly reflect the subspecialties of some centres. The most common allergen was nickel sulfate (17.3%); however, large international variations were observed. The prevalence of contact allergy to Myroxylon pereirae resin (balsam of Peru) (5.8%) is coming close to the frequency found with the fragrance mix (6.4%). Regarding contact allergy to chromium compounds, different frequencies were noted in the 2 centres focused on occupational dermatitis (2.3% in the FIOH versus 7.4% in the Nofer Institute). These most likely reflect the beneficial effect of addition of ferrous sulfate in one, but not the other country. As differences may partly be due to different patch-test reading, standardization may need to be refined further. By providing post-marketing surveillance in the field of contact allergy, ESSCA will meet its objective of increased consumer safety across Europe.

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Surveillance of contact allergy in the clinical population of patch-tested patients has proven useful to detect time trends, such as decrease of nickel allergy in young females (1, 2) and glyceryl monothioglycolate allergy in hairdressers (3). Whilst downward trends may reflect the success of primary prevention programmes, as in the previous examples, surveillance mainly focuses on increasing frequencies of sensitization. It is

only by identifying increasing prevalences or risks, whether generally or in certain definable subgroups, that targeted action can be taken. In the past, there have been several well-illustrated examples including the infamous Cl + Me-isothiazolinone sensitization 'epidemic' in the late 1980s, and the more recent problems with one of its substitutes, methyldibromo glutaronitrile (MDBGN). Interestingly, such 'epidemics' often

start locally, or are particularly pronounced in certain centres. Hence, analysis should not only focus on global trends, but also on between-centre variation to derive valuable starting points for the in-depth investigation of possible riskful exposures.

While an increasing proportion of patients with positive (allergic) reactions to a certain allergen will slowly suggest a definite trend in single centres, pooled data from several centres provide more power to timely identify trends, especially in smaller subgroups – notwithstanding the variability introduced by the inclusion of several centres, which has been criticized by some (4). In fact, the quality control of patch-test data, with the aim of increasing standardization, is both an outcome and a prerequisite for the analysis of a large set of pooled data, for which the trinational ‘Information Network of Departments of Dermatology’ (IVDK, <http://www.ivdk.org>) can serve as an example (5). Given sufficient standardization, the variability between centres may be a first indicator of the impact of certain demographic or clinical characteristics of the patients seen in this centre (6, 7).

A European network collecting ‘routine’ patch-test data has potential advantages which the European Surveillance System on Contact Allergies (ESSCA) aims to exploit:

- (1) Continual analysis of the set of most important allergens collected in the standard or other series, in contrast to occasional studies, often addressing just 1 or a few study allergens
- (2) A greater variation of allergen exposure across countries, which should facilitate the identification of their impact on sensitization, including a downward trend after successful intervention
- (3) Collective expertise (‘network of excellence’) to pursue ad-hoc issues, such as research into additional cosmetic and perfume allergens
- (4) Communication of research and other issues, including standardization, between the European network and the national contact dermatitis research groups, thus fostering scientific exchange beyond the limited format of, e.g. the meetings of the European Society of Contact Dermatitis (ESCD, <http://orgs.dermis.net/content/e01escd>) and journal articles
- (5) Communication of results to European regulatory authorities, providing a sound scientific basis necessary for regulatory decisions

This article reflects 2 years of work collating data from participating centres and the results of discussions at an intermediate workshop addressing standardization issues. These first results will, by their very nature, not yet meet the objectives mentioned – for this, more time is needed – but they do provide a unique first comparative insight into the current spectrum of patient characteristics and contact allergy across 9 European countries.

