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Patch test results in children and adolescents across Europe Analysis of the ESSCA Networkª 2002-2010

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ABSTRACT

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Patch test results in children and adolescents across Europe

Analysis of the ESSCA network[a] 2002-2010

Background: contact sensitization in children is more frequent than previously thought.

Methods: the ESSCA collected patch-test data from 11 European countries aggregated to 4 European regions.

Results: 6708 patients aged 1-16 years old with suspected allergic contact dermatitis were analysed during a period of 8 years (2002-2010). The overall prevalence of at least one positive reaction to a hapten was 36.9%. The 10 most frequent haptens were: nickel sulfate, cobalt chloride and potassium dichromate, neomycin sulfate, *Myroxylon pereirae* resin (balsam of Peru), para-phenylendiamine, chloromethylisothiazolinone/methylisothiazolinone 3:1, fragrance mix, lanolin alcohols and colophony. No difference was found in the prevalence of at least one positive reaction to at least one hapten between boys and girls

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and between children with atopic dermatitis and children without. Children without atopic dermatitis, when compared with those with, had a significantly higher prevalence of contact sensitization for nickel sulfate (20.91% vs 16.87% respectively), 4-tert.butylphenol formaldehyde resin (1.61% vs. 0.7%) and para-phenylendiamine (2.49% vs. 1.3%).

Limitations of the study: chamber loading is not an exact science and variation may occur between staff and departments. Inter-institution variations in readings can occur. A possible geographical confounder is that the southern regions tested more children in the younger age group.

Relevance was not addressed due to difficulties in the application of a set of uniform definitions.

Conclusions: Our study adds information on the most common contact allergens detected in children which could help to define a Standard European *Pediatric* Baseline Series.

Key words: allergic contact dermatitis, atopic dermatitis, children, contact allergy, epidemiology, ESSCA, patch test, sensitization.

Abbreviations:

ACD	Allergic Contact Dermatitis
AD	Atopic Dermatitis
EBS	European Baseline Series
ESSCA	European Surveillance System on Contact Allergies

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MCI/MI Chloromethylisothiazolinone/Methylisothiazolinone 3:1 (e.g, Kathon ® CG)

PPD Para-phenylendiamine

INTRODUCTION

Contact sensitization in children is increasingly recognized. However there are still few sufficiently large epidemiological studies on this subject. [1,2,3] The aim of our study was to evaluate contact sensitization in a large cohort of children and adolescents with suspected ACD (allergic contact dermatitis) who were patch tested at centres of the ESSCA (European Surveillance System on Contact Allergies) network from 2002 to 2010.

METHODS

Our retrospective analysis was based on data from the ESSCA network. The ESSCA network has already been described in previous publications. [4,5] Briefly, clinical and demographic data, along with patch test results obtained with the EBS (European Baseline Series), of all patients patch tested in the departments participating in ESSCA are documented electronically in the local departments, using diverse data capture software and partly the multilingual software WinAlldat/ESSCA provided by ESSCA. [6]

All centres used their usual baseline series which included haptens common to all centres and some haptens specific to the individual centres, but not specifically related to history or geographical area. The results refer to consecutive patients in order to minimise selection bias due to selective testing.

Test results with the TrueTest® baseline series were considered separately for better comparability.

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For the present analyses, 6708 children and adolescents patch tested in the years 2002 to 2010 were considered and subdivided into 3 age groups: 1 to 5, 6 to 12, and 13 to 16 years. Table 1.

Centres were aggregated to 11 European Countries and further to 4 European regions, as previously described. [4] The distribution of these age groups in the countries and regions is shown in table 1.

All patients had a suspected diagnosis of ACD. Patch testing followed international recommendations. [7] The maximum patch test reaction between day 3 and day 5 (inclusive) was considered as outcome. Reactions designated as either 1+, 2+ or 3+ were classified as positive.

In cases where patch testing with the baseline series had been repeated within the study period, the first patch testing results were chosen. We calculated the overall prevalence of at least one positive reaction to a hapten of the EBS in the study population, in the different age groups and in children with and without AD (atopic dermatitis). AD was evaluated according to the Hanifin and Rajka criteria. [8] Patients in whom information about AD was missing were excluded from this latter analysis.

Data were pooled in the ESSCA data centre in Erlangen for further analysis, using R (version 3.1.0) software [9] and following pertinent guidelines for the analysis of patch test data. [10] Sensitization frequencies in the 3 age strata are given as crude prevalences, accompanied by a 95% CI (confidence interval). Interval estimates (confidence intervals) are considered more appropriate for the descriptive, exploratory purpose of the present analysis than abundant statistical hypothesis testing.

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RESULTS

Data of 6708 patients were analysed. The prevalence of at least one positive reaction to a hapten of the EBS series in the study population was 2476 (36.9%), including tests both with petrolatum-based, investigator-loaded systems (overall positive: 36.5%), and baseline series including TRUE-test® allergens (overall positive: 39.5%, used in *n*= 210 children). The study population included 3965 girls and 2743 boys. The prevalence of at least one positive reaction to the EBS among girls of the study population was 1451 (36.6%), among boys was 987 (36%). *p*=0.72. The prevalence of at least one positive reaction in children of 1-5 years was 45.3%, in children of 6-12 years was 33.3% and in children of 13-16 years was 34.4%. The difference in prevalence of at least one positive reaction was statistically significant between group 1 and group 2 and between group 1 and group 3 ($p<0.001$ each). The 10 most frequent haptens in the study population were: nickel sulfate (16.7%), cobalt chloride (7.5%), potassium dichromate (5.2%), neomycin sulfate (3.2%), *Myroxylon pereirae* resin (2.6%), para-phenylendiamine (PPD, 2.5%), chloromethylisothiazolinone/methylisothiazolinone 3:1 (MCI/MI, 2.4%), fragrance mix (2.3%), lanolin alcohols (1.8%) and colophony (1.4%).

