

## ORIGINAL ARTICLE

# Contact sensitization in patients with suspected cosmetic intolerance: results of the IVDK 2006–2011

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## Abstract

**Background** Ingredients of leave-on cosmetics and body care products may sensitize. However, not every case of cosmetic intolerance is due to contact sensitization.

**Objective** To describe the frequency of contact sensitization due to cosmetics in a large clinic population, and a possible particular allergen pattern.

**Methods** Retrospective analysis of data from the Information Network of Departments of Dermatology, 2006–2011.

**Results** Of 69 487 patients tested, ‘cosmetics, creams, sunscreens’ was the only suspected allergen source category in 10 124 patients (14.6%). A final diagnosis ‘allergic contact dermatitis’ was stated in 2658 of these patients (26.3%). Compared to a control group, there were significantly more reactions to fragrance mixes I and II, balsam of Peru, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and lanolin alcohols. No special pattern of fragrance sensitization could be identified. Among the preservatives, MI was by far the leading allergen, while sensitization to other widely used compounds like parabens or phenoxyethanol was rare.

**Conclusions** True allergic reactions to cosmetic ingredients are rarer than generally assumed. Limitation of exposure to MI in leave-on cosmetics and body care products is urgently needed.

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## Conflicts of interest

The IVDK is sponsored by the cosmetic and fragrance industry (associations). A.W. has accepted honoraria or travel reimbursement for presentations from cosmetic producing companies. A.S. works as *ad hoc* consultant for cosmetic industry (associations), partly remunerated. A.D., M.W. and J.G. have no conflicts to declare.

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## Introduction

Cosmetics and body care products are widely used and frequently suspected to cause allergic contact dermatitis in the public awareness. However, a closer look reveals that assumed or verified cosmetic intolerance reactions often have other reasons.<sup>1–3</sup> There are two large studies on the frequency of contact allergy in the general population caused by cosmetics supporting this view. In the course of a pilot study organized by the Council of Europe Committee of Experts on Cosmetic Products, Danish dermatologists diagnosed 328 cases of contact allergy caused by cosmetic products substantiated by patch testing. As the catchment area of the study was approximately 1 million inhabitants, the incidence of cosmetic-induced contact allergy was approximately 0.03%.<sup>4</sup> Because only 15%–30% of people affected by contact allergy seek medical advice with subsequent patch

testing, the true incidence can be estimated as 0.1%–0.2%. An unpublished analysis of data from the Information Network of Departments of Dermatology (IVDK) gathered between 2000 and 2004 resulted in a frequency of 5.1% of cosmetic-related contact allergy (positive patch test of cosmetic-related allergens together with a positive history of undesired effects through cosmetics). On the basis of 400 000 standard patch tests used per year in Germany, the total number of affected cases in the general population was extrapolated of 20 400. Correlated to the size of the general population in Germany (80 million) this would be 0.03% (for further explanation see Ref. [5]). After correction for non-consultation, the IVDK study delivered the same result as the Danish study, namely an incidence of 0.1%–0.2%.<sup>6</sup>

Routine patch test series, such as the baseline, ointment base, preservative or fragrance series contain compounds found in

cosmetics and body care products. However, exposure to several of these allergens may also occur from other contactants. It is therefore of interest whether patients patch tested under the suspicion of cosmetic intolerance reveal a particular allergen pattern. This may give a hint to substances of special concern. However, it is obvious that the commercially available patch test series do not fully cover the spectrum of potential sensitizers in cosmetics and body care products. In many cases of allergic contact dermatitis due to cosmetics, the allergen is only discovered by patch testing with the product ingredient, but not by routine patch testing alone.<sup>1,2,7–10</sup>

Against this background, it was our intention to describe the allergen spectrum of patients who were patch tested due to suspected intolerance reactions to leave-on cosmetics in the departments of dermatology joining the IVDK.