Methods

The ESSCA (<http://www.essca-dc.org>) was founded as an ESCD working group during the Jadassohn Centennial Congress in London, 1996 (8). After preparatory work (9), data registration started in January 2002, supported by the EU (QLK4-CT-2001-00343). In 2003, the Nofer Institute in Lodz, Poland, joined the group of active participants (QLK4-CT-2001-2812). In 2004, 3 more Italian centres contributed their retrospective data (2 departments from Padova, 1 from Trieste). The main objective of ESSCA is the surveillance of contact allergies, i.e. (i) recognition of contact allergy time trends in the clinical population of patch-test patients and (ii) recognition of certain subgroups at risk for contact sensitization to a given allergen. At the same time, the pooling of patch-test data from different centres enables quality control, which is both a prerequisite for surveillance and an outcome of the co-operation.

The main technical challenge of the ESSCA project was the integration of patch-test data from various sources, in terms of computer systems. The following practical difficulties were encountered:

- (1) Austrian, German and Swiss participants used the MS-Access-based patch-test software ‘WINALLDAT/IVDK’, developed and used by the IVDK network, in which these partners also took part. Only a few additional items had to be added to the patient history data to ensure full compatibility with ESSCA requirements.
- (2) Several centres used proprietary software systems (the UK, the Danish, the 2 Finnish centres and the northeast Italian subgroup), which needed an ‘export interface’ for structured output of data relevant for ESSCA.
- (3) Some centres (Groningen, NL, Lodz, PL, Nopoli, Italy) required a custom patch-test software, either because they did not previously use one or because they wanted to upgrade to a ‘state-of-the-art’

system. For these centres, the multilingual patch-test software 'WINALLDAT/ESSCA' was developed and delivered (10).

Data of all patients patch tested in the participating centres arriving from these different sources were collected at the ESSCA data centre in Erlangen, checked for consistency and plausibility and, if necessary, mapped to the catalogues used by ESSCA. For instance, occupations were coded in some centres with different (national) catalogues, which were, upon import into the central pool, mapped to the ISCO-88 (11)-based classification used for ESSCA. Important demographic and clinical characteristics were summarized according to the 'MOAHLFA' index (6). However, ESSCA has decided to define the first 'A' as 'atopic dermatitis' (12), i.e. not including allergic bronchial asthma or rhinoconjunctivitis, as in the original MOAHL index. The scope of patch-test data comprised test results at least with the European standard series (ESS) (13), partly supplemented by results with national or local standard series, along with selected demographic and clinical data (9): 'minimal dataset', see <http://www.ivdk.gwdg.de/essca/doc/minidat8-2003-06.pdf>.

Routine patch-test exposure time was 48 hr, except in Kiel, Germany (DE-06), where it was 24 hr. Results were recorded according to international guidelines (14). The standard 'positive outcome' (allergic reaction) of the patch test was defined as a morphologically + to +++ reaction (14) between day 3 (D3) and day 5 (D5)

after the application of the patch test. Descriptive analysis of data followed current guidelines as elaborated by ESSCA (12), in particular employing age and sex standardization of sensitization prevalences (15). For data management and descriptive analysis, the statistical software package SASTM (version 8.2, SAS Institute, Cary, NC, USA) was used.

Results

Between January 2002 and December 2003, a total of 10 511 patients were patch tested in the 17 centres actively participating in ESSCA during this period; details are summarized in Table 1. In patients seen more than once during this period, the most recent 'case' (consultation) was selected for analysis. Demographic characteristics according to the MOAHLFA index (6) are presented in Table 2. A wide variation of most characteristics is evident. This includes a high proportion of males and of patients with hand dermatitis in the 2 centres with a special interest in occupational dermatitis (FIOH [FI-01] and Nofer Institute [PL-01]). Excluding the specialized paediatric dermatology department in Padova (IT-03, where only 3 out of 465 patients were older than 20), Napoli (IT-01) had the youngest patients. A considerable number of patients were not formally employed, but retirees (20.0%), 'housewives' (8.5%), students (11.4%) or unemployed (3.5%). Common occupations included office work (10.3%), nursing and midwifery (3.8%), teachers (2.9%), sales persons

