

Time trends of contact allergy to the European baseline series in Lithuania

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Summary

Background. Monitoring trends of positive patch test reactions is useful for epidemiological surveillance and contact allergy prevention, and has not previously been reported in Lithuania.

Objectives. To examine and compare changes in the prevalence of contact allergy to European baseline series allergens in adults with suspected contact dermatitis during a 9-year period.

Methods. In this retrospective study, patch test results of 297 consecutive patients, tested with the European baseline series in 2014–2015, were analysed and compared with the data published earlier in Lithuania.

Results. The most common allergens were nickel sulfate (30.6%), methylisothiazolinone (MI) (13.5%), methylchloroisothiazolinone (MCI)/MI (7.4%), potassium dichromate (6.1%), cobalt chloride (6.1%), *Myroxylon pereirae* resin (5.4%), *p*-phenylenediamine (5.4%), fragrance mix I (4.7%), formaldehyde (4.4%), and methyl dibromo glutaronitrile (3.7%). Increases in the prevalence of sensitization to MCI/MI (2.3% in 2006–2008 and 7.4% in 2014–2015; $p < 0.0001$) and nickel sulfate (16.4% in 2006–2008 and 30.6% in 2014–2015; $p < 0.0001$) and decreases in the prevalence of sensitization to paraben mix (3.2% in 2006–2008 and 0.3% in 2014–2015; $p = 0.006$) were observed. Prevalences for the other allergens remained stable or showed a decreasing trend (*Myroxylon pereirae* resin; $p = 0.06$).

Conclusion. This study provides current information on the prevalence of contact allergy in Lithuania. Changing trends in sensitivity to some allergens probably reflect changes in exposure.

Key words: contact allergy; epidemiology; European baseline series; MCI/MI; nickel sulfate; paraben mix; time trends.

Patch testing is used to investigate causes of contact allergy and allergic contact dermatitis (ACD). The most important contact allergens are traditionally assembled in a baseline series, which is usually applied to every

patient who is patch tested as a general screening test (1). Monitoring time trends of contact allergy allows evaluation of the need for, and effectiveness of, preventive measures. High allergy prevalences can prompt attempts to decrease exposure nationally or at the European level. The aims of our study were to (i) analyse the prevalences of contact allergy to the European baseline series in consecutively tested dermatitis patients at Vilnius University Santariskiu Klinikos, and (ii) to compare these with the compiled patch test data obtained in 2006–2012 at dermatology and allergy clinics in Lithuania.

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Table 1. MOAHLEAP characteristics of the tested population

Characteristics	2014–2015		2010–2012		2006–2008	
	N	Positive reaction, n (%)	N	Positive reaction, n (%)	N	Positive reaction, n (%)
Male	297	40 (13.5)	214	26 (12.1)	816	215 (26.3)
Occupational	297	0 (0)	214	0 (0)	816	192 (23.5)
Atopic dermatitis	297	70 (23.6)	214	155 (72.4)	816	144 (17.9)
Hand	297	91 (30.7)	214	61 (28.5)	816	273 (33.5)
Leg	297	16 (5.4)	214	34 (15.9)	816	78 (9.6)
Face	297	140 (47.3)	214	119 (55.6)	816	250 (30.6)
Age >40 years	297	161 (54.4)	214	84 (39.3)	816	496 (60.8)
Positivity (≥ 1 positive reaction)	297	164 (55.4)	214	115 (53.7)	816	384 (47.4)

N, number of tested patients; n, (%), number (percent) positive reactions.

Methods

In this retrospective study, we analysed patch tests results of the 297 consecutive patients referred to our clinic in 2014–2015 with suspected ACD. Demographic data are shown according to the MOAHLEAP (male, occupational, atopic, hand, leg, foot, age >40 years, percentage positive to at least one baseline series allergen) set of descriptors (Table 1) (2). We also compared the data with the results of the previous studies performed in 2006–2008 (816 patients referred to a dermatology department) and in 2010–2012 (214 patients referred to an allergy department) (3, 4).