In the subgroup (*n*=210) tested with TRUE-test® allergens, the corresponding prevalences were: nickel sulfate (22.9%), cobalt chloride (3.4%), potassium dichromate (1.9%), neomycin sulfate (0.5%), *Myroxylon pereirae* resin (1.9%), PPD (1.4%), MCI/MI (3.4%), fragrance mix (3.4%), lanolin alcohols (1%) and colophony (4.3%).

In the patients tested with primin (n= 2959) and 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol, n= 521) there were no positive reactions. Table 2.

The prevalence of contact sensitization to some haptens (nickel sulfate, neomycin sulfate, and potassium dichromate) was higher in children of group 1 compared with children of

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group 2 or group 3. Conversely, the prevalence of contact sensitization to a number of other haptens (2-MBT, colophony, fragrance mix 1, and PPD) was higher in children of group 2 and group 3 compared with children of group 1. The prevalence of positive reactions to each hapten of the EBS for each age group is shown in table 2 with 95% CI.

The number of patients with past (*n*=2523) or current (*n*=720) diagnosis of AD, with considerable overlap, was 2644, while the number of patients who had never suffered from AD was 2498. Information about previous or current diagnosis of AD was missing in 1566 patients; these patients were not included in the following analyses involving presence of AD. The prevalence of at least one positive reaction to an hapten of the EBS in patients who had never suffered from AD was (39.7%), the prevalence of at least one positive reaction in patients who had a past or current diagnosis of AD was (37.7%), *p*=0.14.

In a sensitivity analysis, the prevalence of at least one positive reaction to an EBS allergen *excluding nickel* was compared between different subgroups. No statistically significant difference in the prevalence of at least one positive reaction to a hapten, excluding nickel, was found when comparing boys and girls (*p*=0.066), patients with *vs.* without AD (*p*=1) or between the three age groups (*p*=0.077).

Neither age (*p*=0.31) nor gender (*p*=0.44, test) differed significantly between patients with current or past diagnosis of AD vs. children who had never suffered from AD, hence the comparison of sensitization prevalences was not confounded by these two factors.

We also calculated the prevalence of 1+ reactions for each allergen in children with AD and in children without and no statistically significant difference was found. Table 3.

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The 10 most frequent haptens in children with AD were: nickel sulfate (16.87%), cobalt chloride (7.85%), potassium dichromate (6.85%), neomycin sulfate (3.52%), *Myroxylon perairae* (3.07%), fragrance mix (2.56%), lanolin alcohols (2.17%), MCI/MI (2.06%), sesquiterpene lactone mix (1.72%). The 10 most frequent haptens in children without AD were: nickel sulfate (20.91%), cobalt chloride (8.31%), potassium dichromate (5.39%), neomycin sulfate (4.43%), MCI/MI (3.22%), *Myroxylon pereirae* resin (2.95%), PPD (2.49%), fragrance mix (1.94%), lanolin alcohols (1.91%), thiuram mix (1.7%). Children without AD, compared to children with AD, had a significantly higher prevalence of contact sensitization for nickel sulfate (see above), 4-tert. butylphenol formaldehyde resin (1.61% and 0.7%, respectively), and PPD (2.49% and 1.3%, respectively). Table 3.

The geographical distribution across the 4 'European regions' represented in the ESSCA networks of the prevalence of positive reactions to EBS haptens has been analysed. Table 4a, 4b and 4c. It should be noted that 'West' exclusively corresponds to the United Kingdom, and that 'Northeast' includes 2 departments with a focus on occupational skin disease (FIOH, Helsinki and Nofer Institute, Lodz).

Finally, time trends for nickel and fragrance mix were addressed by a descriptive analysis, stratified for geographic region. Figure 1.

DISCUSSION

Our multi-centre international retrospective study on 6708 patch tested children, the largest study of this kind, confirms that contact sensitization in children is frequent. [1,2,3] The highest sensitization rate was found in children between the ages of 1 and 5 years. This high prevalence is not easy to explain; it is possibly due to stricter selection criteria when patch

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testing very young children or possibly due to more false-positive reactions in the very young. [11] Another possible confounding geographical factor is that the younger age group is dominated by the southern regions. However similar high prevalences have been reported by other authors not only from similar areas [12,13] but also from different areas and continents [1,3].

As can be seen from table 4a, 4b and 4c, there are regional differences in the frequency of contact sensitization to single haptens. However the top 10 allergens were substantially the same in all European regions and in all age groups. Furthermore, the proportion of children with positive reaction to at least one hapten of the EBS was high in all European regions.

The most frequent haptens in our study population were: metals (nickel sulfate, potassium dichromate and cobalt chloride), neomycin sulfate, *Myroxylon pereirae*, PPD, MCI/MI, fragrance mix, lanolin alcohols and colophony. These findings are in agreement with most recent epidemiological reports. [3,13,14,15] The prevalence of nickel sensitization in patch tested children is reported in the literature to vary between 6% and 27%. [13,16] In our study population the overall prevalence of contact sensitization to nickel was 16.7% and thus within the range of commonly observed sensitisation frequencies. Nickel remains the most frequent contact allergen in all our age groups, despite the EU Nickel Directive (currently under [REACH 2009]). [17] Thus it would seem that in many countries the Directive only partially protects the consumers effectively from new nickel sensitization. [18,19] Recent studies have revealed that some white gold jewellery from the Italian market and some earrings sold in London and in Warsaw, release nickel at concentrations capable of inducing contact allergy to this metal. [20,21] However there is a decrease in positive reactions to nickel in the last few years. Figure 1. It must also be underlined that positive nickel patch test

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reactions in very young children may be of low clinical relevance and are often not reproducible. [11]

The high sensitization prevalence for fragrance mix observed in our population of children (2.3%) confirms other reports. [3,22,23,24] This finding is not surprising, as fragrances are ubiquitous in the environment, including not only toys, but also cosmetics and fragrances specifically targeted at children. [23,25]

The increasing prevalence in positive reactions to fragrance mix showed from our data could point to increasing exposure and sensitization of children and adolescents. Figure 1.