Table 1. Overview of ESSCA centres active in the years 2002/2003 regarding patch testing with the standard series

Centre	Allergen supplier(s)		Consultations	Patients	% positive to any allergen*
Austria, Graz	AU-25	HT	737	732	51
Denmark, Gentofte	DK-01	HT	1730	1725	26
Finland, Helsinki	FI-01	HT, CH	234	234	41
Finland, Lahti†	FI-02	CH	281	281	57
Germany, Dortmund	DE-01	HT	782	776	35
Germany, Göttingen	DE-03	HT	537	527	41
Germany, Kiel	DE-06	HT	561	559	44
Germany, Jena	DE-12	HT	702	691	42
Germany, Erlangen	DE-24	HT	690	635	46
Italy, Napoli†	IT-01	CH	376	376	42
Italy, Padova	IT-02	CH	428	428	64
Italy, Padova (Ped.)	IT-03	CH	465	465	54
Italy, Trieste†	IT-04	CH	488	488	34
Netherlands, Groningen	NL-01	TT	819	814	39
Poland, Lodz†	PL-01	CH	283	283	33
Switzerland, Basel	CH-42	TT	596	576	34
UK, Amersham	UK-01	HT, CH	921	921	47

CH = Chemotechnique, Malmö, Sweden; HT = Hermal/Trolab, Reinbek, Germany; TT = True Test, Mekos Laboratories AS, Hillerød, Denmark.

*% positive to at least 1 allergen of the European standard series (13) among those tested with it. NB: some centres did not test with the full range of allergens.

†Started in 2003.

Table 2. The MOAHLFA index (6), summarizing important determinants of the allergen spectrum observed of pooled ESSCA data, with the most extreme proportions found in certain centres

			Minimum percentage		Maximum percentage	
ESSCA 2002–2003			Centre	%	Centre	%
Male	M	37.1	FI-02	26.7	FI-01	48.3
Occupational dermatitis	O	13.1	IT-01	0.3	FI-01	34.6
Atopic dermatitis	A	18.0	IT-02	2.8	IT-03*	41.5
Primary site: hand	H	28.7	IT-03*	10.5	FI-01	59.0
Primary site: leg	L	9.1	PL-01, NL-01	3.2	DE-06	17.0
Primary site: face†	F	13.4	IT-04	3.1	UK-01	26.0
Age, above 40‡	A	57.8	IT-01	41.2	DE-06	69.2

*IT-03: only paediatric patients.

†In 3 centres, face was included in the category 'head'; these are disregarded in this analysis.

‡IT-03 not included.

(2.0%), hairdressers (1.9%) and cleaners (1.8%). After patch testing, allergic contact dermatitis was diagnosed in 20.5% of the patients, partly combined with irritant and/or endogenous eczema (data not shown).

Table 3 presents test results obtained with the ESS. The strongest reaction recorded on D3 through D5 was used as the standard outcome measure to take account of inter-departmental reading practices. The series was not tested in its originally proposed composition (13) throughout, which accounts for the variable numbers of patients tested. For instance, clioquinol (5-chloro-7-iodo-8-quinolinol), primin and especially the 2 corticosteroid screening agents, budesonide and tixocortol pivalate, have been tested on consecutive patients only by a few centres. To ensure comparability, the results presented in Tables 3 and 4 are based only on allergens tested in the context of the standard series, as aimed testing in special test series will usually yield a higher relative frequency of positive reactions. In addition to the pooled results, the lowest and highest age- and sex-adjusted prevalence observed in different centres is shown to illustrate between-centre variability. This particular analysis excludes the purely paediatric centre because of the impossibility of standardizing for an age- and sex-adjusted comparison. The national and centre-specific standard series may differ, containing additional important allergens like MDBGN, with or without phenoxyethanol (PE). Results with such allergens tested in more than 1 centre are summarized in Table 4, again displaying considerable variability between centres.

