

Monitoring the European standard series in 10 centres 1996–2000

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A 5-year retrospective study of the frequency of sensitization to the 25 allergens of the European standard series (ESS) was conducted in 10 centres in 8 European countries. Included were the results of 26 210 patients. The range in sensitivities differed moderately between the centres. Combining results of different centres and drawing conclusions on incidences can be done only with great care. The information on the ranking of the allergens and their sensitization incidence in the clinics are useful for decisions on the future composition of the standard series. The ESS is still a valid screening tool, and no substances should be deleted.

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The need for a revision of the Danish standard patch test series, which originally came from Bonnevie (1), and one basic test series in the Scandinavian countries in 1962 led to several investigations. These studies proved that contact allergies varied from country to country. The need was felt to undertake larger studies and to include other European countries. The International Contact Dermatitis Research Group (ICDRG) was formed: 7 European countries, 9 clinics, were represented. In 1969, they published an important paper on the clinical epidemiology of contact dermatitis (2). One of the main results was the outcome of patch testing 4825 patients and the differences in the frequencies between these European clinics. These investigations led to improved, more uniform patch testing and a European standard series (ESS). The standard series evolved to the basic series we are currently using; however, many substances used for testing have changed over the years. A basic series is always

subject to changes; as new allergens are introduced, our environmental exposure changes year by year.

The European Environmental and Contact Dermatitis Research Group (EECDRG) has taken over the European activities of the ICDRG. The EECDRG advises the European Society of Contact Dermatitis on changes in the ESS (3). Although the conclusion from almost 40 years ago remains valid that, due to regional differences in contact allergy, it is not accurate to add up the figures of clinics in different countries, we decided to present the data of the group. Recently, we compiled data from 10 years on preservatives (4). The results of such an investigation are informative, although they must be interpreted carefully (5). Therefore, we provide the results of patch testing with the basic series in the last 5 years of the 20th century, with the aim of indicating a ranking order of the allergens and to check if the series is still a valid screening tool. The investigation comprised 10 centres in 7 European countries and 26 210 patients.

Patients and Methods

The data were retrospectively compiled from 1996 to 2000. 10 European centres participated, covering a large part of the area involved in the study by the ICDRG in 1969. Included were consecutive patients attending the contact dermatitis clinic, in total 26 210 (Table 1).

Patch testing was based on the ICDRG guidelines, with an application time of 2 days (6). Readings were taken on days 2 and 3 or 4; the results are based on the, according to the clinic concerned, relevant reading, usually day 3 or 4. Finn Chambers[®] were used in 7 and Van der Bend Square Chambers[®] in 2 centres. One centre used the TRUE Test[®] system. Some centres tested particular allergens in a modified way or not routinely during the complete test period. These results were excluded.

A MOAHL index and the age distribution were not available. Therefore, it was not possible to perform a multivariate analysis and to adjust for these variables. All data analyses were performed by using the SAS statistical package. The *P* values given are descriptive and are based on the chi-squared test or Fisher's exact test.

Results

Table 2 gives the average sensitivity, in percentages, over 5 years for the allergens from the ESS in each centre. This has been calculated by combining the positive patch test results for each allergen over the study period for each centre. An overall average is also tabulated and split into male and female. There were no important sex differences when comparing the centres.

There is a moderate variation in range of sensitivity between the centres. This is clearly shown when we list top-10 of the most frequent sensitizers (Table 3). The top-10 gives, nevertheless, a reasonable picture of the 'problem' allergens in Europe. This is partly a distorted image as, for

example, none of the preservatives are in the top-10, but they would have ranked high if they were regarded as one group of allergens.

The frequencies of sensitizations in the centre in which the TRUE test[®] was used did not differ significantly from the frequencies found in other centres. There were no statistical differences between the centres for 10 allergens (Table 4).

Discussion

The ESS has not changed significantly in the study period (3, 7). Most clinics had added 2 corticosteroids, budesonide and tixocortol pivalate to the series, although this was not done officially until 2000. Therefore, these allergens were incorporated in the evaluation. This has the advantage that we will be able to compare the figures in the future from an earlier time point. Practically, all centres have their own additions and modifications in the series used for routine testing and have studies going on, explaining why no figures are available for some standard allergens. This did not really interfere with the overall results. One centre uses as standard the TRUE Test[®] material. Differences between the results with this material and allergens in petrolatum are possible (8). However, we found no significant differences between the centre which used this material and the other centres.