### Patients and methods

The IVDK is a network of currently 56 departments of dermatology in Germany, Switzerland and Austria dedicated to the epidemiology of contact allergy. Its structure and routine operating procedure are described in detail elsewhere.<sup>11</sup> Briefly, anonymized anamnestic and clinical data as well as patch test results of all patients tested in the participating centres are transmitted to the IVDK central office at the University of Göttingen twice a year. Data are subject to standardized quality control and analysed according to international standards.<sup>12, 13</sup>

Among other items, up to three putative allergen source categories can be documented in every case. We selected patients from the IVDK database, in whom ‘cosmetics, creams, sunscreens’ were noticed as the only potential allergen source. Exclusion of patients with related additional allergen exposures was done for the following reasons. Patients with medical ointments and rinse-off body care products, such as shampoos, shower gels etc. as putative allergen sources were excluded because these may contain similar potential allergens like leave-on cosmetics. Additionally, to focus on fragrance materials from leave-on cosmetics, we excluded patients with suspected allergic reactions to perfumes, deodorants etc. to avoid contamination of the study group with patients suffering from fragrance allergy acquired by other exposures.

However, despite our strict selection, patients of the study group were of course exposed to allergens from other sources than cosmetics, like any other patients. To find out if sensitization rates to ubiquitous allergens are increased or diminished in our study group, a control group was established. When selecting patients for this control group, again those with the above mentioned suspected allergen sources, which might interfere with the study group allergen pattern, were excluded. In addition, patients with occupational dermatitis and those with very special patch test indications, i.e. drug exanthema or suspected denture or implant intolerance, were excluded from data analysis.

Patch tests were performed and read according to internationally accepted guidelines, revised by the DKG.<sup>14</sup> Analysis of the patch test results was done based on the reactions at day 3 (D3). In few exceptional cases, when a reading was done at D4 instead, this reaction was selected. Patch test reactions were regarded as positive if they were characterized by erythema plus infiltration, papules and/or vesicles (+, ++, or +++). Age- and sex-standardization of reaction frequencies was calculated according to published formulae<sup>15,16</sup> and supplemented with exact 95%-confidence intervals (95%-CIs). On a 5% level statistically significant differences were concluded from non-overlapping 95%-CIs when comparing disjunct subgroups. Reaction index and positivity ratio of single patch test preparations were calculated according to published formulae.<sup>17,18</sup> Data analysis was done in the IVDK central office at the University of Göttingen, using the program package SAS® 9.3 (SAS Institute, Cary, NC, USA).

### Results

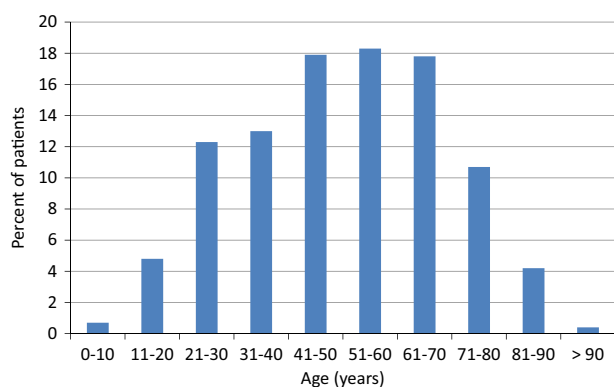
During the study period (2006–2011), altogether 69 487 patients were patch tested in the 52 departments of dermatology joining the IVDK. In 19 463 of these patients (28.0%), ‘cosmetics, creams, sunscreens’ was listed as one of the categories of putative allergen sources. In about half of the cases, additionally external drugs (ointments), soaps, shower gels, shampoos, deodorants or perfumes etc. were mentioned. In 10 124 patients (52.0%), ‘cosmetics, creams, sunscreens’ was the only suspected allergen source category. These patients, representing 14.6% of the total IVDK patient population of the years 2006–2011, were defined as the study group. According to the clinical focus of the participating clinics, the percentage of ‘cosmetic patients’ ranged from 0% to 37%, with a median of 13% (25%-percentile: 4%; 75%-percentile: 19%).

A description of the study group is given in Table 1. About 70% were women, and about one quarter had past or present atopic dermatitis. Remarkably, more patients (49.5%) were tested in order to rule out contact allergy than due to suspected contact allergy (45.8%). A final diagnosis of allergic contact dermatitis was made in only 26.3%. The face was the main localization of the dermatitis in 32.1% of the patients ( $n = 3254$ ), and of these, 1154 (35.5%) had eyelid dermatitis. The age distribution of the study group is shown in Fig. 1. Fifty-four per cent of the patients were between 41 and 70 years old, while 25.3% were at the age of 21–40.

