

20 Years of standard patch testing in an eczema population with focus on patients with multiple contact allergies

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Results of standard patch tests performed with the same methodology in one centre are rarely available over a large time span. This gives the unique opportunity to study not only prevalence but also persistency of contact allergy and characterize subpopulations. The objectives were to investigate sensitivity rates and persistencies of patch test results and characterize patients with multiple contact allergies. A 20-year retrospective database-based study of 14 998 patients patch tested with the European Standard Series was performed. 34.5% were sensitized, primarily women. Sensitivity to nickel was most frequent and least frequent to mercaptobenzothiazole, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine and benzocaine. Yearly proportion of negative, mono/double-allergic, and multiple-allergic cases remained stable. Persistency of positive reactions was high for para-phenylenediamine, Cl(Me)isothiazolinone, and primin and poor for paraben mix. 5.1% were multiple allergic, primarily women, and 90% got diagnosed by the first test. Frequency of multiple allergies increased with age. More multiple- than mono/double-allergic patients were tested multiple times. Persistency and sensitivity rates in a Danish eczema population are provided and are useful for decisions regarding the standard series. Patients with multiple contact allergies are typically elderly women who might have long-lasting and hard-to-treat eczema. Cumulative environmental exposure seems necessary to develop multiple allergies.

Key words: contact allergy; database; European Standard Series; multiple contact allergies; multiple patch tests; persistence; persistency rate; polysensitization; sensitivity rate; sensitization. © Blackwell Munksgaard, 2007.

Accepted for publication 5 March 2007

Contact allergy is a delayed-type hypersensitivity reaction triggered by direct skin contact with low-molecular weight molecules in the environment. Contact allergy is generally perceived as being life-long, and patients are advised to avoid specific allergens for the rest of their lives. In contrast, studies on persistency of patch test results with varying time lapse between tests show a more complex picture with persistency rates less than 100% (1–3).

The European Standard Series is composed of 23 allergens. The European Standard Series detects approximately 75% of all contact allergies as about 15% of individuals tested are positive to other allergens only and 10% are positive to both allergens in the Standard Series and other allergens (4). Variations in sensitivity rates exist within Europe (5) and even between different patch-testing centres in the same country (6). In Denmark, legislation of nickel release from consumer objects

and addition of ferrous sulfate to cement have had marked impact on the prevalence of nickel and chrome sensitivity (7). Sensitivity rates for allergens in the European Standard Series have not previously been reported for our region and patient mix.

Patients with multiple contact allergies have received limited research focus. Knowledge about patients with multiple contact allergies mainly relies on a few studies and general perceptions. Patients with multiple contact allergies probably do exhibit a special entity in the field of contact allergies as the observed frequency exceeds the predicted frequency in both general (8) and eczema populations (9).

All results from individuals patch tested since 1979 have been electronically registered in a database at the Copenhagen University Hospital Gentofte, Denmark. Using the information gathered in the database, the aim of this study is to

investigate sensitivity rates and persistency of positive patch test results over time and to identify and characterize patients with multiple contact allergies within a Danish eczema population.

Methods

At the Department of Dermatology, Copenhagen University Hospital Gentofte, Denmark, patients suspected of suffering from allergic contact dermatitis are tested with the European Standard Series and, if relevant, additional allergens dependent on exposure. All the patch test results are consecutively registered in a database. Patch test results from 1985 to 2005 regarding 23 allergens contained in the European Standard Screening Tray were selected and analysed.

In the entire period, patch testings were done using Finn Chambers® and Scanpor tape applied to the upper back. The occlusion time was 48 hr. Readings were done on D2, D3 or D4, and D7 according to the recommendation from the International Contact Dermatitis Research Group (10). Homogeneous redness and infiltration in the entire test area was scored as a 1+ reaction. Homogeneous redness, infiltration, and vesicles in the test area were scored as a 2+ reaction, and homogeneous redness, infiltration, and coalescing vesicles in the test area as a 3+ reaction.

A 1+, 2+, or 3+ reading was interpreted as a positive response. An irritative response, doubtful (+?), or negative reading was interpreted as a negative response. Not all patients were tested with the complete standard series because of known sensitivity diagnosed by previous patch test at the Department. A registration of known sensitivity was interpreted as a positive response. A few patients were not tested to the complete standard series of unknown reasons. This registration was categorized as missing data.