Discussion

This article summarizes the results of a newly established European Network of Departments

of Dermatology (<http://www.essca-dc.org>), co-operating in the field of contact allergy research. Before this pooled analysis was possible, structurally heterogeneous data from 7 different systems had to be amalgamated: the 'WINALLDAT/IVDK' system used in the Austrian, German and Swiss centres, the sister patch-test software 'WINALLDAT/ESSCA' (10) used in Groningen, NL, Napoli, IT, and Lodz, PL, and different systems used in the remaining centres. However, these technical achievements shall not be discussed here.

The practice of patch testing

Before commenting the spectrum of allergens and other results, possible variation introduced by methodological differences should be considered. While patch-test exposure is 48 hr in all but 1 centre, the test material is obtained from different manufacturers (Table 1). A recent study has found 'a high level of reproducibility' with patch-test preparations of the same allergens from 2 manufacturers (16). However, as this equivalence study lacked power, these reassuring results still await confirmation. Some differences were partly observed between those centres using investigator-loaded, petrolatum (or water)-based patch tests, supplied by Hermal/Trolab (Reinbek, Germany) or Chemotechnique (Malmö, Sweden), for instance, and those using the True Test™, using a gel vehicle. According to initial validation studies of this test, however, the diagnostic properties of the True Test™ can most likely be regarded as largely equivalent (17), if somewhat less sensitive (18).

Patch-test reading times largely depend on the local organization of the patch-test clinic. Among the German ESSCA centres, many rely on patch-test readings up to and including D3; in fact,

Table 3. Patch test results with the European standard series (13)