The control group consisted of 14 728 patients. Of these, 56.8% were women, and 20.6% had past or present atopic dermatitis. Age distribution was similar to the study group (data not shown in detail). Indication for patch testing was suspected contact allergy in 39.4%, and ruling out contact allergy in 36.8%. Allergic contact dermatitis was the final diagnosis in 23.3% of the control group patients, and in 9.8%, it was atopic dermatitis. The face was affected in 10.2% of the patients

**Table 1** IVDK, 2006–2011: patients patch tested due to suspected cosmetic intolerance ( $n = 10\,124$ )

|                                                              | <i>n</i> | %    |
|--------------------------------------------------------------|----------|------|
| <b>Sex</b>                                                   |          |      |
| Female                                                       | 7061     | 69.7 |
| Male                                                         | 3063     | 30.3 |
| <b>Atopy (past or present)</b>                               |          |      |
| Atopic dermatitis                                            | 2543     | 25.1 |
| Allergic rhinitis                                            | 2199     | 21.7 |
| Allergic asthma                                              | 736      | 7.3  |
| <b>Indication for patch testing</b>                          |          |      |
| Exclusion of contact allergy                                 | 5012     | 49.5 |
| Contact allergy suspected                                    | 4636     | 45.8 |
| Others                                                       | 476      | 4.7  |
| <b>Final diagnosis</b>                                       |          |      |
| Allergic contact dermatitis                                  | 2658     | 26.3 |
| Atopic dermatitis                                            | 1539     | 15.2 |
| Non-classified eczema                                        | 1213     | 12.0 |
| Exclusion of contact sensitization (no current skin disease) | 944      | 9.3  |
| Chronic irritant dermatitis                                  | 475      | 4.7  |
| Other forms of dermatitis, other skin diseases               | 3295     | 32.5 |
| <b>Main localization</b>                                     |          |      |
| Face without eyelids                                         | 2100     | 20.7 |
| Periocular (eyelids)                                         | 1154     | 11.4 |
| Hands                                                        | 2068     | 20.4 |
| Generalized                                                  | 1123     | 11.1 |
| Legs                                                         | 910      | 9.0  |
| Trunk                                                        | 365      | 3.6  |
| Other localization                                           | 2404     | 23.7 |

**Figure 1** IVDK, 2006–2011: age distribution of patients patch tested due to suspected cosmetic intolerance ( $n = 10\,124$ ).

(including 407 patients with eyelid dermatitis), while 28.7% had hand dermatitis and 7.3% leg dermatitis.

Table 2 shows the 20 most frequent contact sensitizers among patients of the study group, and for comparison the corresponding age- and sex-standardized reactions frequencies in the

control group. In the study group, we found sensitization to nickel, cobalt, dichromate and thiurams (expressed as reactions to thiuram mix) markedly and significantly reduced. In contrast, positive reactions to fragrance mix (FM), fragrance mix II (FM II), balsam of Peru, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), lanolin alcohols and bufexamac were significantly increased. With hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), more reactions were noted in the study group (2.3% vs. 1.8%). However, the difference did not reach statistical significance. There was no difference in frequencies of sensitization to the preservatives methyltribromo glutaronitrile (MDBGN), bronopol and paraben mix. Among bufexamac-positive patients, there were significantly more atopsics than among bufexamac-negative patients (38.3% vs. 24.9%;  $P = 0.001$ , chi-square-test).

Altogether, 7874 patients were patch tested with the DKG ointment base series. The results are presented in Table 3. For comparison, patch test results with lanolin alcohols and cetyl stearyl alcohol in these patients are added to the table. Most frequently, positive test reactions were observed with Amerchol L 101, with a high proportion of concomitant reactions to lanolin alcohols. Of 7458 patients tested with both, 298 (4.0%) reacted to Amerchol L 101, and 182 (2.4%) to lanolin alcohols. Reactions to both of these were seen in 109 patients, representing 60% of those reacting to lanolin alcohols, and 37% of those reacting to Amerchol L 101. Positive reactions to cocamidopropyl betaine and octyl gallate ranked second and third, respectively. However, these test preparations elicited mainly weak positive reactions, and even more doubtful and irritant reactions, resulting in high PRs (camidopropyl betaine, 92%; octyl gallate, 93%) and very low RIs (camidopropyl betaine, -0.4; octyl gallate, -0.7). In contrast, tert-butyl hydroquinone, which elicited 2.4% positive reactions, had a PR of only 65% and a RI of only -0.2.

