

ORIGINAL ARTICLE

The European baseline series in Lithuania: results of patch testing in consecutive adult patients

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Summary

Background In Lithuania, data on patch testing are lacking and the applicability of the European baseline series needs to be evaluated.

Objective The aim of the study was to examine the prevalence of contact allergy to the European baseline series in the population of patients with suspected allergic contact dermatitis in Lithuania.

Methods Between April 2006 and October 2008, 816 consecutive adult patients referred to the Department of Skin and Venereal Diseases, Kaunas University of Medicine, with suspected allergic contact dermatitis were patch tested with the European baseline series. Demographic data were collected in accordance with the European Surveillance System on Contact Allergies 'minimal data set'.

Results The positive patch test was observed in 384 (47.4%) patients. The most prevalent contact allergens were nickel sulphate (17.1%), *Myroxylon pereirae* resin (8.0%), *p*-phenylenediamine (6.0%), methyl dibromo glutaronitrile (5.5%) and colophonium (5.0%). The sex and age factors strongly influenced the prevalence of nickel sensitization. The lowest sensitization prevalences were found to *N*-isopropyl-*N'*-phenyl-*p*-phenylene diamine (0.1%) and 2-mercaptobenzothiazole (0.1%). Differences in the sensitization prevalences to some allergens of the European baseline series compared with other European countries were recognized.

Conclusion The current European baseline series is a suitable diagnostic tool for contact allergy in Lithuania.

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Keywords

European baseline series, Lithuania, patch testing

Conflict of interest

None declared.

Introduction

The frequencies of sensitization to allergens of the European baseline series, often supplemented by region-specific contact allergens, are continuously analysed in most European countries.^{1–5} On the basis of resulting findings, the composition of the European baseline series is constantly revised (last modified in 2008⁶) and the relevance to allergen exposure is maintained.

However, in Lithuania data on patch testing are lacking and the applicability of the European baseline series to this country requires further evaluation. In 2004, the Department of Skin and Venereal Diseases, Kaunas University of Medicine, joined the European Surveillance System on Contact Allergies (ESSCA).⁷ This article provides the first results of patch testing in consecutive

adult patients. The aim of the study was to examine the prevalence of contact allergy to the European baseline series in the population of adult patients with suspected allergic contact dermatitis in Lithuania.

Patients and methods

Between April 2006 and October 2008, we prospectively recruited 816 consecutive adult (age 18 and above) patients referred to the Department of Skin and Venereal Diseases, Kaunas University of Medicine, with suspected allergic contact dermatitis. Demographic and clinical data on these patients were collected in accordance with the ESSCA 'minimal data set' (see: <http://www.ivdk.gwdg.de/>

essca/doc). Concomitant atopic dermatitis (past or current) was determined from medical documentation and/or by clinical examination at the time of patch testing using standard criteria of Hanifin and Rajka.⁸ Patch testing was then performed following to the guidelines of the International Contact Dermatitis Research Group.⁹ In the process, we used allergens of the European baseline series, proposed by the European Society of Contact Dermatitis in 2005 except for tixocortol-21-pivalate.¹⁰ Additionally, the patients were tested for hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) and fragrance mix II. All allergens were provided by Tro-lab Hermal, Reinbek, Germany. The allergens were applied for 48 h using Finn Chambers on Scanpor (Epitest Ltd Oy, Tuusula, Finland). Readings were performed at day 2 and day 3. Positive reactions between '+' and '+++' at day 3 were considered positive. The clinical relevance of positive reactions was evaluated in accordance with the ESSCA 'minimal data set' (see: <http://www.ivdk.gwdg.de/essca/doc>). Only 'current certain' relevance was considered in this study. The study was approved by the regional Bioethics Committee. Written informed consent was obtained from all the patients.