The prevalence of sensitization to PPD greatly increases over age: 0.65 % in group 1, to 1.31% in the middle group, to 5.25% in the oldest group, probably as a result of a progressive exposure over time. This high prevalence of PPD sensitization in children requires special attention. A widely discussed cause of sensitization is temporary tattoos painted with henna that may be supplemented with PPD. It has been shown that henna tattoos may contain > 15% PPD. [26] Hair dyes may seem a source of marginal importance for children but children may become sensitized to PPD coming in close contact with their mother's dyed hair. [13] Furthermore, in adolescents self-exposure to oxidative hair dyes may start at an early age: in a Danish study, the median age of first dyeing was 16, [27] with half of the persons starting at 16 or younger. Other possible causes of exposure to PPD are fur dyes, textiles or industrial rubber products. Positive reactions to PPD may also be an expression of cross-reactivity with textile azo-dyes present in stockings and footwear. [28,29]

The prevalence of contact sensitization to MCI/MI was high (2.4%), as it has been widely used, since the 1980s, as preservative in cosmetic products, such as wet wipes, detergents

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and moisturizers. It must be pointed out that recent studies have demonstrated the importance of including also MI in the standard patch test series as MCI/MI may fail to detect sensitisation only to MI, [30] which increased to epidemic proportions due to the massive increase in cosmetic and other exposures. [25,31]

A topic much debated is the difference in contact sensitization between children with AD and children without. Therefore, we calculated the prevalence of sensitization in these two groups of children separately. In view of the very similar age- and sex-distribution of both subgroups compared, confounding by these two important markers of exposure or possibly also susceptibility appears unlikely. As regards the prevalence of at least a positive reaction to a hapten of the EBS, in our study population we found virtually no difference between children with AD and children without. This finding is in accordance with other studies. [12,13,14,32] Nickel sensitization is often caused by piercing, which bypasses the epidermal barrier presumably impaired in AD. This route of sensitization may introduce a bias in the analysis if not addressed separately. [33] Thus we also calculated the overall prevalence of at least one positive reaction disregarding nickel. Again, we found no statistical difference between children with AD and children without. As 1+ reactions might sometimes be irritants and not true positives, especially in children with AD, we calculated the prevalence of 1+ reactions and 2+/3+ reactions separately: we found no statistically significant difference in the prevalence of 1+ reactions between children with AD and children without. Table 3.

Children without AD show a significantly higher prevalence of contact sensitization for: nickel, 4-tert.butylphenol formaldehyde resin and PPD. From a purely speculative point of view, this higher prevalence might be possibly explained by the fact that children without AD do not perform the environmental prevention that is often performed in children with AD

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and thus, over the years, may become more frequently sensitized to the most common haptens. [32]

Finally, as regards primin and 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol), the baseline series used in Germany, Austria and Switzerland do not include these two allergens because they are regarded as too rare to be included in the baseline series.

We found no positive reactions to these two allergens in the population tested (2959 patients tested with primin and 521 tested with clioquinol); therefore we suggest that routine testing is not necessary with these allergens, at least in pediatric patients.

In children it is often difficult to determine the relevance, as it is difficult to know with what children have come into contact during their daily activities. For this reason and because of the difficulty in using a common approach in such a large study involving many different centres, we did not evaluate relevance for the aim of this study.

Conclusions: contact sensitization does not always lead to ACD, however, as our study underlines, contact sensitization is quite common also in young children and this should be kept in mind when dermatitis does not respond to conventional treatments.

Our study also adds some information on the most common allergens detected in children and this may help us to define a Standard European Baseline *Pediatric* Series.

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Table 1: Distribution of patients in the three age groups across the countries represented. The age distribution in the regions is significantly heterogeneous (Chi² test: $p<0.0001$).

Country	Shorthand	Age 1-5	Age 6-12	Age 13-16
United Kingdom	UK	206 (9.4%)	961 (43.8%)	1026 (46.8%)
West	W	206 (9.4%)	961 (43.8%)	1026 (46.8%)
Spain	ES	14 (12.1%)	50 (43.1%)	52 (44.8%)
Italy	IT	1326 (40.7%)	1376 (42.3%)	553 (17%)
Slowenia	SI	1 (1.3%)	31 (39.2%)	47 (59.5%)
South	S	1341 (38.9%)	1457 (42.2%)	652 (18.9%)
Austria	AT	0 (0%)	15 (13.8%)	94 (86.2%)
Switzerland	CH	7 (3.5%)	44 (22%)	149 (74.5%)
Germany	DE	25 (9.5%)	92 (35%)	146 (55.5%)
Denmark	DK	5 (5.8%)	36 (41.9%)	45 (52.3%)
Netherlands	NL	21 (8.4%)	80 (31.9%)	150 (59.8%)
Central	C	58 (6.4%)	267 (29.4%)	584 (64.2%)
Finland	FI	0 (0%)	21 (36.8%)	36 (63.2%)
Poland	PL	2 (2%)	36 (36.4%)	61 (61.6%)
Northeast	NE	2 (1.3%)	57 (36.5%)	97 (62.2%)
Total		1607(24%)	2742(40.9%)	2359(35.2%)

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Table 2: Results with the European Baseline Series in children and adolescents, stratified into 3 age groups: crude percent positive with 95% confidence interval (CI).