The DKG preservative series was patch tested in 7084 patients (Table 4). The test concentration of MDBGN was changed during the study period. It was tested at 0.3% until July 2008, and at 0.2% from August 2008 on. With MDBGN 0.3% pet., 4.2% positive reactions were seen, and with MDBGN 0.2% pet., 2.5%. Methylisothiazolinone (MI; 0.05% Aqu.), which was also added to this series in August 2008, elicited positive reactions in 3.8% of the patients tested. Concomitant reactivity to MCI/MI was frequent. Of 3974 patients tested with both, 169 (4.3%) reacted to MCI/MI, and 150 (3.8%) to MI. Reactions to both of these were seen in 105 patients, representing 62% of those reacting to MCI/MI, and 70% of those reacting to MI.

Positive reactions to FM and FM II were among the most frequently observed. Single components of FM were patch tested in 405 out of 859 patients (47%) with a positive reaction to the mix. With FM II, this proportion was 137 out of 559 (24.5%). Results are shown in Table 5. Among the FM components, oakmoss absolute (*Evernia prunastri*) was by far

**Table 2** The 20 most frequent allergens among patients patch tested due to suspected cosmetic intolerance (study group;  $n = 10\,124$ ), and corresponding age- and sex-standardized reaction frequency with 95%- confidence interval (95%-CI) in the control group ( $n = 14\,728$ )

| Allergen                                                                 | Concentration | $n$ positive | Study group               |                                      | Control group                        |
|--------------------------------------------------------------------------|---------------|--------------|---------------------------|--------------------------------------|--------------------------------------|
|                                                                          |               |              | % positive (non-adjusted) | % positive age- and sex-standardized | % positive age- and sex-standardized |
| Nickel sulphate                                                          | 5%            | 1387         | 14.6                      | 15.4<br>[14.6–16.1]                  | 17.9<br>[17.2–18.7]                  |
| Fragrance mix                                                            | 8%            | 859          | 9.0                       | 8.1<br>[7.5–8.7]                     | 5.9<br>[5.5–6.4]                     |
| Balsam of Peru ( <i>Myroxylon pereirae</i> )                             | 25%           | 755          | 7.9                       | 7.0<br>[6.5–7.6]                     | 5.4<br>[5.1–5.8]                     |
| Fragrance mix II                                                         | 14%           | 559          | 5.9                       | 5.4<br>[4.9–5.9]                     | 3.8<br>[3.5–4.1]                     |
| Cobalt chloride                                                          | 1%            | 494          | 5.2                       | 5.7<br>[5.2–6.2]                     | 6.9<br>[6.4–7.4]                     |
| Colophony                                                                | 20%           | 389          | 4.1                       | 3.9<br>[3.5–4.3]                     | 3.9<br>[3.5–4.2]                     |
| Potassium dichromate                                                     | 0.5%          | 367          | 3.9                       | 3.8<br>[3.4–4.2]                     | 5.2<br>[4.8–5.6]                     |
| Methylchloroisothiazolinone/<br>Methylisothiazolinone (MCI/MI; in water) | 0.01%         | 304          | 3.2                       | 2.8<br>[2.5–3.2]                     | 2.0<br>[1.8–2.3]                     |
| Methyldibromo glutaronitrile (MDBGN) <sup>†</sup>                        | 0.2%/0.3%     | 299          | 3.2                       | 2.8<br>[2.4–3.1]                     | 2.8<br>[2.5–3.1]                     |
| Propolis                                                                 | 10%           | 272          | 2.9                       | 2.6<br>[2.2–2.9]                     | 2.1<br>[1.8–2.3]                     |
| Lanolin alcohols                                                         | 30%           | 246          | 2.6                       | 2.6<br>[2.2–2.9]                     | 1.8<br>[1.5–2.0]                     |
| Hydroxyisohexyl 3-cyclohexene<br>carboxaldehyde (HICC)                   | 5%            | 242          | 2.5                       | 2.3<br>[2.0–2.7]                     | 1.8<br>[1.5–2.0]                     |
| Oil of turpentine                                                        | 10%           | 200          | 2.1                       | 1.9<br>[1.6–2.2]                     | 1.8<br>[1.6–2.1]                     |
| Thiuram mix                                                              | 1%            | 127          | 1.3                       | 1.2<br>[1.0–1.4]                     | 1.9<br>[1.6–2.1]                     |
| Bronopol                                                                 | 0.5%          | 120          | 1.3                       | 1.1<br>[0.9–1.4]                     | 1.0<br>[0.8–1.2]                     |
| Bufexamac                                                                | 5%            | 115          | 1.2                       | 1.2<br>[1.0–1.5]                     | 0.7<br>[0.6–0.9]                     |
| Compositae Mix*                                                          | 5%            | 108          | 1.3                       | 1.2<br>[1.0–1.5]                     | 1.3<br>[1.1–1.5]                     |
| Formaldehyde (in water)                                                  | 1%            | 104          | 1.1                       | 1.1<br>[0.9–1.4]                     | 0.9<br>[0.7–1.1]                     |
| Paraben Mix                                                              | 16%           | 103          | 1.1                       | 1.0<br>[0.8–1.2]                     | 0.9<br>[0.7–1.0]                     |
| Epoxy resin                                                              | 1%            | 97           | 1.0                       | 1.0<br>[0.7–1.2]                     | 1.2<br>[1.1–1.4]                     |