Test concentration	%	n (tested)	?/IR	+	++	+++	++++	% (positive, crude)	% (positives standardized)	95% CI	Lowest percentage positives	Highest percentage positives
Potassium dichromate	0.5	9678	6.4	3.3	2.0			5.3	5.4	4.9–5.9	2.2 (CH-42)	9.5 (IT-02)
<i>p</i> -Phenylenediamine*	1.0	9140	1.4	1.4	1.9			3.3	3.1	2.7–3.4	1.4 (DK-01)	5.6 (DE-12)
Thiuram mix	1.0	9213	0.8	1.2	0.9			2.1	2.0	1.7–2.3	0.0 (IT-04)	4.2 (PL-01)
Neomycin sulfate	20.0	9672	1.5	1.9	1.0			2.9	2.7	2.4–3.1	0.5 (DK-01)	6.3 (FI-02)
Cobalt(II) chloride	1.0	9377	8.0	4.9	2.9			7.8	8.0	7.4–8.6	2.2 (DK-01)	26.2 (IT-02)
Benzocaine	5.0	7224	0.7	0.6	0.2			0.8	0.8	0.6–1.0	0.0 (PL-01)	1.5 (DE-01)
Nickel sulfate	5.0	9520	5.1	7.0	11.0			18.0	17.3	16.5–18.1	8.1 (DK-01)	31.7 (IT-02)
5-Chloro-7-iodo-8-quinolinol	5.0	2792	0.5	0.2	0.2			0.4	0.3	0.3–0.8	0.0 (PL-01)	0.4 (DK-01)
Colophony (Colophonium*)	20.0	9676	1.2	2.1	1.5			3.6	3.3	2.8–3.7	0.6 (IT-04)	6.2 (DE-03)
Paraben mix	16.0†	8857	2.3	0.9	0.3			1.2	1.2	0.9–1.4	0.0 (PL-01)	3.7 (AU-25)
<i>N</i> -isopropyl- <i>N</i> -phenyl- <i>p</i> -phenylenediamine	0.1	7898	0.4	0.3	0.3			0.6	0.7	0.5–0.9	0.2 (DE-01)	2.1 (DE-24)
Lanolin alcohol*	30.0	9415	1.9	2.4	0.6			3.0	2.7	2.3–3.0	0.0 (FI-02)	7.3 (AU-25)
Mercapto mix	2.0	2384	0.2	0.2	0.5			0.7	0.9	0.4–1.3	0.0 (UK-01)	1.1 (IT-02)
Mercapto mix (only CBS, MBTS, MOR)	1.0	6235	0.7	0.5	0.3			0.8	0.9	0.6–1.2	0.4 (DK-01)	1.6 (DE-24)
Epoxy resin	1.0	9681	0.4	0.7	0.6			1.3	1.5	1.2–1.8	0.6 (DE-03)	3.4 (FI-02)
Myroxylon pereirae resin*	25.0	9672	3.9	4.3	1.8			6.1	5.8	5.1–6.1	2.3 (NL-01)	12.9 (AU-25)
(balsam of Peru)												
4-tertiary butylphenol	1.0	9685	0.8	0.9	0.6			1.5	1.4	1.2–1.7	0.0 (PL-01)	2.5 (CH-42)
formaldehyde resin												
2-Mercaptobenzothiazole	2.0	9660	0.3	0.5	0.4			0.9	0.9	0.7–1.1	0.1 (DE-06)	2.7 (FI-02)
Formaldehyde*	1.0	9213	2.2	1.1	0.9			2.0	2.0	1.7–2.3	0.0 (IT-04)	9.4 (PL-01)
Fragrance mix	8.0	9663	3.9	4.2	2.9			7.1	6.4	5.8–6.8	3.7 (DE-01)	10.4 (FI-02)
Sesquiterpene lactone mix	0.1	4104	0.6	0.4	0.6			1.0	0.9	0.6–1.2	0.6 (DE-01)	1.3 (UK-01)
Quaternium-15	1.0	5848	0.7	0.6	0.7			1.3	1.2	0.9–1.5	0.4 (DE-01)	2.6 (UK-01)
Primin	0.01	3826	0.4	0.1	0.3			0.4	0.2	0.1–0.4	<0.1 (DK-01)	0.9 (AU-25, IT-02)
Cl + Me-isothiazolinone (methyl-hloroisothiazolinone (and) ethylisothiazolinone*)	0.01	9689	0.8	1.3	0.9			2.2	2.3	1.9–2.6	0.0 (PL-01)	9.8 (IT-02)
Budesonide	0.01	1328	0.1	0.5	0.6			1.1	0.9	0.4–1.5	0.9 (IT-02)	1.5 (PL-01)
Tixocortol-21-pivalate	0.1	2320	0.5	1.0	0.3			1.3	1.1	0.7–1.5	0.1 (IT-02)	0.8 (FI-01)

Outcome: strongest reaction observed between D3 and D5.

All allergens in petrolatum except formaldehyde and Cl + Me-isothiazolinone (methyl-chloroisothiazolinone (and) methylisothiazolinone) which are in water. NL-01 and CH-42 used TrueTest™ standard panels.

*INCI names.

†12% in IT-02–IT-04.

Table 4. Patch-test results with selected allergens contained in national or local standard series

Test concentration	%	n (tested)	?/IR	+	++	+++	+	% (positive, crude)	% (positives standardized)	95% CI	Lowest percentage positives	Highest percentage positives
Oil of turpentine	10.0	3767	0.6	1.2	0.4			1.6	1.5	1.1–1.9	0.4 (DE-01)	4.3 (DE-03)
Cetyl stearyl alcohol (cetearyl alcohol*)	20.0	4207	0.9	1.2	0.3			1.5	1.3	0.9–1.6	0.6 (DE-03)	2.1 (CH-42)
Zinc diethyldithiocarbamate	1.0	3535	0.1	0.6	0.1			0.7	0.7	0.4–1.0	0.5 (DE-01)	1.0 (AU-25)
Methyldibromo glutaronitrile + 2-phenoxyethanol*	1.0	3525	1.2	3.1	1.0			4.1	3.8	3.1–4.5	0.9 (DE-01)	6.8 (AU-25)
Propolis (Propolis cera*)	10.0	3535	1.0	2.4	0.5			2.9	2.6	2.0–3.1	0.9 (DE-01)	4.9 (AU-25)
Bufexamac	5.0	3538	0.3	0.8	0.8			1.6	1.6	1.1–2.0	0.6 (DE-06)	3.4 (DE-24)
Compositae mix	6.0†	5157	2.1	2.3	1.0			3.3	3.3	2.8–3.8	0.1 (IT-02)	5.7 (AU-25)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde* (e.g. Lyrall®)	5.0	3862	0.9	1.6	0.6			2.2	2.1	1.6–2.6	1.6 (DE-06)	4.9 (CH-42)
Disperse Blue 124/106 mix or Disperse Blue 124	1.0	3017	1.8	1.5	0.6			2.1	1.9	1.4–2.4	0.6 (AU-25)	5.8 (CH-42)