Patch testing was performed and scored according to ESCD guidelines (5). The allergens were provided by Chemotechnique Diagnostics (Vellinge, Sweden). Finn Chambers® (diameter, 8 mm; Epitest, Tuusula, Finland) on Scanpor® tape (Norgesplaster, Vennesla, Norway) were used for patch testing. Fifteen microlitres of liquid test solution was applied with a micropipette to the filter paper discs in the chambers, and 20 mg of test preparations in pet. was applied to the test chambers (6, 7). The chambers were applied and left on the back for 48 h, and readings were performed on day (D) 3, D4 and D7 by an allergologist trained to perform patch testing. In 2010–2012, patch testing was performed by an allergologist using the same methodology and performing readings on D3, D4, and D7 (4). In 2006–2008, patch tests were performed with allergens from Trolab Hermal (Reinbek, Germany) applied with Finn Chambers® (Epitest, Helsinki, Finland), and readings were performed by a dermatologist on D2 and D3 (3). For the present analysis, the maximum patch test reactions from either D3/D4 or D7 were considered as an outcome. Reactions from '+' to '+++' were classified as positive and negative, and irritant or doubtful reactions were classified as non-positive. Atopy was defined according to the nomenclature of the European Academy of Allergy and Clinical Immunology (8).

The data were analysed with Microsoft Excel spreadsheet software. The χ^2 -test or Fisher's exact test was used where appropriate (if $n \leq 5$). All results were expressed as prevalences with 95% confidence intervals, and the threshold for statistical significance was predefined as a p -value of <0.05.

Results

The demographics of patch tested patients are summarized in Table 1. The most common locations of dermatitis were the face (47.3%), hands (30.7%), and legs (5.4%). Of the 297 tested patients, 164 (55.4%) had at least one positive patch test reaction. The frequencies of positive patch test reactions to individual allergens in all tested patients are shown in Table 2. Younger patients were patch test-positive to nickel sulfate almost two times more often than older ones (40.4% versus 22.4%, $p = 0.001$). Women were significantly more often patch test-positive to nickel sulfate than men (34.6% versus 5%, $p < 0.0001$). Older patients were sensitized to fragrance mix I more often than younger patients (7.5% versus 1.5%, $p = 0.02$). The most frequent allergens were nickel sulfate (30.6%), methylisothiazolinone (MI) (13.5%), and methylchloroisothiazolinone (MCI)/MI (7.4%) (Table 2). When allergens were grouped, contact allergies to metals (127/296, 42.8%) and preservatives (93/296, 31.3%) were most common (Table 3). The age distribution of patients with contact allergy to nickel and MI is shown in Fig. 1.

An atopic history was present in 70 (23.6%) of the tested patients. At least one positive patch test reaction was detected in 44 (62.9%) of them. Nearly half of the patch test-positive atopic patients were sensitized to nickel sulfate (45.5%), and it seems that they were more sensitive to nickel than non-atopics, although the difference did not reach statistical significance ($p = 0.07$). According to statistical analysis, more patients with an

Table 2. Frequencies of positive patch test reactions to the European baseline series in 2014–2015