Patients and Materials

14 998 patients (63.6% women and 36.4% men) were patch tested. Median age at first test was 47.40 years [interquartile range (IQR) 28.87]. Stratified into 5 age groups 1.7% (255) patients were under 16 years of age at first patch test, 20.3% (3041) were between 16 and 30 years, 34.8% (5212) were between 31 and 50 years, 29.6% (4437) were between 51 and 70 years, and 13.7% were over 70 years of age at the time of first patch test.

86.2% (12 926) of the patients were patch tested with all 23 allergens or had a known positive reaction diagnosed by a previous patch test performed at the Department. The lowest number of aller-

gens tested per individual was 16 which only concerned 3 patients. The sesquiterpene lactone cocktail was unavailable for testing during 1985–86. Excluding the missing data caused by this circumstance, 95.5% of all patients were tested with all standard allergens available on the time of testing or had a known positive reaction diagnosed by a previous patch test.

16 allergens did not change concentration or composition during the 20-year period. In, respectively, 1988, 1986, and 1995, para-phenylenediamine (PPD) changed concentration from 0.5% to 1%, colophony changed concentration from 60% to 20%, and mercapto mix changed concentration from 2% to 1%. 2 allergens changed composition. Quinoline mix 6% was in 1994 substituted with clioquinol 5%, and black rubber mix 0.6% was in 1993 substituted with *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine (IPPD) 0.1% petrolatum. In 1995 paraben mix changed both composition and concentration as 1 paraben ester was removed and concentration of the remaining 4 esters was changed to 4% each (11). We first started to test with sesquiterpene lactone cocktail 0.1% in 1987. Different allergen concentrations and compositions used were not evaluated separately.

Statistics

The data analysis was done using the statistical software programme SPSS version 13.

6.5% of the patients were tested several times. Overall and allergen-specific sensitivity rates were calculated by using the last patch test performed per individual as point of origin, if not stated otherwise.

Comparison of sensitivity rates was made using the χ^2 test and evaluation of trends with χ^2 for trend. Comparison of age distributions was done using the Mann–Whitney test. Examination of sensitivity rate changes between tests on the same population was done using the McNemar non-parametric test based on binomial distribution. Because of multiple testing, when comparing sex-specific sensitivity rates for each allergen, the *P* value was adjusted according to the method of Bonferroni so that a *P* value below 0.002 was regarded as significant. For the remaining calculations a *P* value below 0.05 was regarded as significant.

Only those patients who had been tested consecutively with the specific allergen of interest were evaluated for the analysis of persistency of positive patch test reactions.

The influence of sex and age on the occurrence of multiple contact allergies was evaluated by

nominal, ordinal, and binary logistic regression models. The occurrence of multiple contact allergies was used as dependent outcome variable, and age, sex, and interaction between age and sex, were used as independent variables. To test if the binary model fitted the data adequately, Hosmers goodness-of-fit test was used and the fit was adequate. The nominal and ordinal regression model was performed because the binary model simplified the data. The nominal and ordinal regression model resulted in almost identical results. The nominal regression model was run with maximum likelihood estimation, and the ordinal model was run with weighted least-square estimation. The almost identical results of the nominal and ordinal regression model indicated that the conditions for the ordinal model had been fulfilled.

Results

Trends

The total number of patients patch tested each year increased steadily (Fig. 1); however, the proportion of positive and negative cases per year remained stable (Fig. 2). Distributing the positive cases into patients with 1–2 contact allergies and patients with ≥ 3 contact allergies, the proportion of both groups also remained stable over the years as illustrated in Fig. 2 with parallel trend lines (χ^2 for trend, $P = 0.647$). Age median increased by approximately 5 years from 1985 to 2005 (results not shown). The fraction of women tested each year varied greatly; overall, showing only a marginal increase from 1985 to 2005 (results not shown).

Allergies in an eczema population

In total, 34.5% (5178) had at least 1 contact allergy (range 1–12). 40% of the women tested

had a contact allergy versus 25% of the men tested (χ^2 , $P < 0.001$). As more women than men were tested, 73.7% of all diagnosed allergies were among women.

Positive reactions to all the 23 allergens or mixes of allergens in the standard series were found. The sensitivity rate for each specific allergen is illustrated in Table 1. Sensitivity was most frequent to nickel (12.0%) and least frequent to mercaptobenzothiazole (MBT), IPPD, and benzo-caine (for all three 0.5%).