	Age 1-5			Age 6-12			Age 13-16		
Allergen	Nr. tested	% pos.	(95% CI)	Nr. tested	% pos.	(95% CI)	Nr. tested	% pos.	(95% CI)
2-Mercaptobenzothiazole	1575	0.25	(0.07-0.65)	2686	1.08	(0.72-1.55)	2296	1	(0.64-1.5)
4-tert. butylphenol formaldehyde resin	1570	1.34	(0.83-2.04)	2648	1.02	(0.67-1.48)	2298	0.48	(0.24-0.85)
5-Chloro-7-iodo-8-hydroxyquinoline	19	0	(0-14.59)	190	0	(0-1.56)	312	0	(0-0.96)
Benzocaine	1333	0.45	(0.17-0.98)	1550	0.06	(0-0.36)	872	1.49	(0.8-2.54)
Budesonide	1515	0.07	(0-0.37)	2442	0.12	(0.03-0.36)	1714	0.23	(0.06-0.6)
Cl+Me-isothiazolinone (w)	1583	3.1	(2.3-4.07)	2673	2.06	(1.55-2.67)	2276	2.24	(1.67-2.94)
Cobalt(II) chloride	1527	9.36	(7.95-10.94)	2618	7.91	(6.9-9.01)	2289	5.85	(4.93-6.9)
Colophony	1586	0.5	(0.22-0.99)	2687	1.45	(1.03-1.98)	2306	2.04	(1.5-2.7)
Epoxy resin	1549	0.32	(0.1-0.75)	2637	0.3	(0.13-0.6)	2296	0.44	(0.21-0.8)
Formaldehyde (w)	1101	0.45	(0.15-1.06)	2175	0.18	(0.05-0.47)	2242	0.85	(0.51-1.32)
Fragrance mix	1567	0.96	(0.54-1.57)	2679	2.39	(1.84-3.04)	2307	2.99	(2.33-3.77)

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Fragrance Mix II	175	1.14	(0.14-4.07)	825	1.33	(0.67-2.37)	1098	1.28	(0.7-2.13)
HICC (Lyral)	213	0	(0-1.4)	1128	0.27	(0.05-0.78)	1735	0.52	(0.24-0.98)
Lanolin alcohols	1573	2.67	(1.93-3.59)	2637	1.59	(1.15-2.15)	2282	1.49	(1.03-2.08)
Mercapto mix	230	0.43	(0.01-2.4)	1139	1.05	(0.55-1.83)	1383	0.87	(0.45-1.51)
Mercapto mix (only CBS,MBTS,MOR)	49	2.04	(0.05-10.85)	277	2.17	(0.8-4.65)	692	0.29	(0.04-1.04)
Methyldibromoglutaronitrile	257	1.17	(0.24-3.37)	1285	0.16	(0.02-0.56)	1841	0.49	(0.22-0.93)
Methyldibromoglutaronitrile + 2-PE	1329	0.38	(0.12-0.88)	1389	0.5	(0.2-1.04)	520	1.92	(0.93-3.51)
Methylisothiazolinone (w)	91	0	(0-3.24)	390	0	(0-0.77)	416	0	(0-0.72)
Myroxylon Pereirae resin	1290	2.48	(1.7-3.48)	2334	3.26	(2.57-4.06)	2235	1.92	(1.4-2.58)
Neomycin sulphate	1575	4.76	(3.76-5.93)	2634	3.91	(3.2-4.72)	2082	1.25	(0.82-1.82)
Nickel sulphate	1588	26.7	(24.54-28.95)	2692	13.22	(11.97-14.56)	2303	13.94	(12.55-15.42)
N-isopropyl-N’-phenyl-p-phenylenediamine	1563	0.9	(0.49-1.5)	2585	0.62	(0.35-1)	2147	1.35	(0.91-1.93)
Paraben mix	1553	0.45	(0.18-0.93)	2618	0.57	(0.32-0.94)	2264	0.8	(0.47-1.25)
Potassium dichromate	1572	9.16	(7.78-10.7)	2648	5.4	(4.57-6.33)	2295	2.35	(1.77-3.06)
p-Phenylenediamine	1544	0.65	(0.31-1.19)	2586	1.31	(0.91-1.83)	2133	5.25	(4.34-6.28)

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Primin	233	0	(0-1.28)	1205	0.08	(0-0.46)	1521	0	(0-0.2)
Quaternium-15	1547	0.32	(0.11-0.75)	2480	0.48	(0.25-0.84)	1715	0.35	(0.13-0.76)
Sesquiterpene lactone mix	238	1.68	(0.46-4.25)	1207	1.16	(0.64-1.94)	1542	0.52	(0.22-1.02)
Thiuram mix	298	1.68	(0.55-3.87)	1433	0.42	(0.15-0.91)	2119	1.04	(0.65-1.57)
Tixocortol-21-pivalate	1467	0.48	(0.19-0.98)	2321	0.52	(0.27-0.9)	1629	0.49	(0.21-0.97)

Cl+Me-isothiazolinone: Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) 3:1. All allergens in petrolatum, except where indicated otherwise: [w)] water.