No.	Substance	Concentration (%)	Total, n = 297		95%CI	Age <40 years (n = 136)	Age >40 years (n = 161)		Male (n = 40)		Female (n = 257)	
			n positive	% positive			n/% positive	n/% positive	n/% positive	(95% CI)	n/% positive	(95% CI)
1.	Nickel sulfate	5.0	91	30.6	25.7–36.2	55/40.4*	36/22.4*	2/5**	0.5–17.4	89/34.6**	29.9–40.6	
2.	Methylisothiazolinone	0.2	40	13.5	10–17.2	18/13.2	22/13.7	4/10	3.4–23.6	36/14.0	10.3–18.8	
3.	Methylisothiazolinone/ methylchlorisothiazolinone	0.02	22	7.4	4.9–11.0	9/6.6	13/8.1	1/2.5	0–14	21/8.2	5.3–12.2	
4.	Potassium dichromate	0.5	18	6.1	3.8–9.4	9/6.6	9/5.6	1/2.5	0–14	17/6.6	4.1–10.4	
5.	Cobalt(II) chloride hexahydrate	1.0	18	6.1	3.8–9.4	11/8.1	7/4.3	1/2.5	0–14	17/6.6	4.1–10.4	
6.	<i>Myroxylon perei</i> resin	25.0	16	5.4	3.3–8.7	4/2.9	12/7.5	2/5.0	0.5–17.4	14/5.4	3.2–9.0	
7.	<i>p</i> -Phenylenediamine	1.0	16	5.4	3.3–8.7	10/7.4	6/3.7	1/2.5	0–14	15/5.8	3.5–9.5	
8.	Fragrance mix I	8.0	14	4.7	2.8–7.8	2/1.5***	12/7.5***	1/2.5	0–14	13/5.1	2.9–8.5	
9.	Formaldehyde ^a	2.0	13	4.3	2.5–7.4	4/2.9	9/5.6	1/2.5	0–14	12/4.7	2.6–8.1	
10.	Methyldibromo glutaronitrile	0.5	11	3.7	2.0–6.6	2/1.5	9/5.6	3/7.5	1.8–20.5	8/3.1	1.5–6.1	
11.	Neomycin sulfate	20.0	7	2.4	1.0–4.9	3/2.2	4/2.5	1/2.5	0–14	6/2.3	0.9–5.1	
12.	Colophonium	20.0	7	2.4	1.0–4.9	4/2.9	3/1.9	1/2.5	0–14	6/2.3	0.9–5.1	
13.	Quaternium-15	1.0	6	2.0	0.8–4.5	3/2.2	3/1.9	1/2.5	0–14	5/1.9	0.7–4.6	
14.	Fragrance mix II	14.0	6	2.0	0.8–4.5	2/1.5	4/2.9	0/0	–	6/2.3	0.9–5.1	
15.	Sesquiterpene lactone mix	0.1	5	1.7	0.6–3.9	2/1.5	3/1.9	1/2.5	0–14	4/1.6	0.4–4.1	
16.	Benzocaine	5.0	4	1.4	0.4–3.5	1/0.7	3/1.9	0/0	–	4/1.6	0.4–4.1	
17.	Thiuram mix	1.0	3	1.0	0.2–3.1	2/1.5	1/0.6	1/2.5	0–14	2/0.8	0.03–2.9	
18.	Lanolin alcohol	30.0	3	1.0	0.2–3.1	1/0.7	2/1.2	0/0	–	3/1.2	0.02–3.5	
19.	Mercaptobenzothiazole	2.0	2	0.7	0–2.6	1/0.7	1/0.6	0/0	–	2/0.8	0.03–2.9	
20.	Paraben mix	16.0	1	0.3	0–2.1	0/0	1/0.6	1/2.5	0–14	0/0	–	
21.	<i>N</i> -isopropyl- <i>N</i> -phenyl- <i>p</i> -phenylenediamine	0.1	1	0.3	0–2.1	1/0.7	0/0	0/0	–	1/0.4	0–2.4	
22.	Epoxy resin	1.0	1	0.3	0–2.1	1/0.7	0/0	0/0	–	1/0.4	0–2.4	
23.	<i>p</i> -tert-Butylphenol formaldehyde resin	1.0	1	0.3	0–2.1	1/0.7	0/0	0/0	–	1/0.4	0–2.4	
24.	Tixocortol-21-pivalate	0.1	1	0.3	0–2.1	1/0.7	0/0	1/2.5	0–14	0/0	–	
25.	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	1	0.3	0–2.1	1/0.7	0/0	0/0	–	1/0.4	0–2.4	
26.	Textile dye mix	6.6	1	0.3	0–2.1	1/0.7	0/0	0/0	–	1/0.4	0–2.4	
27.	Quinolol	5.0	0	0	–	0/0	0/0	0/0	–	0/0	–	
28.	Mercapto mix	2.0	0	0	–	0/0	0/0	0/0	–	0/0	–	
29.	2-Methoxy-6-n-pentyl-4-benzoquinone	0.01	0	0	–	0/0	0/0	0/0	–	0/0	–	
30.	Budesonide	0.01	0	0	–	0/0	0/0	0/0	–	0/0	–	

CI, confidence interval; n, number of patients.

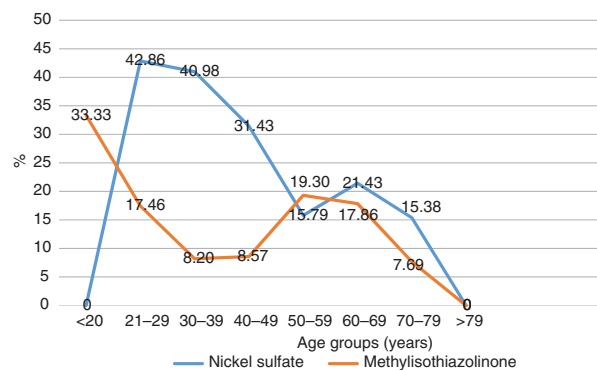
Chi-square or Fisher's exact test (if $n \leq 5$).Significant results ($p < 0.05$) are shown in bold.^a1.0% aq. until 31 December 2014.* $p = 0.0002$.** $p < 0.0001$.*** $p = 0.02$.