Significantly more women than men were sensitized to cobalt, formaldehyde, colophony, *p*-tert-butylphenol-formaldehyde resin (PTBFR), fragrance mix, quaternium 15, nickel, Cl(Me)isothiazolinone (MCI/MI), primin, and sesquiterpene lactone cocktail (Table 1) (Bonferroni-adjusted χ^2 , $P < 0.002$).

Persistency of positive patch test reactions

Persistency of positive patch test reactions means that a positive reaction observed at one patch test is reproduced at a second patch test performed at a varying time span after the first test. The degree of persistency of positive patch test reactions differed between the allergens. In Table 2 allergens are ranked in 5 categories according to persistency: poor (<20%), fair (21%–40%), moderate (41%–60%), good (61%–80%), and very good ($\geq 81\%$). 9 of 23 allergens ranked as good or very good, whereas only 5 allergens ranked as poor or fair. PPD, MCI/MI, and primin had a very high degree of persistency ($\geq 81\%$). In contrast paraben mix had a poor persistency (11%).

Multiple contact allergies

Multiple contact allergies were defined as 3 or more than 3 contact allergies. 759 patients

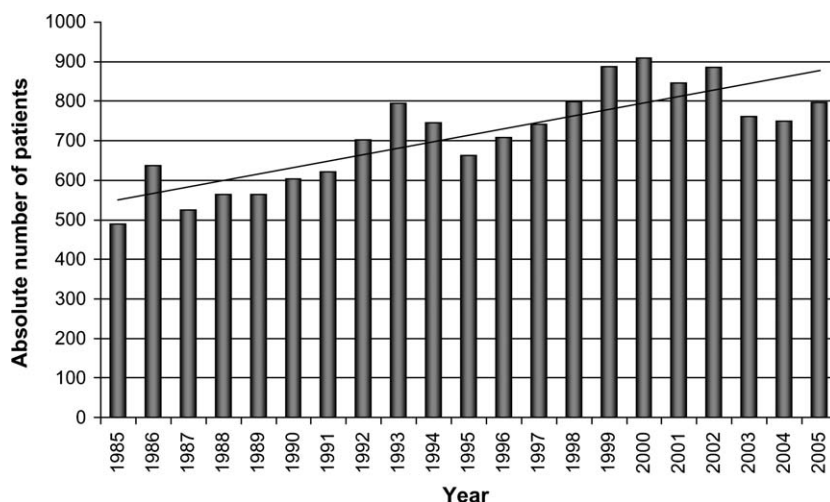


Fig. 1. Total number of patients patch tested with the European Standard Series between 1985 and 2005 at the Department of Dermatology, Copenhagen University Hospital Gentofte, Denmark. Trend line interposed.

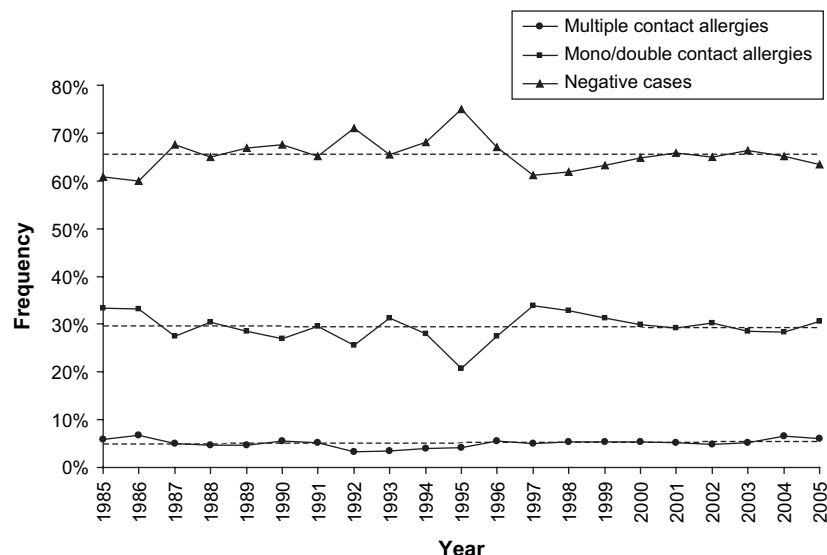


Fig. 2. Proportion of negative, mono/double-allergic, and multiple-allergic patients each year from 1985 to 2005 tested with the European Standard Series. Trend lines are illustrated for each reaction group.