Outcome: strongest reaction observed between D3 and D5.

All allergens in petrolatum.

*INCI names.

†5% in IT-02–IT-04.

within the IVDK, a ‘morphologically positive test reaction at D3’ is the standard outcome. Other ESSCA centres read D2 and D4 or D5 – hence the flexible standard outcome chosen here: ‘maximum reaction observed D3–D5’. Extending the time frame further, e.g. from D3 to D6 or D7, would make this outcome even more sensitive, because more late reactions would be included. However, at the same time, increased heterogeneity would be introduced, as in the centres limiting readings to D3, more and more subsequent reactions will systematically be missed, compared to centres reading routinely until D6 or D7. Thus, the present time frame is considered a reasonable compromise.

The conventional classification of patch-test reactions to allergens, using the international scale (14), is primarily morphologically orientated, with + to +++ reactions implicitly considered allergic. However, the distinction between doubtful (erythematous) reactions and + reactions is sometimes not easy and there may be differences between centres (19). These problems may be lessened by relating to a set of standardized images of patch-test reactions and in particular by patch-test training sessions, but presumably such differences will be hard to eliminate entirely, as with any visual outcome. Moreover, knowing that some + reactions (to certain substances in certain concentrations) may be irritant, the supplementation of every patch-test reaction with an expert judgement as to whether this is allergic, irritant, indicative of cross-reactivity, etc. is surely a benefit and can help to further qualify data on ‘% positives’, especially on ‘weak positives’, but also on ‘doubtful’ reactions. Hence, in the context of ESSCA, the morphological classes, +, ++ and +++ have been supplemented with an attribute ‘a’ for ‘regarded as allergic’, ‘i’ for ‘...irritant’ and ‘u’ for ‘...unclear’ to be used by those centres who feel confident to do so; otherwise, the usual reaction symbol is used. We considered any reaction between + and +++ (D3–D5) that was not contradicted by the ‘i’ attribute as a positive outcome. However, it is important to note that the validity of such a judgement relies heavily on the personal expertise of the observer.

Patient selection

There is great heterogeneity amongst the 17 participating ESSCA centres: 2 are highly specialized national centres for the assessment of occupational skin diseases (the FIOH [FI-01] and the Nofer Institute [PL-01]), which is reflected by the demographic characteristics and partly in

the spectrum of allergens. The dermatology unit of the paediatric department in Padova (IT-03) only patch tests children and adolescents. The remaining centres do have special research interests, but are less specialized regarding the patients they patch test. The number of patients patch tested per year also varies, with most centres testing several hundred patients per year, while Gentofte (Copenhagen) is the biggest clinic with a large catchment area attending to nearly a 1000 patients each year. Interestingly, the proportion of patients positive to at least 1 standard series allergen (as far as these have been tested locally) is the lowest there, which might (i) indicate a low level of sensitization in the Danish patients; (ii) a high level of suspicion of allergic contact dermatitis, i.e., a lower threshold to patch test a patient, relative to other centres; or (iii) partly reflect the possibly more conservative definition of a positive patch-test reaction (19). Conversely, those centres with >50% positive patients may be seeing a more highly selected group of patients at the end of a referral process.