The accumulation, processing and statistical analysis of data were made using the software 'WinAlldat/Essca',⁷ SAS version 9.1 (The SAS Institute Inc., Cary, NC, USA) and SPSS version 13.0 (Chicago, IL, USA) following current guidelines.¹¹ In view of the exploratory nature of analyses, no alpha adjustment techniques were employed. Sensitization rates were standardized for age on the basis of two age groups (below 40 and 40 and above years) of equal size and for sex on the standard distribution of 35% men and 65% women according to the recommendation on PAFS (population adjusted frequency of sensitization).¹²

Results

During the study 816 consecutive adult patients with suspected allergic contact dermatitis were patch tested. The age of the patients ranged from 18 to 87 years [median = 46, interquartile range (IQR) 31–57]. The duration of the symptoms of dermatitis ranged from one to 504 months (median = 12, IQR 4–36). Common occupations included office work (11.95%), cleaners (4.02%), mathematicians and statisticians (3.54%), teachers (3.41%), sales persons (2.8%), nursing and midwifery (2.56%), medical doctors (2.32%), cooks (1.71%), tailors (1.71%), legislators, senior officials and managers (1.71%), builders and building finishers (1.69%), electrical technicians (1.22%), cashiers (1.1%).

34.02% of patients were not formally employed at the time of the study: retirees (13.29%), unemployed (8.66%), students and pupil (7.8%), housewives (4.27%).

Descriptive characteristics of the tested population according to the MOALFHA index are presented in Table 1. At least one positive patch test reaction (positive patch test) was observed in 384 (47.4%) patients. The proportion of positive patch tests was significantly lower among men than women (40.5% vs. 49.9%, $P = 0.017$). The frequencies of positive patch test reactions to individual allergens in all tested patients as well as for age and sex subgroups separately are presented in Table 2. Women under 40 years were sensitive to nickel almost four times more often than older ones (37.7% vs. 10.5%, $P < 0.0001$). Current clinical relevance was certain in 58.6% of positive patch test reactions. The percentages of currently relevant positive reactions to individual allergens are presented in Table 2.

Among the patients with atopic dermatitis, the patch test was positive in 46.5%. In these patients, as opposed to those without atopic dermatitis, a higher sensitization prevalence to methyl-dibromomethyl glutaronitrile (MDBGN) was found: 9.0% vs. 4.8% respectively ($P = 0.042$).

Among the patients with primary hand dermatitis, the patch test was positive in 48.7% of the cases. Higher sensitization prevalences to nickel sulphate (21.2% vs. 14.0%, $P = 0.008$) and *Myroxylon pereirae* resin (11.4% vs. 7.2%, $P = 0.045$) were observed in these patients, when compared with the patients with other primary sites of dermatitis.

Among the patients with primary facial dermatitis, the patch test was positive in 41.2% of the cases. In this subgroup, a lower sensitization prevalence was determined to *Myroxylon pereirae* resin (4.8% vs. 10.2% in the patients with other primary sites of dermatitis, $P = 0.01$).

Of 78 patients with primary leg dermatitis, the patch test was positive in 57.7%. In this subgroup, significantly higher sensitization prevalences to colophonium (17.9% vs. 4.3%, $P < 0.0001$), benzocaine (16.7% vs. 1.4%, $P < 0.0001$), lanolin alcohol (9.0% vs. 1.5%, $P < 0.0001$), neomycin sulphate (3.8% vs. 0.8%, $P = 0.015$), 5-chloro-7-iodo-8-quinolinol (3.8% vs. 0.4%, $P = 0.001$) and *N*-isopropyl-*N'*-phenyl-*p*-phenylene diamine (1.3% vs. 0%, $P = 0.002$) were revealed than in the patients with other primary sites of dermatitis. Conversely, nickel sulphate showed a lower percentage of positive reactions: 5.1% vs. 17.6% in the patients with primary dermatitis at sites other than legs ($P = 0.005$).