(77.3% women and 22.7% men) had multiple contact allergies, correlating to a prevalence of 5.1%. 683 individuals had multiple contact allergies at time of first patch test, correlating to 90% of all diagnosed multiple-allergic individuals. Median age at time of diagnosis of multiple contact allergies was 52.98 years (IQR 26.50). The rate of patients with multiple contact allergies increased

with age (Table 3). The frequency of 1–2 allergies did not show the same increasing trend with age (Table 3).

The occurrence of multiple contact allergies was significantly associated with sex and age and sex $\times$ age in combination (nominal regression model, for all 3 factors $P < 0.0001$). The sensitivity rates of multiple contact allergies at different ages and sex are illustrated in Fig. 3.

Table 1. Total and sex-specific sensitivity rates for each allergen in the European Standard Series 1985–2005

Allergens (n)	Men (%)	Women (%)	Total (%)
Chrome (14 979)	2.3	2.5	2.4
Neomycine (14 978)	2.6	2.9	2.8
Thiuram mix (14 982)	2.3	2.9	2.7
Para-phenylenediamine (14 966)	1.8	2.3	2.1
Cobalt (14 976)	2.4	4.3	3.6*
Benzocaine (14 995)	0.3	0.7	0.5
Formaldehyde (14 980)	2.2	3.2	2.9*
Colophony (14 985)	3.1	4.4	3.9*
Clioquinol (14 996)	1.0	0.6	0.7
Balsam of Peru (14 988)	3.7	4.8	4.4
N-isopropyl-N-phenyl-p-phenylenediamine (14 964)	0.7	0.4	0.5
Wool alcohols (14 994)	1.0	0.8	0.9
Mercapto mix (14 989)	0.8	0.6	0.7
Epoxy resin (14 987)	1.3	1.0	1.1
Paraben mix (14 996)	0.7	0.5	0.6
p-tert-butylphenol-formaldehyde resin (14 994)	0.8	1.4	1.2*
Fragrance mix (14 971)	5.9	8.8	7.7*
Quaternium 15 (14 993)	0.5	1.1	0.9*
Nickel (14 845)	3.1	17.2	12.0*
(Cl)Me-isothiazolinone (14 878)	1.2	2.1	1.8*
Mercaptobenzothiazole (14 852)	0.6	0.5	0.5
Primin (14 986)	0.3	1.6	1.1*
Sesquiterpene lactone cocktail (13 198)	0.8	1.5	1.2*

Significant difference in sensitivity rate between sex exists for 10 allergens marked with asterisk (χ^2 test, $P < 0.002$). n, total number of patients tested.

Multiple testing

Mainly patients with chronic and recurrent dermatitis may be subjected to retests. 977 individuals (67.6% women and 32.4% men) were patch tested between 2 and 5 times. 153 (15.7%) had 3 or more than 3 contact allergies and 347 (35.5%) had 1 or 2 allergies. 477 (48.8%) did not have any contact allergies.

The median age, fraction of women, and proportion of multiple-allergic patients increased with number of tests performed (Table 4). There were significantly more women and more mono/double- and multiple-allergic individuals and a higher age median at time of first test in the multiple-tested group compared with the single-tested group (Table 4). 11.2% of patients diagnosed with multiple contact allergies and 7.6% of patients diagnosed with mono/double contact allergies at time of first test ended up being tested multiple times (χ^2 , $P < 0.001$).

Discussion

We report results from a Danish contact allergy database. It is unique as it compiles results from 20 years of patch testing in a specialist unit. We found a 34.5% sensitivity rate of contact allergy in

Table 2. Persistency rates, positives in first and second patch test and new and lost positives in the second patch test for each allergen in the European Standard Series