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Table 3: results with the European Baseline Series in children with *versus* without current or previous atopic dermatitis ("AD"): crude percent positive with 95% confidence interval (CI). *p*-value is for Fisher test of the proportion of weak positive patch test reactions in one group vs. that of all other reactions, vs. the respective proportions in the other group.

	with AD					without AD					p- value
Allergen	Nr. tested	Nr. + (%)	Nr. ++/+++	% pos.	(95% CI)	Nr. tested	Nr. + (%)	Nr. ++/+++	% pos.	(95% CI)	Nr. + AD vs. w/o AD
2-Mercaptobenzothiazole	2575	4(0.16)	5	0.35	(0.16-0.66)	2436	7(0.29)	10	0.7	(0.41-1.12)	0.57
4-tert. butylphenol formaldehyde resin	2555	11(0.43)	6	0.7	(0.42-1.11)	2417	14(0.58)	25	1.61	(1.15-2.2)	0.55
5-Chloro-7-iodo-8-hydroxyquinoline	210	0(0)	0	0	(0-1.42)	205	0(0)	0	0	(0-1.45)	nd
Benzocaine	1560	3(0.19)	0	0.19	(0.04-0.56)	2027	7(0.35)	6	0.69	(0.38-1.16)	0.53
Budesonide	2238	2(0.09)	1	0.13	(0.03-0.39)	1971	0(0)	2	0.1	(0.01-0.37)	0.50
Cl+Me-isothiazolinone (w)	2568	24(0.93)	29	2.06	(1.55-2.69)	2424	28(1.15)	50	3.22	(2.55-4)	0.49
Cobalt(II) chloride	2523	122(4.84)	71	7.85	(6.83-8.97)	2370	123(5.19)	71	8.31	(7.23-9.5)	0.60
Colophony	2587	12(0.46)	13	0.97	(0.63-1.42)	2443	17(0.70)	19	1.56	(1.1-2.13)	0.35
Epoxy resin	2543	7(0.28)	0	0.28	(0.11-0.57)	2399	8(0.33)	3	0.46	(0.23-0.82)	0.62
Formaldehyde (w)	2169	10(0.46)	2	0.55	(0.29-0.96)	1829	8(0.33)	3	0.6	(0.3-1.07)	1.0
Fragrance mix	2577	48(1.86)	15	2.56	(1.99-3.25)	2424	32(1.32)	14	1.94	(1.43-2.57)	0.15
Fragrance Mix II	1011	9(0.89)	1	1.19	(0.61-2.06)	415	4(0.96)	1	1.69	(0.68-3.44)	1.0

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HICC (Lyral)	1137	2(0.18)	1	0.26	(0.05-0.77)	669	1(0.15)	1	0.45	(0.09-1.3)	1.0
Lanolin alcohols	2539	42(1.65)	10	2.17	(1.64-2.81)	2408	34(1.41)	12	1.91	(1.4-2.54)	0.56
Mercapto mix	964	2(0.21)	2	0.41	(0.11-1.06)	375	0(0)	2	0.53	(0.06-1.91)	1.0
Mercapto mix (only CBS,MBTS,MOR)	411	2(0.49)	1	0.73	(0.15-2.12)	495	2(0.40)	0	0.81	(0.22-2.06)	1.0
Methyldibromoglutaronitrile	1234	3(0.24)	3	0.65	(0.28-1.27)	663	2(0.30)	2	0.6	(0.16-1.54)	1.0
Methyldibromoglutaronitrile + 2-PE	1368	6(0.44)	4	0.73	(0.35-1.34)	1799	5(0.28)	6	0.61	(0.31-1.09)	0.55
Methylisothiazolinone (w)	583	0(0)	0	0	(0-0.51)	73	0(0)	0	0	(0-4.02)	nd
Myroxylon Pereirae resin	2278	52(2.28)	16	3.07	(2.4-3.87)	2035	39(1.91)	20	2.95	(2.26-3.78)	0.46
Neomycin sulphate	2474	78(3.15)	8	3.52	(2.83-4.32)	2300	80(3.48)	22	4.43	(3.63-5.36)	0.57
Nickel sulphate	2591	227(8.76)	207	16.87	(15.44-18.36)	2444	241(9.86)	265	20.91	(19.31-22.58)	0.19
N-isopropyl-N'-phenyl-p-phenylenediamine	2451	12(0.49)	4	0.69	(0.4-1.11)	2325	15(0.65)	7	0.95	(0.59-1.43)	0.56
Paraben mix	2517	11(0.44)	5	0.72	(0.42-1.13)	2378	8(0.34)	2	0.5	(0.26-0.88)	0.65
Potassium dichromate	2556	107(4.19)	67	6.85	(5.9-7.9)	2414	90(3.73)	40	5.39	(4.52-6.36)	0.42
p-Phenylenediamine	2461	12(0.49)	20	1.3	(0.89-1.83)	2288	7(0.31)	50	2.49	(1.89-3.22)	0.36
Primin	1022	0(0)	0	0	(0-0.29)	523	0(0)	0	0	(0-0.57)	nd
Quaternium-15	2286	8(0.35)	4	0.52	(0.27-0.92)	1991	4(0.20)	2	0.3	(0.11-0.65)	0.40
Sesquiterpene lactone mix	1048	10(0.95)	8	1.72	(1.02-2.7)	520	1(0.19)	0	0.19	(0-1.07)	0.11

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Thiuram mix	1388	6(0.43)	2	0.65	(0.3-1.23)	942	8(0.85)	8	1.7	(0.97-2.74)	0.28
Tixocortol-21-pivalate	2255	9(0.40)	0	0.4	(0.18-0.76)	1988	9(0.45)	1	0.5	(0.24-0.92)	0.82

Cl+Me-isothiazolinone: Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) 3:1. All allergens in petrolatum, except where indicated otherwise: [w)] water.

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Table 4a:Results with the European Baseline Series in children and adolescents, stratified for European region and into 3 age groups (except for 'NE' region, where sample size was considered prohibitive of further subdivision): crude percent positive with 95% confidence interval (CI).