The considerable differences in sensitization incidence for at least 10–15 standard allergens are not surprising, we have known this for nearly 40 years (2), but surprisingly 10 allergens did not differ significantly. The reasons for the differences are multiple. Although the test method and readings are standardized and done by the EECDRG, according to ICDRG advice (6), readings and especially their interpretation may still differ. Environmental exposure to allergens can vary widely from region to region, even over relatively short distances. This results in a wide

Table 1. EECDRG centres who participated in the study and the number of patients tested with the European standard series 1996–2000. Included were 26 210 patients

Centres	Number of patients	Male (%)	Female (%)
Oulu, Finland	2542	28.6	71.4
Malmö, Sweden	3301	38.6	61.4
Odense, Denmark	2372	36.6	63.4
Copenhagen, Denmark	4180	33.9	66.1
Amersham, UK	3067	33.3	66.7
Leuven, Belgium	3286	33.2	66.8
Amsterdam, the Netherlands	2915	29.2	70.8
Dortmund, Germany	1956	45.7	54.3
Erlangen, Germany	2041	35.7	64.3
Almada (Lisbon), Portugal	550	37.3	62.7

Table 2. European standard series 1996–2000. Percentage of positive reactions by centre and the combined results

Allergen	Centre										Combined		
	Oul	Mal	Ode	Cop	Ame	Leu	Ams	Dor	Erl	Alm	Total	Male	Female
Nickel sulfate 5%	21.3	21.1	16.6	12.7	14.0	19.7	17.6	12.6	19.2	24.6	17.9	4.8	25.5
Cobalt chloride 1%	8.9	9.9	3.8	3.9	2.7	5.2	4.6	4.8	6.3	9.1	5.9	3.7	7.2
Potassium dichromate 0.5%	4.5	7.5	2.7	2.2	1.0	4.2	2.9	5.6	4.7	11.0	4.6	5.5	4.1
Fragrance mix 8%	6.7	8.3	10.6	11.0	5.0	11.2	12.8	10.4	12.4	8.4	9.7	7.2	11.1
Myroxylon pereirae 25%	5.2	5.5	–	5.3	2.8	6.5	6.2	7.6	10.9	3.9	6.0	5.1	6.7
Colophonium 20%	3.6	4.1	4.3	4.1	3.6	5.2	3.6	4.5	5.2	2.2	4.0	3.2	4.5
Formaldehyde 1%	4.3	2.3	2.9	3.2	2.3	1.4	2.0	1.8	1.5	0.9	2.3	2.0	2.4
Quaternium-15.1%	1.6	1.2	2.7	0.9	2.3	0.5	1.3	0.7	0.9	0.9	1.3	1.0	1.5
Cl + Me-isothiazolinone 0.01%	2.3	2.8	2.6	2.1	1.8	1.0	2.5	2.8	3.2	0.6	2.2	1.9	2.3
Parabens 16%	0.3	0.7	0.3	0.4	0.5	0.6	0.4	0.8	1.2	0.8	0.6	0.6	0.6
Thiuram mix 1%	2.4	1.4	3.5	2.6	2.5	2.4	2.9	3.2	3.9	7.0	3.2	3.5	3.1
IPPD 0.1%	0.8	0.5	–	0.4	0.8	0.7	0.8	0.7	1.5	1.5	0.9	1.3	0.7
Mercapto mix 2%	0.6	0.3	0.9	0.6	0.8	1.1	1.0	1.1	1.0	1.7	1.0	1.1	0.8
Mercaptobenzothiazole 2%	0.5	0.4	0.6	0.5	0.9	0.8	1.4	1.0	2.0	1.6	1.0	1.2	0.8
Neomycin sulfate 20%	7.7	3.0	1.6	2.4	3.0	1.9	1.6	2.5	3.6	2.9	3.0	3.2	2.9
Benzocaine (*caine mix) 5%	1.7	0.4	0.6*	0.5	1.6	2.0	2.1	1.4	2.3	2.3	1.6	1.5	1.7
Clioquinol (*quinoline mix) 5%	0.9	0.6	1.1*	0.3	0.9	0.5	0.7	1.7	1.4	0.4	0.8	1.2	0.6
Lanolin alcohol 30%	0.9	2.8	0.6	1.1	1.3	5.3	3.2	5.7	5.2	1.3	2.9	2.6	3.1
Budesonide 0.01%	0.6	0.1	–	–	0.5	2.0	0.8	5.2	1.0	2.3	1.6	0.9	2.0
Tixocortol pivalate 0.1%	3.0	0.7	–	–	1.3	2.0	0.7	1.0	–	0.7	1.3	1.0	1.6
p-Phenylenediamine base 1%	2.3	1.6	1.3	2.7	1.7	7.4	3.1	5.6	6.3	7.1	3.9	3.2	4.3
Epoxy resin 1%	1.2	0.8	2.1	1.1	0.8	1.3	1.4	0.9	2.0	1.6	1.3	1.7	1.1
PTBP-formaldehyde resin 1%	0.8	1.3	1.0	1.1	0.5	1.6	1.9	1.2	1.1	1.5	1.3	1.1	1.4
Primin 0.01%	0.1	0.9	1.0	1.2	0.8	0.4	0.6	1.1	0.0	–	0.7	0.1	1.0
Sesquiterpene lactone mix 0.1%	1.2	0.9	1.9	1.4	0.9	0.7	1.1	0.8	1.7	0.1	1.1	1.0	1.1

One centre used TRUE test[®] allergens.

The vehicle for the allergens is petrolatum.