Table 1 Descriptive characteristics of test population ($N = 816$) according MOALFHA index

	Male	Occupational dermatitis	Atopic dermatitis	Primary site: hand	Primary site: leg	Primary site: face	Age 40 and above
	M	O	A	H	L	F	A
Number of patients	215	192	144	273	78	250	496
Proportion (%)	26.3	23.5	17.9	33.5	9.6	30.6	60.8

Table 2 Patch test results in all the patients tested with the European baseline series: number, crude rate, standardized for age and sex rate with 95% confidence interval (CI), relevance of positive reactions, stratified for age rates and in male and female subgroups: crude rate, standardized for age rate with 95% CI of positive reactions

Substance	Concentration (%)	Total (N = 816) n	% positive crude	% positive standardized (95% CI)	Relevance (%)	Age < 40 (n = 320) % positive	Age ≥ 40 (n = 496) % positive	Male (n = 215) % positive crude	% positive standardized (95% CI)	Female (n = 601) % positive crude	% positive standardized (95% CI)
Nickel sulphate	5.0	134	16.4	17.1 (14.6–19.5)	62	28.8	8.5	3.7	4.0 (1.3–6.8)	21.0	24.1 (20.6–27.6)
Myroxylon pereirae resin	25	70	8.6	8.0 (6.1–9.9)	57	4.7	11.1	9.3	9.1 (5.2–13.0)	8.3	7.4 (5.4–9.4)
p-Phenylenediamine	1.0	47	5.8	6.0 (4.3–7.8)	57	5.9	5.6	7.9	7.9 (4.2–11.6)	5.0	5.0 (3.2–6.8)
Colophonium	20	46	5.6	5.0 (3.6–6.5)	48	3.4	7.1	3.7	3.3 (1.1–5.6)	6.3	5.9 (4.1–7.8)
Methyldibromo glutaronitrile	0.3	45	5.5	5.5 (3.9–7.1)	73	5.0	5.8	6.1	6.1 (2.9–9.5)	5.3	5.1 (3.4–6.9)
Cobalt (II) chloride	1.0	40	4.9	5.6 (3.9–7.4)	53	8.8	2.4	5.6	5.9 (2.6–9.2)	4.7	5.5 (3.5–7.5)
Fragrance mix I	8.0	33	4.0	3.6 (2.3–4.8)	67	2.2	5.2	2.8	2.7 (0.5–4.9)	4.5	4.1 (2.5–5.6)
Potassium dichromate	0.5	33	4.0	4.4 (2.9–6.0)	58	4.7	3.6	6.5	6.5 (3.2–9.9)	3.2	3.3 (1.8–4.8)
Paraben mix	16	26	3.2	3.5 (2.1–4.9)	62	3.8	2.8	5.1	5.4 (2.2–8.5)	2.5	2.5 (1.2–3.8)
Formaldehyde*	1.0	24	2.9	3.1 (1.8–4.4)	71	4.1	2.2	2.8	2.9 (0.6–5.2)	3.0	3.2 (1.7–4.8)
Benzocaine	5.0	23	2.8	2.9 (1.7–4.1)	48	2.2	3.2	4.2	4.2 (1.5–7.0)	2.3	2.1 (1.0–3.8)
Fragrance mix II	14	21	2.6	2.5 (1.4–3.6)	52	3.1	2.2	1.4	1.4 (0.0–2.9)	3.0	3.2 (1.7–4.8)
Methylchloroisothiazolinone/ Methylisothiazolinone*	0.01	19	2.3	2.2 (1.2–3.3)	53	2.2	2.4	1.9	1.6 (0.1–3.1)	2.5	2.6 (1.3–3.9)
Linolin alcohol	30	18	2.2	2.1 (1.1–3.1)	72	0.9	3.0	3.3	2.8 (0.8–4.8)	1.8	1.7 (0.7–2.8)
Epoxy resin	1.0	12	1.5	1.6 (0.7–2.5)	42	1.9	1.2	1.9	1.6 (0.1–3.1)	1.3	1.6 (0.5–2.7)
Neomycin sulphate	20	9	1.1	0.9 (0.3–1.6)	0	0.3	1.6	0.9	0.8 (0.0–1.9)	1.2	1.0 (0.3–1.8)
Quaternium-15	1.0	9	1.1	1.2 (0.4–1.9)	33	2.2	0.4	0.0	–	1.5	1.8 (0.6–3.0)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	7	0.9	0.9 (0.2–1.6)	71	1.3	0.6	0.9	0.8 (0.0–1.9)	0.8	1.0 (0.1–1.9)
Sesquiterpene lactone mix	0.1	7	0.9	0.8 (0.2–1.4)	29	0	1.4	1.4	1.2 (0.0–2.5)	0.7	0.5 (0.01–1.1)
Thiuram mix	1.0	6	0.7	0.6 (0.1–1.1)	67	0.3	1.0	0.0	–	1.0	0.9 (0.2–1.6)
Primin	0.01	6	0.7	0.5 (0.1–1.0)	50	0	1.2	0.0	–	1.0	0.8 (0.2–1.5)
5-Chloro-7-iodo-8-quinolinol	5.0	6	0.7	0.7 (0.1–1.4)	67	0.3	1.0	1.4	1.4 (0.0–2.9)	0.5	0.4 (0.0–0.9)
4-tert-Butylphenol formaldehyde resin	1.00	6	0.7	0.6 (0.1–1.2)	83	0.6	0.8	0.0	–	1.0	1.0 (0.2–1.8)
Budesonide	0.01	4	0.5	0.5 (0.0–0.9)	100	0	0.8	0.9	0.8 (0.0–1.9)	0.3	0.3 (0.0–0.6)
Mercapto mix (only CBS, MBTS, MOR)	1.0	2	0.3	0.2 (0.0–0.6)	100	0	0.4	0.5 (0.0–1.2)	–	0.2 (0.0–0.4)	–
N-isopropyl-N'-phenyl-p- phenylene diamine (IPPD)	0.10	1	0.1 (0.0–0.4)	–	100	0	0.2	0.5 (0.0–1.2)	–	0.0	–
2-Mercaptobenzothiazole	2.0	1	0.1 (0.0–0.4)	–	100	0	0.2	0.5 (0.0–1.2)	–	0.0	–