	'central' region									'North-East'		
	Age 1-5			Age 6-12			Age 13-16			Age 1-16		
Allergen	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)
2-Mercaptobenzothiazole	39	0	(0-7.39)	223	1.79	(0.49-4.53)	541	0	(0-0.55)	147	1.36	(0.17-4.83)
4-tert. butylphenol formaldehyde resin	24	0	(0-11.73)	184	0.54	(0.01-2.99)	535	0.56	(0.12-1.63)	154	1.3	(0.16-4.61)
5-Chloro-7-iodo-8-hydroxyquinoline	6	0	(0-39.3)	60	0	(0-4.87)	110	0	(0-2.69)	128	0	(0-2.31)
Benzocaine	12	0	(0-22.09)	75	0	(0-3.92)	175	4.57	(1.99-8.81)	97	0	(0-3.04)
Budesonide	8	0	(0-31.23)	63	0	(0-4.64)	188	0.53	(0.01-2.93)	147	0	(0-2.02)
Cl+Me-isothiazolinone (w)	39	0	(0-7.39)	223	2.24	(0.73-5.15)	542	1.29	(0.52-2.64)	154	2.6	(0.71-6.52)
Cobalt(II) chloride	25	16	(4.54-36.08)	184	5.43	(2.64-9.77)	535	8.04	(5.88-10.67)	150	12.67	(7.8-19.07)
Colophony	38	2.63	(0.07-13.81)	223	3.14	(1.27-6.36)	542	2.77	(1.56-4.52)	154	0	(0-1.93)
Epoxy resin	24	4.17	(0.11-21.12)	183	0.55	(0.01-3.01)	533	0.38	(0.05-1.35)	154	0	(0-1.93)
Formaldehyde (w)	24	0	(0-11.73)	183	0	(0-1.62)	535	0.56	(0.12-1.63)	155	1.94	(0.4-5.55)
Fragrance mix	39	2.56	(0.06-13.48)	223	9.87	(6.29-14.56)	541	4.99	(3.31-7.18)	155	3.23	(1.06-7.37)
Fragrance Mix II	26	0	(0-10.88)	122	4.92	(1.83-10.4)	316	2.22	(0.9-4.51)	78	0	(0-3.77)
HICC (Lyral)	14	0	(0-19.26)	131	0	(0-2.26)	439	0.68	(0.14-1.98)	75	0	(0-3.92)
Lanolin alcohols	25	8	(0.98-26.03)	184	3.26	(1.21-6.96)	535	2.62	(1.44-4.35)	121	1.65	(0.2-5.84)

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Mercapto mix	5	0	(0-45.07)	49	0	(0-5.93)	131	0	(0-2.26)	97	1.03	(0.03-5.61)
Mercapto mix (only CBS,MBTS,MOR)	34	2.94	(0.07-15.33)	183	3.28	(1.21-7)	433	0.23	(0.01-1.28)	57	1.75	(0.04-9.39)
Methyldibromoglutaronitrile	28	7.14	(0.88-23.5)	148	0.68	(0.02-3.71)	386	1.3	(0.42-3)	122	0	(0-2.43)
Methyldibromoglutaronitrile + 2-PE	8	0	(0-31.23)	52	0	(0-5.6)	142	1.41	(0.17-5)	46	2.17	(0.06-11.53)
Methylisothiazolinone (w)	1	0	(0-95)	18	0	(0-15.33)	43	0	(0-6.73)	29	0	(0-9.81)
Myroxylon Pereirae resin	24	0	(0-11.73)	184	5.98	(3.02-10.44)	535	3.36	(2.01-5.27)	154	1.3	(0.16-4.61)
Neomycin sulphate	27	3.7	(0.09-18.97)	168	2.98	(0.97-6.81)	318	0.31	(0.01-1.74)	153	5.23	(2.28-10.04)
Nickel sulphate	40	15	(5.71-29.84)	226	10.62	(6.92-15.39)	542	17.34	(14.25-20.8)	155	25.81	(19.12-33.44)
N-isopropyl-N'-phenyl-p-phenylenediamine	20	0	(0-13.91)	154	1.95	(0.4-5.59)	456	2.63	(1.37-4.55)	97	0	(0-3.04)
Paraben mix	25	0	(0-11.29)	184	2.17	(0.6-5.47)	536	1.87	(0.9-3.4)	97	1.03	(0.03-5.61)
Potassium dichromate	24	4.17	(0.11-21.12)	185	3.24	(1.2-6.93)	535	2.43	(1.3-4.12)	155	5.16	(2.25-9.92)
p-Phenylenediamine	17	0	(0-16.16)	133	3.01	(0.83-7.52)	371	7.01	(4.63-10.1)	153	5.23	(2.28-10.04)
Primin	6	0	(0-39.3)	63	0	(0-4.64)	120	0	(0-2.47)	154	0	(0-1.93)
Quaternium-15	10	0	(0-25.89)	94	0	(0-3.14)	199	0.5	(0.01-2.77)	154	0.65	(0.02-3.56)
Sesquiterpene lactone mix	10	0	(0-25.89)	89	2.25	(0.27-7.88)	198	0	(0-1.5)	96	0	(0-3.07)
Thiuram mix	39	10.26	(2.87-24.22)	222	1.8	(0.49-4.55)	542	1.85	(0.89-3.37)	154	0.65	(0.02-3.56)
Tixocortol-21-pivalate	8	0	(0-31.23)	73	0	(0-4.02)	234	0	(0-1.27)	153	1.31	(0.16-4.64)

Cl+Me-isothiazolinone: Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) 3:1. All allergens in petrolatum, except where indicated otherwise: [w)] water.

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Table 4b:Results with the European Baseline Series in Children and Adolescents, stratified for European region ('West') and into 3 age groups: crude percent positive with 95% confidence interval (CI).