The pattern of distribution of the MOAHLFA factors seems plausibly explained mainly by the occupational background of the FIOH department (FI-01), while occupational dermatitis is an exception, for instance, in Napoli (IT-01). Slightly different definitions of the notoriously hard-to-define (20, 21) item 'atopic eczema' may partly explain the striking differences we observed.

Allergens

Taking account of the above, a review of the range of contact allergens and the differences between centres is interesting:

- (1) Nickel sulfate is the leading allergen, as in most previous analyses. Although possibly biased by a 'dilution effect', the lowest prevalence is observed in Gentofte, i.e. in a country where nickel release from consumer objects such as costume jewellery has been regulated for a long time (1). In contrast, the proportion of nickel (and cobalt)-sensitized patients is above average in most Italian centres, which might indicate heavier exposure. Indeed, it has been noted previously that children are often exposed to costume jewellery at a very early age there (22). The nickel directive has been set in force in Italy in July 2001, and hence little effect on sensitization prevalence can be expected. In fact, nickel-

releasing jewellery is still common on the Italian market (23).

- (2) Sensitization to chromium is often caused by occupational exposure to soluble chromium compounds in cement or leather. From a geographical point of view, dichromate was often the leading allergen in Eastern European publications (24), in particular Poland (25). This is still reflected by the data from Lodz, where chromium contact allergy was almost 4 times more frequent than in the FIOH, i.e. the other centre specialized in the assessment of occupational dermatitis. This is most likely a reflection of the beneficial effect of the addition of ferrous sulfate to cement in Finland, while in Poland upcoming regulations, e.g. in the framework of the EU Directive 76/769/EEC (CONSLEG: 1976L0769–16/03/2004), will only be able to reduce chromium dermatitis due to cement and concrete in the future.
- (3) Formaldehyde was previously used as a preservative in cosmetics and as a disinfectant, which resulted in generally higher sensitization rates (26) than nowadays (27). Since its use in cosmetics was largely abandoned due to allegations of carcinogenicity, and as a disinfectant it was partly replaced by other compounds like glutaraldehyde or glyoxal, the frequency of formaldehyde allergy remains at a relatively low, stable level across many European countries, at least in a general patch-test population (27). However, in another country, in a centre with many cases of occupational dermatitis, including health care workers who are exposed to floor and instrument disinfectants, the prevalence may be much higher (Lodz). Thus, the spectrum of sensitization reflects the (past) socioeconomic differences between Eastern and Western Europe.
- (4) Whereas contact allergy to thiurams or dithiocarbamates is not very common in general patch-test patients, an occupational background again renders the proportion of sensitized higher, as illustrated by an above-average proportion in Lodz.
- (5) Both neomycin and Myroxylon pereirae resin (balsam of Peru) are allergens with a strong age gradient. Hence, it is plausible that in comparatively young groups of patients low frequencies are observed, even after age and sex standardization. In contrast, the highest proportion of contact allergy to both Myroxylon pereirae resin

and the fragrance mix has been found in Padova – as with other allergens like nickel and cobalt – which may be related to the fact that a highly selected group of patients is being tested.

- (6) There may be little exposure to certain allergens in some areas and, hence, no cases of sensitization – albeit taking the relative small size of the local subgroup into account, which still would not preclude a certain, low frequency of sensitization. This is particularly evident regarding the preservative and industrial biocide MCI/MI, which, in the meantime, is not infrequently associated with occupational exposure in western countries (6). Despite the high proportion of occupational cases in Lodz, there were no sensitizations to this biocide, probably indicative of the rare (industrial) use in eastern countries. In fact, a previous comparison of sensitization prevalences between East (former GDR) and West German (Federal Republic) patients revealed a low frequency of sensitization to MCI/MI, as well as to parabens and benzocaine in the former (6, 28).