Allergens were tested in petrolatum, except (*) in water.

In bold – significant differences in age and sex subgroups ($P < 0.05$).

Discussion

In this study, we provide the first results of patch testing of consecutive adult patients with the European baseline series in Lithuania. Like in other European countries, nickel was found to be the leading allergen in Lithuania, with the sex and age factors strongly influencing the prevalence of nickel sensitization. Our analysis, in line with the previous research findings in the area, also revealed much higher sensitization rates to nickel sulphate in women than in men and in younger women than in older ones. These differences are accounted for by distinct sex- and age-related patterns of nickel exposure, mainly by early ear piercing and the ensuing wearing of nickel-releasing jewellery, popular among women at a young age.^{13–15} In Lithuania, the European Parliament and Council Directive 94/27/EEC¹⁶ that prohibits trading in consumer products intended to be in direct and prolonged contact with the skin for which the level of nickel release exceeds 0.5 µg/cm²/week, entered into force at the beginning of 2003. Since September 2005, subsequent restriction on the use of alloys releasing nickel in amounts of 0.2 µg/cm²/week or higher for piercing post assemblies and certain other products (see: Commission Directive 2004/96/EC¹⁷) has been implemented in the country. Further studies are required to assess the regulatory impact of the above-mentioned EU Directives on national sensitization rates to nickel.

The contact allergy to potassium dichromate in European countries varies from 1.0% in the United Kingdom to 11.0% in Portugal.¹ Our data (4.4% of standardized positive reactions) is close to the average observed by European multicentre studies.^{1,4,5} Occupational exposure to chromates can explain the higher prevalence of sensitization found in men than in women. Pursuant to the EU Directive 2003/53/EC,¹⁸ legislation limiting the maximum allowable amounts of soluble chromium (IV) in cement, the main source of occupational exposure to chromates, has been enacted in Lithuania since the beginning of 2005. As in the case of nickel, this regulatory framework is expected to reduce the incidence of chromate allergy in the future.¹⁹