Table 3. Sensitization prevalences and differences in positive patch test reactions to common contact allergens

Allergen group	2014–2015 % (positive test reactions/total tests)	2010–2012 % (positive test reactions/total tests)	2006–2008 % (positive test reactions/total tests)	p-value*
Metals: potassium dichromate, cobalt chloride, nickel sulfate	14.5 (127/891)	13.1 (84/642)	8.5 (207/2448)	<0.0001
Preservatives: paraben mix, formaldehyde, quaternium-15, methylchloroisothiazolinone/methylisothiazolinone, methyltribromo glutaronitrile, methylisothiazolinone	5.2 (93/1782)	3.7 (48/1283)	3.0 (123/4080)	<0.0001
Plants: colophonium, <i>Myroxylon pereirae</i> resin, sesquiterpene lactone mix	3.1 (28/891)	3.2 (21/642)	5.0 (123/2448)	0.021
Fragrances: fragrance mix I, fragrance mix II, hydroxyisohexyl 3-cyclohexene carboxaldehyde	2.4 (21/891)	3.7 (16/428)	2.5 (61/2448)	0.82
Dyes: <i>p</i> -phenylenediamine	5.3 (16/297)	4.2 (9/214)	5.8 (47/816)	0.81
Drugs: neomycin, benzocaine, clioquinol, budesonide, tixocortol	0.8 (12/1485)	1.0 (9/856)	1.3 (42/3264)	0.15
Rubber chemicals: thiuram mix, isopropylphenylphenylenediamine, mercapto mix, mercaptobenzothiazole	0.6 (5/891)	0.8 (5/642)	0.3 (8/2448)	0.35
Resins: epoxy resin, <i>p</i> -tert-butylphenol formaldehyde	0.3 (2/594)	1.2 (5/428)	1.1 (18/1632)	0.13

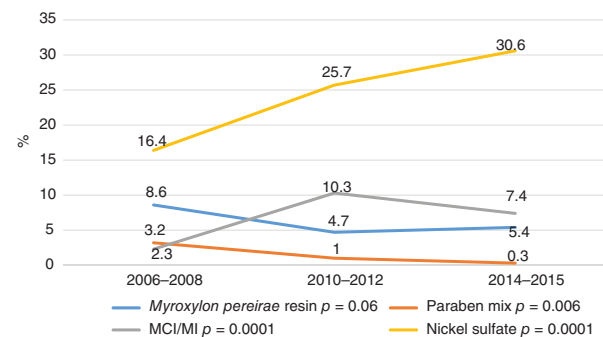
* χ^2 -test or Fisher's exact test (if $n \leq 5$).

Significant results ($p < 0.05$) are shown in bold.

**Fig. 1.** Sensitization to nickel sulfate and methylisothiazolinone in different age groups.

atopic history than non-atopics were sensitized to drugs (neomycin, benzocaine, clioquinol, budesonide, and tixocortol; $p = 0.03$). There was a trend towards more positive reactions to plant materials [colophonium, *Myroxylon pereirae* resin (MPR), and sesquiterpene lactone mix] in atopic patients ($p = 0.05$).

Primary facial dermatitis was diagnosed in 80 (57.1%) of the patients, and the main contact sensitizers in this group were nickel sulfate (43/80, 53.4%), MI (20/80, 25%), and MPR (11/80, 13.8%), with no statistical significance as compared with dermatitis in other locations. Patch tests were positive in 51 (56%) patients with hand dermatitis. The most common allergens for the patients

**Fig. 2.** Statistically significant changes in sensitization over the years. MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

with primary hand dermatitis were metals (nickel, cobalt, and potassium dichromate) (43/51, 84.3%). Of 16 patients with primary leg dermatitis, 6 (37.5%) had at least one positive patch test reaction.