Rank	Allergens (n)	Persisted positive (%)	Positives in first test	Positives in second test	Lost positives	New positives
Very good	Primin (964)	10 (91)	11	11	1	1
	MCI/MI (956)	7 (88)	8	23	1	16
	PPD (962)	5 (83)	6	30	1	25
Good	Neomycine (959)	17 (68)	25	27	8	10
	Quaternium 15 (977)	6 (67)	9	13	3	7
	Benzocaine (976)	4 (67)	6	10	2	6
	IPPD (971)	4 (67)	6	12	2	8
	Mercapto mix (966)	2 (67)	3	9	1	7
	SL mix (817)	8 (62)	13	23	5	15
	Cobalt (954)	13 (57)	23	38	10	25
Moderate	Epoxy resin (967)	4 (57)	7	9	3	5
	Fragrance mix (919)	31 (57)	54	87	23	56
	Colophony (934)	20 (56)	36	50	16	30
	Nickel (887)	26 (54)	48	61	22	35
	Chrome (957)	10 (48)	21	36	11	26
	Balsam of Peru (944)	11 (48)	23	56	12	45
	Formaldehyde (956)	9 (43)	21	30	12	21
	Thiuram mix (954)	10 (42)	24	45	14	35
	PTBFR (969)	3 (38)	8	7	5	4
	MBT (957)	1 (33)	3	5	2	4
	Wool alcohols (968)	5 (31)	16	16	11	11
Fair	Clioquinol (969)	2 (29)	7	11	5	9
	Paraben mix (976)	1 (11)	9	8	8	7
	Total	209 (54)	387	617	178	408

Median time lapse between first and second test was 4.4 years for SL mix, 4.7 years for cobalt and formaldehyde, and 4.8 years for the rest of the standard allergens. n, total number of patients tested. IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine; MBT, mercapto-benzothiazole; MCI/MI, Cl(Me)isothiazolinone; PPD, para-phenylenediamine; PTBFR, *p*-tert-butylphenol-formaldehyde resin; SL mix, sesquiterpene lactone cocktail.

Table 3. Age and sex distribution of patients with 0, 1–2 and ≥ 3 contact allergies at the time of first test

Age	No allergies (%) (<i>n</i> = 9909; 42% males, 58% females)	1–2 Allergies (%) (<i>n</i> = 4406; 27% males, 73% females)	≥ 3 Allergies (%) (<i>n</i> = 683; 21% males, 79% females)
<16 years	82.0	16.9	1.2
16–30 years	70.3	27.0	2.7
31–50 years	63.3	31.9	4.8
51–70 years	65.2	29.7	5.1
>70 years	66.6	27.3	6.1

Frequency of multiple contact allergies and age are significantly associated ($P < 0.001$). *n*, absolute number of patients.

our eczema population, a rate of multiple contact allergies at 5%, and allergen-specific prevalence correlating well with data from other European centres (5, 9, 12). Nickel is the most frequent allergy followed by fragrance mix and IPPD, benzocaine, and MBT, the rarest allergies. Primarily women get a diagnosis of contact allergy. An inherent female susceptibility has been speculated (13), although female-related behaviour with increased exposure and female-dominated professions with exposure to wet work and other irritants could be explanatory in themselves (14).

Despite an increase in patients tested during the last 20 years, the frequency of positive and nega-

tive and mono/double- and multiple-allergic cases each year is stable. From the small increase in age median and marginal increase in fraction of women tested each year over the 20-year period, a slight increase in sensitivity rate could be expected. As this is not the case, a small effective decrease of contact allergy during the 20 years cannot be excluded. 1 out of 6 positive cases had multiple allergies. Only 0.7% of all tested and therefore 1 out of 21 positive cases had multiple contact allergies in a general Danish population (8). The upconcentration of patients with multiple allergies in the eczema population might be related to severe eczema and a need for medical assistance.

From a diagnostic point of view, it is generally appreciated that sensitivity rates of allergens attained in the European Standard Series should exceed 1%. This does not apply to 8 allergens. In a meta-analysis based on 14 studies with TRUE test-based prevalence of allergens (15), 6 of the 8 allergens identified in our study also rank low in frequency (mercapto mix, MBT, quinoline mix, black rubber mix, quaternium 15, and paraben mix). Introduction of new allergens and changes in exposure continuously challenge the justification of allergens chosen to be part of the European Standard Series. As the number of allergens attained in a Standard Series needs to be limited