\*Reduced patient count ( $n = 8061$ ) because compositae mix was replaced by compositae mix II in 2011.

<sup>†</sup>MDBGN was tested at 0.3% until July 2008, and at 0.2% from August 2008 on.

Only allergens patch tested in more than 93% of the study group patients are listed. Vehicle was petrolatum, if not else specified.

the most frequent allergen, followed by Isoeugenol. In 36 patients, concomitant reactions to cinnamal and cinncamyl alcohol were noted. These are 80% of those reacting to cinncamyl alcohol, and 71% of those reacting to cinnamal. Among the single components of FM II, HICC was the leading allergen, followed by citral.

Additional fragrance allergens are contained in the DKG test series ‘additional fragrances to be declared’ and ‘additional fragrances and essential oils’. These test series have been tested in 719 and 677 patients, respectively. Test results are depicted in Table 6. Among the fragrances to be declared, tree moss was the only one which elicited positive reactions

**Table 3** Patch test results with the DKG ointment base series in the study group

| Allergen                          | Concentration | Patient count | Negative | ?   | +   | ++ | +++ | Irritant | % Positive |
|-----------------------------------|---------------|---------------|----------|-----|-----|----|-----|----------|------------|
| Amerchol L 101                    | 50%           | 7716          | 7138     | 180 | 269 | 41 | 3   | 85       | 4.1        |
| Cocamidopropyl betaine (in water) | 1%            | 7721          | 7107     | 207 | 184 | 15 | 0   | 208      | 2.6        |
| Octyl gallate                     | 0.3%          | 7772          | 6593     | 543 | 184 | 14 | 0   | 438      | 2.5        |
| Lanolin alcohols*                 | 30%           | 7549          | 7259     | 81  | 159 | 24 | 1   | 25       | 2.4        |
| Propylene glycol (in water)       | 20%           | 7765          | 7426     | 104 | 160 | 14 | 0   | 61       | 2.2        |
| tert-Butyl hydroquinone           | 1%            | 7769          | 7416     | 144 | 97  | 35 | 17  | 60       | 1.9        |
| Sorbitan sesquileate              | 20%           | 3211          | 3069     | 77  | 43  | 5  | 3   | 14       | 1.6        |
| Benzophenone-4 (Sulisobenzene)    | 10%           | 5600          | 5409     | 92  | 58  | 2  | 0   | 39       | 1.1        |
| Cetyl stearyl alcohol*            | 20%           | 7554          | 7407     | 50  | 61  | 12 | 5   | 19       | 1.0        |
| Coconut diethanolamide            | 0.5%          | 7719          | 7529     | 85  | 50  | 6  | 0   | 49       | 0.7        |
| Butyl hydroxy anisole             | 2%            | 7771          | 7697     | 26  | 31  | 3  | 3   | 11       | 0.5        |
| Triethanolamine                   | 2.5%          | 7768          | 7648     | 63  | 31  | 1  | 0   | 25       | 0.4        |
| Polyethyleneglycol ointment       | 100%          | 7719          | 7681     | 16  | 16  | 1  | 1   | 4        | 0.2        |
| Butyl hydroxy toluene             | 2%            | 7772          | 7719     | 28  | 13  | 0  | 0   | 12       | 0.2        |

\*Test preparation is part of the baseline series.