After metals, fragrances were the second most important group of allergens in our study. Besides two classic indicators for fragrance allergy, namely, *Myroxylon pereirae* resin and fragrance mix I, we also tested fragrance mix II and HICC, which have been recently included to the European baseline series.⁶ Contact sensitivity to *Myroxylon pereirae* resin was found in 5.7–5.8% and to fragrance mix I in 6.4–7.2% of the patch test population of European multicentre studies.^{4,5} However, our analysis revealed higher sensitization prevalence to *Myroxylon pereirae* resin, yet lower to fragrance mix I. The sensitization prevalence to fragrance mix II was 2.5% (95% CI 1.4–3.6) in our study, the result which not only supports the incorporation of the mix into the European baseline series, but is also contiguous to the values of 2.9%²⁰ or 4.7%²¹ shown in other studies. By contrast, the prevalence of sensitization to HICC was only 0.9% (95% CI 0.2–1.6) as distinct from 1.9% to 2.8% referred to in other

European studies.^{4,22–24} These variations can arguably be associated with different levels of exposure to fragrances. Constituents of fragrance mix II other than HICC might be more important in the case of Lithuania.

The sensitization prevalence to *p*-phenylene diamine (PPD) was found higher in Lithuania than in European multicentre studies (3.1–4.6%^{4,5,25}). Contrary to the well known proposition that permanent hair dyes are the main cause of contact allergy to PPD,²⁶ thus women rather than men tend to be more exposed²⁷ and sensitized to the allergen in Europe,^{25,28} we found a higher, although not significantly, sensitization prevalence to PPD in men (7.9% vs. 5.0%). The discrepancies between the sensitization profile presented in our analysis and in other European studies should presumably be ascribed to differences in exposure to PPD. Besides the exposure to hair dyes as client or after self-application, occupational exposure to hair dye, paint- and rubber-associated exposures, as well as exposures to certain clothing and shoe materials might be other important sources of contact allergy to PPD.²⁹

Among the preservatives, MDBGN and paraben mix were the foremost allergens. Our study was launched 1 year after the use of MDBGN in leave-on cosmetic products³⁰ was prohibited, yet it ran before the ban on the use of the substance in rinse-off cosmetics³¹ came into effect. The high sensitization prevalence to MDBGN reported in our study supports these regulatory measures. Sensitization prevalence to paraben mix was discovered markedly above the 0.6–1.2% range found in multicentre European studies.^{1,4,5,32} This discrepancy in sensitization of relatively safe and ubiquitous preservatives is hard to explain as is the higher frequency of paraben sensitization in men. According to a recent study of the IVDK, 1.7% (CI 1.6–1.9) of men reacted to the parabens, compared to 1.2% (CI 1.1–1.3) in women.³³

Of the other allergens tested, the sensitization prevalences to neomycin sulphate, thiuram mix, 4-tert-butylphenol formaldehyde resin, budesonide, *N*-isopropyl-*N'*-phenyl-*p*-phenylene diamine, 2-mercaptobenzothiazole were lower than those reported in other European studies.^{1–5,34} Conversely, sensitivity to colophonium, cobalt (II) chloride, formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, lanolin alcohol, epoxy resin, quaternium-15, sesquiterpene lactone mix, primin and 5-chloro-7-iodo-8-quinolinol did not differ prominently.^{1–5,34}

Most detected allergens of the European baseline series were currently relevant in more than 50% of cases. However, current clinical relevance of positive reactions to colophonium, benzocaine, epoxy resin, neomycin sulphate, quaternium-15 and sesquiterpene lactone mix was certain in less than 50% of cases.

To be included in a baseline series, a contact allergen has to elicit positive reactions at a rate above 0.5–1.0% in routinely patch tested patients.³⁵ Against this recommendation, exclusion of *N*-isopropyl-*N'*-phenyl-*p*-phenylene diamine and 2-mercaptobenzothiazole might be considered: the upper limit of the 95% CI was less than 0.5%.

In conclusion, the first results of patch testing of consecutive adult patients with suspected allergic contact dermatitis indicate that the current European baseline series is a suitable diagnostic tool for contact allergy in Lithuania. Differences in the sensitization prevalences to some allergens of the European baseline series compared with other European countries possibly imply differences in allergen exposure.

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