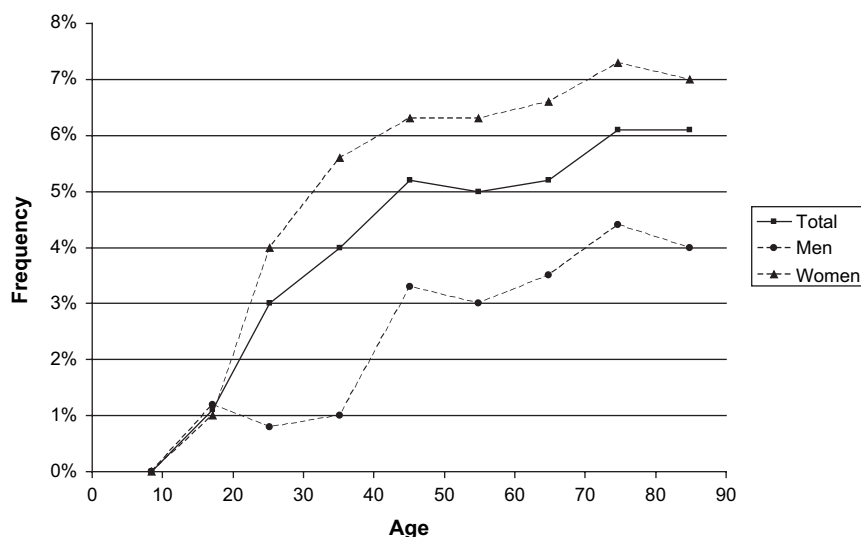


Fig. 3. Association between age and frequency of multiple contact allergies in a Danish eczema patient population at time of first patch test. Sex-specific association is also illustrated. Multiple contact allergies is defined as ≥ 3 contact allergies.

for practical reasons, only allergens that account for the greatest majority of hypersensitivity reactions should be included.

Overall persistency of positive patch test reactions was 54%. The level of persistency varies in different studies (1–3, 16). Primin, MCI/MI, and PPD had a very good persistency of over 80%. These 3 allergens also have a strong allergenic potency (17). In contrast, some of the allergens with a fair or poor persistency, wool alcohols, clioquinol, paraben mix, have a weak allergenic potency (18–20). The same pattern is demonstrated in one other study (1). Weak sensitizers often give weak-positive reactions which more often turn negative on a second testing (1, 21). But even strong sensitizers such as Dinitrochlorobenzene (DNCB) do not exhibit a persistency of 100% as some positive reactions are lost over time (21). Contact allergy is generally perceived as being lifelong, but the level of persistency of positive patch test reactions is never 100% as our results also confirm.

Contact allergy is a dynamic process demonstrated by fluctuations in the patch test reactivity. The intra-individual variation in patch test reactivity is great, sometimes even resulting in negative test results with positive test results to the same allergen at earlier and later testing (22). Skin responsiveness, skin absorption, and seasonal variations also contribute to fluctuations in patch test results (23–25). They are all important factors for persistency of positive reactions in combination with intra-individual variation and allergenic potency for which we cannot control in everyday dermatology practice. In contrast, the test method, preparation, application of test chambers, defined reading times, and standardized interpretations, all factors susceptible to control, were during the last 20 years unchanged and performed by a very small number of specially trained personnel. This procedure minimizes the risk of inconsistencies in methodology and in interpretation. In addition, routine D7 readings

Table 4. Characteristics of patients patch tested multiple times

Sequential count (<i>n</i>)	Age (median age, IQR)	Women (%)	1–2 contact allergies (%)	≥ 3 contact allergies (%)
First patch test (977)	48.5, IQR 27.4*	67.6†	334 (34.2)‡,§	77 (7.9)¶,**
Second patch test (977)	54.4, IQR 26.2	67.6	359 (36.7)‡	135 (13.8)
Third patch test (116)	56.6, IQR 29.3	78.4	47 (40.5)	28 (24.1)

The fourth and fifth patch test have been omitted due to the low number of patients tested 4 ($n = 15$) and 5 times ($n = 2$). IQR, interquartile range; n , number of patients tested.

*Significant difference in age between single-tested and multiple-tested individuals at the time of first test (Mann–Whitney test, $P = 0.04$).

†Significantly more women in the multiple-tested group versus the single-tested group (χ^2 , $P < 0.01$).

‡Significant difference in sensitivity rate regarding mono/double contact allergies between first and second test (McNemar, $P < 0.001$).

§Significantly higher sensitivity rate regarding mono/double contact allergies in the multiple-tested group at the time of first test versus the single-tested group (χ^2 , $P < 0.001$).

¶Significant difference in sensitivity rate regarding multiple contact allergies between first and second test (McNemar, $P < 0.001$).

**Significantly higher sensitivity rate regarding multiple contact allergies in the multiple-tested group at time of first test versus the single-tested group (χ^2 , $P < 0.001$).

were performed for all allergens, supplementing D2 and D3 readings and optimizing the persistency of positive reactions to, e.g. neomycine known to give reactions on D7.