Statistically significant increases in sensitization to MCI/MI (2.3% in 2006–2008 and 7.4% in 2014–2015; $p < 0.0001$) and nickel sulfate (16.4% in 2006–2008 and 30.6% in 2014–2015; $p < 0.0001$) and decreases in sensitization to paraben mix (3.2% in 2006–2008 and 0.3% in 2014–2015; $p = 0.006$) were observed. Contact allergy prevalences for the other allergens remained largely stable or showed a decreasing trend (MPR; $p = 0.06$) (Fig. 2).

Discussion

In the present article, we report contact allergy trends among patients observed at Lithuanian patch test clinics. Sensitization prevalences for 27 allergens were compared over the period 2006–2015. The crude prevalence had decreased for 10 allergens, remained unchanged for 10 allergens, and increased for 7 allergens; for 2 of these, the increase was statistically significant.

In this study, patients with atopic dermatitis are over-represented, especially in the study performed in 2010–2012 (4). This could be related to the different traditions in referring patients. In Lithuania, as in most eastern European countries, atopic dermatitis is considered to be mainly an allergic disease, both by patients and by clinicians. Thus, almost all patients diagnosed with atopic dermatitis are referred first to the allergologist and later to the dermatologist. In Scandinavia and most western European countries, atopic dermatitis is diagnosed and treated mostly by dermatologists.

The main contact allergens in Lithuania are metals (nickel, potassium dichromate, and cobalt). The main allergen of the group is nickel, age and sex strongly influencing the prevalence of sensitization. These results refer to sex-related and age-related patterns of nickel exposure, early ear piercing, and contact with nickel-releasing jewellery. The frequency of sensitization to nickel sulfate nearly doubled, from 16.4% in 2006–2008 to 30.6% in 2014–2015, on the background of the European Directive regulating nickel release from metal items having been approved in Lithuania in 2002 (9, 10). In 1990, Denmark was the first European country to start regulating nickel release from consumer products, including jewellery. According to Thyssen et al., the decrease in nickel sensitization began 16 years after the regulation, and mainly depended on the time of piercing, before or after the regulation (11). According to the trend line for nickel sensitization in Lithuania and the time of the Directive approval, the decrease in sensitization to nickel should start in 2018–2020. The shifting of nickel allergy to the older age group (>40 years) can be expected in the future.

Preservatives constituted the second most prevalent group of allergens. The top 10 allergens remained the same in the 9-year period except for MI, which appeared in 2014–2015. There was no previous information on contact allergy to MI in Lithuania, as MI was added to the European baseline series in 2014 in Lithuania. Since 2000, MI alone has been allowed in industrial products, and in 2005 the highest recommended concentration in leave-on and rinse-off cosmetics was limited to 0.01%, but the concentration was left unrestricted in industrial fluids. MI is a weaker antimicrobial and is

considered to be a weak sensitizer (12, 13). The first data showing that MI sensitization had increased were obtained in 2004 (14). Our results confirm Belgian and French experience (15, 16), and are in agreement with the sensitization frequency for MI in Finland (which is the highest reported so far) (16). The prevalence of sensitization to MCI/MI is higher than that reported in the reference literature, and amounts to 2–4% (15, 17). Our study shows a marked increase in the prevalence of sensitization to MCI/MI, which has risen to 7.4% over a period of 9 years. This study and some other studies indicate that this could be explained by sensitization to MI (15). Also, MCI/MI and/or MI were present in 50% of the investigated cosmetic products on the Lithuanian market, so they are the most prevalent preservatives used in the cosmetics available in Lithuania (18). Facing the MI contact allergy epidemic (19), the organization representing the industry, Cosmetics Europe, advised its members late 2013 that MI should not be used in leave-on products. The Scientific Committee on Consumer Safety advised that, additionally, the MI concentration in rinse-off cosmetics should be lowered to 15 ppm (0.0015%) (20).