IPPD = *N*-isopropyl-*N*-phenyl-4-phenylenediamine; PTBP = para-tertiary-butylphenol.

*Are dissolved in water.

variation of patients, a mix that can be completely different for each of the centres. Local industries but also regionally different therapeutic practices influence allergen exposure. For example, topical neomycin is still used frequently in some, but hardly at all in other, regions. Clinics may develop a particular interest in a special contact allergen, like corticosteroids, and will see, as a result of referral of suspected patients, an increase

in their numbers for the involved allergens. These differences also make clear that it is not simple to compose a basic series that is effective in all European regions. Regional additions may be needed (9). Data on the age distribution of the patients and a MOAHL index for each clinic would have been helpful in demonstrating the differences between the centres and adjusting for well-known factors influencing the distribution of positive sensitizations to different allergens. Multivariate analysis and sophisticated time-trend analysis are therefore not really possible with the present data.

Table 3. The 10 most frequent sensitizers in the standard series

Allergen	Overall %	Range %	Fregert et al. %
Nickel sulfate	17.9	12.6–24.6	6.8 (4)
Fragrance mix	9.7	5.0–12.6	NT
Myroxylon pereirae	6.0	2.8–10.9	6.0 (7)
Cobalt chloride	5.9	2.7–9.9	7.1 (3)
Potassium dichromate	4.6	1.0–11.0	7.6 (2)
Colophonium	4.0	2.2–5.2	3.5 (11)
p-Phenylenediamine base	3.9	1.3–7.4	5.7 (8)
Thiuram mix	3.2	1.4–7.0	NT
Neomycin	3.0	1.6–7.7	3.7 (10)
Lanolin alcohol	2.9	0.6–5.7	2.5 (13)

There is, however, a wide range in sensitization frequency between the different centres. The results of the study published in 1969 by Fregert et al. (2) are given in () as to the ranking order at that time.

NT = not tested/available.

Table 4. For many allergens, the frequencies differ between the centres

Colophonium
Quaternium-15
Parabens
Mercapto mix
Mercaptobenzothiazole
Clioquinol
PTBP-formaldehyde resin
Epoxy resin
Primin
Sesquiterpene lactone mix

No statistical difference ($P \leq 0.05$) was observed for 10 allergens. PTBP = para-tertiary-butylphenol.

In spite of such restrictions, the combined results provide useful information, depending on how they are used. They show which allergens or group of allergens form a demographic problem and indicate a rank order that is not very different between the clinics (Table 3).

It might be surprising that 13 of 20 original allergens from the ICDRG investigation are still in the current series; 8 are even in our top-10 (Table 3). The other 5 allergens are benzocaine, formaldehyde, mercaptobenzothiazole, parabens and clioquinol. This brings us to the question of which allergens belong in an international standard series. Fregert, quoted by Bruze et al. (10), suggested including an allergen when >0.5 – 1% of routinely tested patients react positively. All materials included in today's series fulfil this criterion. Even if the limit is $\geq 1\%$, only 4 allergens would be possible candidates for deletion *N*-isopropyl-*N*-phenyl-4-phenylenediamine (IPPD) (0.9%; range 0.4–1.5), clioquinol (0.8%; range 0.5–1.7), primin (0.7%; range 0–1.1) and parabens (0.6%; range 0.3–1.2). Regarding this range, one could argue that they all should stay. Another argument for keeping some of these materials is that, for example, an important but often a hidden allergen like IPPD would easily be missed as the history is often not clear. Primin has already the status of optional, as it is regarded as important only in some countries and areas. The overall conclusion is that the present ESS is still a valid screening tool.

An interesting option was proposed by Lachapelle et al. (11). They suggested an international basic test series of 20 allergens in combination with an additional series for regionally important materials.

The ICDRG study did not have a fragrance mix, because balsam of Peru (*Myroxylon pereirae*), colophonium, wood tar and turpentine were included as fragrance-allergy indicators. There is an overlap between these allergens. To obtain an impression of the proportion of patients with a possible fragrance allergy, we may compare the figures for balsam of Peru and colophonium. The figures from the 60s are of the same order as ours. The data must be interpreted cautiously, because fragrance composition, exposure and test method have changed considerably over the years, but it is tempting to conclude that possibly the fragrance problems have not changed in all these years.

The difference in nickel sensitivity is striking and has more than doubled. Maybe this is caused by a changing socio-economical situation in Europe with exposure to (inexpensive) jewellery and increased skin exposure to nickel. In contrast, the nickel legislation in Denmark, introduced in the 90s, has a decreasing effect on the sensitization rate (12).

Another intriguing allergen is dichromate. Although there is a moderate difference in results between our centres, just as in the ICDRG paper (2), the overall percentage of 4.6 suggests that the sensitization rate for dichromate is decreasing. This is probably not only due to addition of ferrous sulfate to cement as is done in some Scandinavian countries (in Denmark since 1981). Different measures to reduce the exposition to chromate via cement in construction workers might shed light on the importance of this source in the future (13).

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