The last official revision of the European Standard Series dates back to 2000 (26). Our observation of low persistency and low sensitivity rates for 4 allergens (paraben mix, clioquinol, wool alcohols, and MBT) do not fulfil the demands on a sensitizer proposed by the European Society of Contact Dermatitis (27). Allergens such as wool alcohols, paraben mix, and clioquinol might be candidates for exclusion. Furthermore, they typically occur among specific subpopulations for which additional testing is often performed (20, 28, 29). In contrast, allergens with sensitivity rates above 1% but with a poor persistency (e.g. PTBFR) are candidates for further research into optimizing the patch test method and material.

Subpopulations of eczema patients with different compositions can be identified in the database. Patients tested several times are more often women, and a larger part of the patients have a contact allergy as the total sensitivity rate is higher at the time of first test in comparison with patients only tested once. The group seems to have an increased susceptibility towards developing additional contact allergies as the total sensitivity rate and, in particular, the rate of patients with multiple contact allergies increase with tests performed. The increased susceptibility could be caused by an inherent ability to develop contact allergy as speculated for patients with multiple contact allergies (9, 23). But persistent skin disease and a defect skin barrier, which multiple-tested patients often have, can also increase susceptibility towards developing additional allergies (24). At the time of first test, there are no known characteristics which can identify patients who end up in this subpopulation. But patients for whom a second testing is needed have an increased risk of having multiple contact allergies, and preventive strategies such as avoiding known allergens as well as minimizing exposure to other frequent contact allergens could be introduced at this time.

It is generally perceived that patients with many contact allergies have a longer duration of disease and perhaps more severe and more widespread eczema. This perception has not to our knowledge been the focus of attention in any study. We show that a larger part of the patients with multiple contact allergies diagnosed at first patch test than patients with mono/double allergies end up being tested multiple times. Patients tested several times typically have more long-lasting and hard-to-treat eczema. The finding indicates that the perception about disease severity and disease duration of

multiple-allergic patients is correct. However, the significant difference between the 2 groups is small, and the finding needs to be further investigated in other studies.

Patients with multiple contact allergies are typically elderly women. Patients with 1 or 2 contact allergies exhibit a fairly constant sensitivity rate at different ages, whereas the rate of patients with multiple contact allergies increases with age. If genetics were the determining factor of development of multiple contact allergies, a larger part of the subgroup would probably be younger. A cumulative environmental exposure seems necessary in order to develop multiple contact allergies.

Unfortunately, 90% of multiple-allergic patients get diagnosed at first patch test in the hospital sector excluding the opportunity of primary prevention at this stage. Primary prevention must be executed at an earlier stage in the health care system but characteristics have yet to be established to identify patients at risk of developing multiple contact allergies. It is unknown if the rate is the same or lower when first patch tested in a private dermatology practice.

The population is constituted of eczema patients suspected of having a contact allergy referred to, diagnosed, and treated at a university hospital. The results do not give any information on patients treated in a private dermatology practice, at a primary health facility or on the patterns of contact allergy in the general population. The database provides a unique surveillance opportunity for identifying new culprit allergens or for local quality control of material preparations when fluctuations in sensitivity rates suddenly appear. Information on culprit allergens can lead to preventive strategies as we have seen for nickel (30), and consequences of legislation can be measured. Decreased sensitivity rates can show allergens no longer justified to be in screening series. Different subpopulations can be identified as presented in this study. Clinical epidemiological studies can bring about new information in our understanding of contact allergies. In Denmark we have the unique possibility of linking databases due to a unique personal identifier number assigned to each individual at birth, making identification of individuals over time possible. Results from linking of databases can extend our knowledge of contact allergies as an entity, e.g. in relation to other inflammatory diseases (31).