The results obtained with the ESS illustrate the broad range of prevalences; above a few possible explanations for between-centre differences have been discussed. However, as ‘new’ allergens continuously emerge, a standard series needs to be continuously adapted. The inclusion of allergens in a ‘monitor series’, supplementing the ESS for a brief period, tested in several centres, and analysed rapidly (29), has proven useful to identify those substances which fulfil the criteria proposed for ESS eligibility (30). Conversely, some allergens in the recommended standard series may now be considered irrelevant or even counter-productive by some national groups. Therefore, several centres or national groups modify the ESS systematically by adding or omitting allergens. The analysis of additional allergens (Table 4) can give clues on potential candidates for other standard series, or possibly the ESS:

- (1) MDBGN, alone or combined with PE, which itself is regarded as a very infrequent sensitizer, has been added to the German Contact Dermatitis Research Group (DKG) standard series some years ago. It has evolved as an important allergen (27, 31). In the meantime, the European Environmental and Contact Dermatitis Research Group (EECDRG) has recommended to include MDBGN in the ESS

(32). Most probably, MDBGN allergy will decline in the future, thanks to the current regulation banning its use at least in leave-on products (Commission Directive 2003/83/EC of 24 September 2003, Official Journal L 238, 25/09/2003 P. 0023–0027).

- (2) Hydroxyisohexyl 3-cyclohexene carboxaldehyde (CAS No. 31906-04-4, e.g. Lyrall[®]) has been identified as important fragrance allergen and is part of the DKG standard series already (33). The introduction of the new fragrance mix II, which includes Lyrall[®], albeit in 2.5% and not 5% concentration (19), will possibly reduce the necessity to test with this important single compound.
- (3) Disperse Blue 106 and 124 are hardly separable and can thus be regarded more or less as ‘one allergen’ – both in real-life exposure and when patch testing with the compound (34). Their role as standard series allergens is controversial because of the markedly differing regional and also national variability of contact allergy, which is also evident from our data (Table 4). The fact that textile dermatitis in general, and allergic contact dermatitis (ACD) to the dyes in particular, is not always evident from the patient’s history or the clinical pattern possibly speaks in favour of including this screening allergen to a ESS.
- (4) The composite mix is, in view of the percentage positives, an important screening agent in the centres using it. It has been found to detect sensitized patients not reacting to the sesquiterpene lactone mix, which is part of the current ESS (29). On the other hand, the composite mix carries some risk of active sensitization (35).
- (5) Oil of turpentine (OT) is a ‘historic’ occupational allergen of painters and varnishers. As OT was replaced during the last decades by organic solvents and water for economic reasons, sensitization to OT decreased or even ‘disappeared’ (36). The increase of OT sensitization noted several years ago (37) has been suggested to be due to OT being a marker for terpenes present in alternative cosmetic and medical products recovered from plants (38). This notion was further supported by a multicentre study showing frequent concomitant reactions to tea tree oil (39). However, since its peak in 1998,

OT sensitization has continuously and significantly decreased (40). In the FIOH, the 2 cases of OT sensitization observed during the study period were non-occupational.

Conclusion

The first comparative analysis of demographic data and patch-test results with standard series allergens of the ESSCA network generated a number of interesting observations. The current results have been intensely discussed among the ESSCA members and can be regarded as valid. Many of the observations are in accordance with previous reports, or are plausible taking the respective centre and country into account. As such, they are hopefully the starting point of a series of regular reports on contact allergy frequency across Europe. Obviously the question of systematic or inherent methodological variation will always be an issue and should be addressed by continual standardization efforts, such as suitable workshops and training sessions, especially in view of even more new members joining ESSCA. The observation, discussion and eventual harmonization of differing patch-test practices is a prerequisite for valid between-centre and international comparisons, aiming at identifying true differences due to differing exposure conditions.

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