	Age 1-5			Age 6-12			Age 13-16		
Allergen	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)
2-Mercaptobenzothiazole	541	0	(0-0.55)	959	1.46	(0.8-2.44)	1024	1.46	(0.82-2.4)
4-tert. butylphenol formaldehyde resin	535	0.56	(0.12-1.63)	959	0.21	(0.03-0.75)	1026	0	(0-0.29)
5-Chloro-7-iodo-8-hydroxyquinoline	110	0	(0-2.69)	7	0	(0-34.82)	12	0	(0-22.09)
Benzocaine	175	4.57	(1.99-8.81)	NA	NA	NA	NA	NA	NA
Budesonide	188	0.53	(0.01-2.93)	958	0.1	(0-0.58)	1026	0.1	(0-0.54)
Cl+Me-isothiazolinone (w)	542	1.29	(0.52-2.64)	953	0.73	(0.3-1.51)	1023	1.96	(1.2-3)
Cobalt(II) chloride	535	8.04	(5.88-10.67)	958	3.65	(2.56-5.04)	1024	4.59	(3.39-6.06)
Colophony	542	2.77	(1.56-4.52)	957	1.67	(0.96-2.7)	1025	2.44	(1.58-3.58)
Epoxy resin	533	0.38	(0.05-1.35)	957	0.21	(0.03-0.75)	1024	0.49	(0.16-1.14)
Formaldehyde (w)	535	0.56	(0.12-1.63)	957	0.21	(0.03-0.75)	1025	0.68	(0.27-1.4)
Fragrance mix	541	4.99	(3.31-7.18)	959	2.82	(1.86-4.07)	1026	2.05	(1.27-3.11)
Fragrance Mix II	316	2.22	(0.9-4.51)	600	0.5	(0.1-1.45)	630	0.95	(0.35-2.06)
HICC (Lyral)	439	0.68	(0.14-1.98)	855	0.35	(0.07-1.02)	913	0.55	(0.18-1.27)
Lanolin alcohols	535	2.62	(1.44-4.35)	960	0.94	(0.43-1.77)	1026	0.97	(0.47-1.79)
Mercapto mix	131	0	(0-2.26)	951	1.16	(0.58-2.06)	1007	0.99	(0.48-1.82)

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Mercapto mix (only CBS,MBTS,MOR)	433	0.23	(0.01-1.28)	8	0	(0-31.23)	18	0	(0-15.33)
Methyldibromoglutaronitrile	386	1.3	(0.42-3)	959	0.1	(0-0.58)	1026	0.1	(0-0.54)
Methyldibromoglutaronitrile + 2-PE	142	1.41	(0.17-5)	NA	NA	NA	NA	NA	NA
Methylisothiazolinone (w)	43	0	(0-6.73)	355	0	(0-0.84)	347	0	(0-0.86)
Myroxylon Pereirae resin	535	3.36	(2.01-5.27)	959	1.46	(0.8-2.44)	1026	1.07	(0.54-1.91)
Neomycin sulphate	318	0.31	(0.01-1.74)	959	0.94	(0.43-1.77)	1026	0.58	(0.21-1.27)
Nickel sulphate	542	17.34	(14.25-20.8)	959	5.32	(3.98-6.93)	1021	10.09	(8.31-12.1)
N-isopropyl-N'-phenyl-p-phenylenediamine	456	2.63	(1.37-4.55)	956	0.42	(0.11-1.07)	1025	1.37	(0.75-2.28)
Paraben mix	536	1.87	(0.9-3.4)	960	0.42	(0.11-1.06)	1026	0.49	(0.16-1.13)
Potassium dichromate	535	2.43	(1.3-4.12)	958	2.3	(1.44-3.46)	1025	0.88	(0.4-1.66)
p-Phenylenediamine	371	7.01	(4.63-10.1)	957	1.25	(0.65-2.18)	1023	5.67	(4.33-7.27)
Primin	120	0	(0-2.47)	957	0.1	(0-0.58)	1025	0	(0-0.29)
Quaternium-15	199	0.5	(0.01-2.77)	959	0.1	(0-0.58)	1026	0.39	(0.11-1)
Sesquiterpene lactone mix	198	0	(0-1.5)	959	1.25	(0.65-2.18)	1026	0.49	(0.16-1.13)
Thiuram mix	542	1.85	(0.89-3.37)	959	0.1	(0-0.58)	1025	0.78	(0.34-1.53)
Tixocortol-21-pivalate	234	0	(0-1.27)	833	0.6	(0.2-1.4)	898	0.67	(0.25-1.45)

Cl+Me-isothiazolinone: Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) 3:1. All allergens in petrolatum, except where indicated otherwise: [w)] water.

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Table 4c: Results with the European Baseline Series in Children and Adolescents, stratified for European region ('South') and into 3 age groups: crude percent positive with 95% confidence interval (CI).

	Age 1-5			Age 6-12			Age 13-16		
Allergen	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)	N(test)	% pos.	(95% CI)
2-Mercaptobenzothiazole	1329	0.15	(0.02-0.54)	1448	0.69	(0.33-1.27)	642	1.25	(0.54-2.44)
4-tert. butylphenol formaldehyde resin	1341	1.57	(0.97-2.38)	1448	1.52	(0.95-2.29)	642	1.25	(0.54-2.44)
5-Chloro-7-iodo-8-hydroxyquinoline	11	0	(0-23.84)	76	0	(0-3.87)	111	0	(0-2.66)
Benzocaine	1319	0.45	(0.17-0.99)	1439	0.07	(0-0.39)	638	0.78	(0.25-1.82)
Budesonide	1301	0.08	(0-0.43)	1365	0.15	(0.02-0.53)	411	0.49	(0.06-1.75)
Cl+Me-isothiazolinone (w)	1337	3.52	(2.59-4.65)	1440	2.85	(2.05-3.84)	616	3.57	(2.25-5.36)
Cobalt(II) chloride	1297	10.1	(8.51-11.87)	1420	10.99	(9.41-12.73)	638	4.86	(3.32-6.83)
Colophony	1341	0.52	(0.21-1.07)	1450	1.1	(0.63-1.79)	644	1.09	(0.44-2.23)
Epoxy resin	1320	0.23	(0.05-0.66)	1440	0.35	(0.11-0.81)	644	0.47	(0.1-1.36)
Formaldehyde (w)	870	0.57	(0.19-1.34)	978	0.1	(0-0.57)	586	1.19	(0.48-2.45)
Fragrance mix	1321	0.76	(0.36-1.39)	1440	0.9	(0.48-1.54)	644	2.8	(1.66-4.38)
Fragrance Mix II	13	0	(0-20.58)	74	2.7	(0.33-9.42)	103	0.97	(0.02-5.29)
HICC (Lyral)	21	0	(0-13.29)	117	0	(0-2.53)	334	0.3	(0.01-1.66)
Lanolin alcohols	1341	2.61	(1.82-3.61)	1450	1.79	(1.17-2.62)	644	1.55	(0.75-2.84)