Methyldibromo glutaronitrile (MDBGN) has not been permitted in leave-on cosmetic products since 2005, and has not been permitted in any cosmetic products since 2008 (21). MDBGN is, however, allowed in other types of product, without limitation. A decline in contact allergy to this allergen has been shown since 2008 in different countries. We found a decrease in sensitization to MDBGN from 5.5% in 2006 to 3.7% in 2015. We also noticed a significant decrease in sensitization to paraben mix, which is consistent with the data from other countries. Parabens are the preservatives that have been most commonly used in cosmetic, pharmaceutical and industrial products since 1930 (22). Previous studies have shown that parabens are relatively non-sensitizing preservatives, even in atopic populations (23). However, the cosmetic industry started a campaign to be 'paraben-free', and fewer people may buy products with parabens, owing to putative associations of parabens with certain types of cancer. We noticed increasing sensitization to formaldehyde (2.9% versus 4.3%) and a formaldehyde releaser, namely quaternium-15 (1.1% versus 2 %) over a period of 9 years. The increased use of formaldehyde releasers in cosmetics could be an explanation for this (24), as could the increased test concentration of formaldehyde, which might be capable of diagnosing more positive cases. Also, it was found that some cosmetics produced in Lithuania (as well as in other European countries) contain formaldehyde even if they are labelled as not containing it (18). The use of such products might theoretically facilitate sensitization to formaldehyde.

In our study, sensitization to MPR showed a decreasing trend over time, from 8.6% in 2006 to 5.4% in 2015, although the difference was non-significant. Thyssen et al. showed that the frequency of contact allergy to MPR decreased significantly from 1999 (5.4%) to 2007 (2.6%) (22). Uter et al. found an increase in the prevalence of sensitization to MPR from 1999 (6.4%) to 2012 (8.5%) (24). Our results can be explained by changes in the daily habits of many people, who are showing a preference to use ecofriendly and fragrance-free cosmetics, and household cleaning fluids containing natural ingredients. The use of crude MPR in perfumery is banned; however, it is used in extracts and distillates (22). Sensitization to fragrance mix I (4.0% versus 4.7%) and fragrance mix II (2.6% versus 2%) has showed no change since 2006. Lower frequencies of sensitization to fragrances than in other European countries was already noted in 2006–2008 (3). Patients aged >40 years are more often sensitized to fragrances, MPR, and colophonium. This may be associated with more frequent use of natural medicine, which is linked to statistically significant sensitization to fragrance mix I in older patients. One theoretical explanation could be that the use of fine fragrances and deodorants has increased only over the last 25 years, because during the Soviet occupation, these items were not easily available to the general population.

Sensitization to rubber chemicals has not changed significantly over the last 9 years: mercapto mix, 0.3% in 2006–2008 versus 0% in 2014–2015; mercapto-benzothiazole, 0.1% versus 0.7%; and thiuram mix, 0.7% versus 1.0%. Overall, sensitization to rubber chemicals increased from 1.2% in 2006–2008 and 1.6% in 2010–2012 to 2.0% in 2014–2015, without a statistically significant difference. Similar results were obtained in Sweden (4); the sensitization prevalence is slightly above 3.1% in Denmark, as published by Schwensen et al. in 2016 (25). The low frequency of sensitization to rubber chemicals could be explained by the lower number of patients being referred because of occupational dermatitis. The prevalence of contact allergy to *p*-phenylenediamine remains high, at 5.4% (5.8% in 2006–2008 and 4.2% in 2010–2012), and is higher

than that in Sweden [2.3% (4)] and The Netherlands (3.3%) published in 2015 (26). It is a common habit in Lithuania to dye hair at home. During this process, much more dye may come in direct contact with the skin than during dyeing at a hairdressing salon.

This study shows data for subgroups for 2006–2008, 2010–2012, and 2014–2015, which were collected from earlier published studies, and this is considered to be a limitation. Also, the relevance of the positive reactions was not recorded. The study is retrospective, and the referral patterns for patch testing differ in all of the allergy and dermatology clinics. However, the data were obtained from two clinics using the same methodology for patch testing (except for the D7 reading at a dermatology clinic in 2006–2008), and the physicians performing the patch tests were specially trained.

Lower prevalences of sensitization to some allergens were detected, and these could be a sign of decreasing sensitization. In 2002–2008, nickel, chromium and MDBGN were subjected to regulations that resulted in a decrease in exposure to them, and there was also a decrease in exposure to parabens, owing to voluntary restriction of its use by the cosmetic industry. The actual exposure to some allergens (e.g. *M. pereirae* balsam) is more uncertain. Although we have identified some changes in contact allergy prevalence, this may not necessarily reflect changes in contact sensitization in the general population.

Conclusion

This retrospective study provides an up-to-date view on the prevalence of contact allergy to allergens of the European baseline series in Lithuania. Changing trends in sensitivity for some contact allergens probably reflect increasing changes in exposure. Population-based studies could add more and valuable information.

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