References

1. Jensen C D, Andersen K E. Course of contact allergy in consecutive eczema patients patch tested with TRUE test

- panels 1 and 2 at least twice over a 12-year period. *Contact Dermatitis* 2005; 52: 242–246.
2. Ayala F, Balato N, Lembo G et al. Statistical evaluation of the persistence of acquired hypersensitivity by standardized patch tests. *Contact Dermatitis* 1996; 34: 354–358.
 3. Katsarou A, Baxevas C, Armenaka M, Volonakis M, Balamotis A, Papamihail M. Study of persistence and loss of patch test reactions to dichromate and cobalt. *Contact Dermatitis* 1997; 36: 87–90.
 4. Menne T, Dooms-Goossens A, Wahlberg J E, White I R, Shaw S. How large a proportion of contact sensitivities are diagnosed with the European Standard Series? *Contact Dermatitis* 1992; 26: 201–202.
 5. Bruynzeel D P, Diepgen T L, Andersen K E et al. Monitoring the European Standard Series in 10 centres 1996–2000. *Contact Dermatitis* 2005; 53: 146–149.
 6. Schnuch A, Geier J, Uter W et al. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; 37: 200–209.
 7. Johansen J, Menne T, Christophersen J, Kaaber K, Veien N. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000; 142: 490–495.
 8. Nielsen N H, Menne T. Allergic contact sensitization in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Acta Derm Venereol* 1992; 72: 456–460.
 9. Moss C, Friedmann P S, Shuster S, Simpson J M. Susceptibility and amplification of sensitivity in contact dermatitis. *Clin Exp Immunol* 1985; 61: 232–241.
 10. Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; 50: 287–292.
 11. Bruynzeel D P, Andersen K E, Camarasa J G, Lachapelle J M, Menne T, White I R. The European Standard Series. European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1995; 33: 145–148.
 12. Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. *Allergy* 2005; 60: 372–378.
 13. Rees J L, Friedmann P S, Matthews J N. Sex differences in susceptibility to development of contact hypersensitivity to dinitrochlorobenzene (DNCB). *Br J Dermatol* 1989; 120: 371–374.
 14. Modjtahedi B S, Modjtahedi S P, Maibach H I. The sex of the individual as a factor in allergic contact dermatitis. *Contact Dermatitis* 2004; 50: 53–59.
 15. Krob H A, Fleischer A B Jr, D'Agostino R Jr, Haverstock C L, Feldman S. Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. test data. *J Am Acad Dermatol* 2004; 51: 349–353.
 16. Nielsen N H, Linneberg A, Menne T, Madsen F, Frolund L, Dirksen A, Jorgensen T. Persistence of contact allergy among Danish adults: an 8-year follow-up study. *Contact Dermatitis* 2001; 45: 350–353.
 17. Schlede E, Aberer W, Fuchs T et al. Chemical substances and contact allergy—244 substances ranked according to allergenic potency. *Toxicology* 2003; 193: 219–259.
 18. Mowad CM. Allergic contact dermatitis caused by parabens: 2 case reports and a review. *Am J Contact Dermat* 2000; 11: 53–56.
 19. Goh C L. Contact sensitivity to topical antimicrobials. (II) Sensitizing potentials of some topical antimicrobials. *Contact Dermatitis* 1989; 21: 166–171.
 20. Kligman A M. The myth of lanolin allergy. *Contact Dermatitis* 1998; 39: 103–107.
 21. Valsecchi R, Rossi A, Bigardi A, Pigatto P D. The loss of contact sensitization in man. *Contact Dermatitis* 1991; 24: 183–186.
 22. Hindsen M, Bruze M, Christensen O B. Individual variation in nickel patch test reactivity. *Am J Contact Dermat* 1999; 10: 62–67.
 23. Friedmann P S. The immunology of allergic contact dermatitis: the DNCB story. *Adv Dermatol* 1990; 5: 175–195.
 24. Kligman A M. The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol* 1966; 47: 375–392.
 25. Basketter D A, Griffiths H A, Wang X M, Wilhelm K P, McFadden J. Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. *Contact Dermatitis* 1996; 35: 208–213.
 26. Isaksson M, Brandao F M, Bruze M, Goossens A. Recommendation to include budesonide and tixocortol pivalate in the European Standard Series. ESCD and EECDRG. European Society of Contact Dermatitis. *Contact Dermatitis* 2000; 43: 41–42.
 27. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White I R. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999; 41: 241–250.
 28. Morris S D, Rycroft R J, White I R, Wakelin S H, McFadden J P. Comparative frequency of patch test reactions to topical antibiotics. *Br J Dermatol* 2002; 146: 1047–1051.
 29. Machet L, Couhe C, Perrinaud A, Hoarau C, Lorette G, Vaillant L. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. *Br J Dermatol* 2004; 150: 929–935.
 30. Menne T, Rasmussen K. Regulation of nickel exposure in Denmark. *Contact Dermatitis* 1990; 23: 57–58.
 31. Engkilde K, Menne T, Johansen J D. Inverse relationship between allergic contact dermatitis and type 1 diabetes mellitus: a retrospective clinic-based study. *Diabetologia* 2006; 49: 644–647.

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