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Mercapto mix	18	0	(0-15.33)	103	0.97	(0.02-5.29)	186	1.08	(0.13-3.83)
Mercapto mix (only CBS,MBTS,MOR)	15	0	(0-18.1)	65	0	(0-4.5)	205	0	(0-1.45)
Methyldibromoglutaronitrile	22	0	(0-12.73)	133	0	(0-2.23)	354	0.85	(0.18-2.46)
Methyldibromoglutaronitrile + 2-PE	1320	0.38	(0.12-0.88)	1320	0.45	(0.17-0.99)	350	2.29	(0.99-4.45)
Methylisothiazolinone (w)	2	0	(0-77.64)	4	0	(0-52.71)	10	0	(0-25.89)
Myroxylon Pereirae resin	1059	2.83	(1.92-4.02)	1134	4.32	(3.21-5.67)	579	2.42	(1.33-4.02)
Neomycin sulphate	1341	5.15	(4.03-6.47)	1450	5.79	(4.65-7.12)	644	2.64	(1.55-4.19)
Nickel sulphate	1341	30.2	(27.75-32.74)	1450	18.41	(16.45-20.51)	644	15.22	(12.53-18.23)
N-isopropyl-N'-phenyl-p-phenylenediamine	1338	0.97	(0.52-1.66)	1439	0.63	(0.29-1.18)	607	0.49	(0.1-1.44)
Paraben mix	1320	0.45	(0.17-0.99)	1438	0.49	(0.2-1)	643	0.31	(0.04-1.12)
Potassium dichromate	1341	10.22	(8.65-11.96)	1448	7.67	(6.35-9.16)	639	4.38	(2.93-6.27)
p-Phenylenediamine	1320	0.61	(0.26-1.19)	1440	0.97	(0.53-1.63)	644	3.73	(2.4-5.49)
Primin	20	0	(0-13.91)	128	0	(0-2.31)	281	0	(0-1.06)
Quaternium-15	1330	0.38	(0.12-0.88)	1370	0.8	(0.4-1.43)	395	0	(0-0.76)
Sesquiterpene lactone mix	21	0	(0-13.29)	123	0	(0-2.41)	260	1.15	(0.24-3.33)
Thiuram mix	52	1.92	(0.05-10.26)	195	0.51	(0.01-2.82)	457	0.66	(0.14-1.91)
Tixocortol-21-pivalate	1292	0.54	(0.22-1.11)	1358	0.52	(0.21-1.06)	403	0	(0-0.74)

Cl+Me-isothiazolinone: Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) 3:1. All allergens in petrolatum, except where indicated otherwise: [w)] water.

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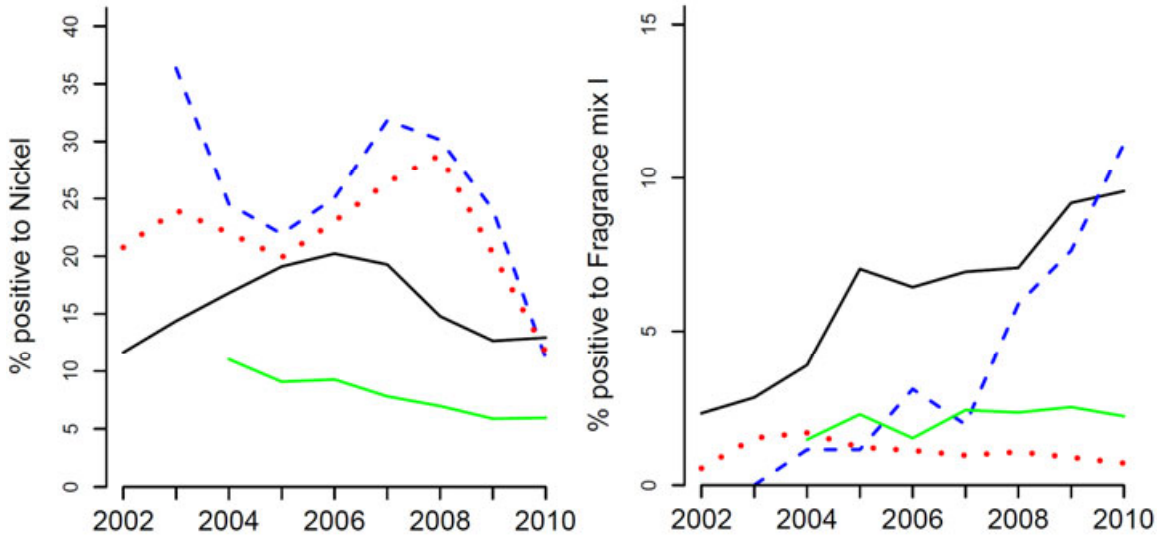

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