Differing patient counts result from adding or deleting single substances from the series during the study period. Vehicle was petrolatum, if not else specified. For comparison, test results in these patients with two ointments bases from the baseline series are added.

**Table 4** Patch test results with the DKG preservative series in the study group

| Allergen                                                                  | Concentration | Patient count | Negative | ?   | +   | ++ | +++ | Irritant | % positive |
|---------------------------------------------------------------------------|---------------|---------------|----------|-----|-----|----|-----|----------|------------|
| Methyldibromo Glutaronitrile (MDBGN)*†                                    | 0.3%          | 2787          | 2603     | 52  | 93  | 22 | 1   | 1        | 4.2        |
| Methylisothiazolinone (MI; in water)                                      | 0.05%         | 4089          | 3901     | 21  | 89  | 53 | 15  | 10       | 3.8        |
| Methylchloroisothiazolinone/<br>Methylisothiazolinone (MCI/MI; in water)* | 0.01%         | 6797          | 6523     | 29  | 156 | 67 | 9   | 13       | 3.4        |
| Methyldibromo Glutaronitrile (MDBGN)*†                                    | 0.2%          | 3994          | 3813     | 63  | 74  | 25 | 2   | 17       | 2.5        |
| Bronopol*                                                                 | 0.5%          | 6792          | 6626     | 56  | 72  | 16 | 3   | 19       | 1.3        |
| Iodopropynyl butylcarbamate                                               | 0.2%          | 6974          | 6748     | 128 | 71  | 6  | 0   | 21       | 1.1        |
| Paraben mix*                                                              | 16%           | 6784          | 6582     | 90  | 61  | 6  | 1   | 44       | 1.0        |
| Formaldehyde (in water)*                                                  | 1%            | 6786          | 6671     | 33  | 54  | 11 | 2   | 15       | 1.0        |
| Imidazolidinyl urea (Germall 115)                                         | 2%            | 6981          | 6906     | 18  | 41  | 11 | 0   | 5        | 0.7        |
| Diazolidinyl urea (Germall II)                                            | 2%            | 6979          | 6911     | 15  | 38  | 8  | 2   | 5        | 0.7        |
| Sorbic acid                                                               | 2%            | 6978          | 6899     | 23  | 41  | 5  | 1   | 9        | 0.7        |
| Quaternium 15                                                             | 1%            | 6981          | 6923     | 10  | 30  | 10 | 3   | 5        | 0.6        |
| Chloroacetamide                                                           | 0.2%          | 6982          | 6926     | 11  | 26  | 8  | 3   | 8        | 0.5        |
| Sodium benzoate                                                           | 5%            | 6934          | 6819     | 60  | 31  | 2  | 0   | 22       | 0.5        |
| Chlorhexidine digluconate (in water)                                      | 0.5%          | 6984          | 6923     | 23  | 25  | 5  | 0   | 8        | 0.4        |
| Benzyl alcohol                                                            | 1%            | 6933          | 6876     | 23  | 18  | 3  | 1   | 12       | 0.3        |
| DMDM Hydantoin (in water)                                                 | 2%            | 6931          | 6883     | 19  | 18  | 2  | 0   | 9        | 0.3        |
| Triclosan                                                                 | 2%            | 6933          | 6883     | 22  | 14  | 6  | 0   | 8        | 0.3        |

\*Test preparation is part of the baseline series.

†MDBGN was tested at 0.3% until July 2008, and at 0.2% from August 2008 on.

Differing patient counts result from adding or deleting single substances from the series during the study period. Vehicle was petrolatum, if not else specified. For comparison, test results in these patients with four preservatives and formaldehyde from the baseline series are added.

in more than 1% of the patients. In 33 of 46 patients reacting to tree moss, oak moss was also tested. Of these, 21 (64%) reacted to both preparations. In the other test series, three essential oils which are meanwhile part of the DKG baseline series reacted most frequently. In addition,

lemongrass oil and clove oil elicited reactions in more than 10 patients, while reactions to the remainder were only few.

For some fragrance and preservative allergen preparations, we analysed time trends in age- and sex-standardized reactivity. In Fig. 2, reactions to MCI/MI, FM, FM II and HICC in the DKG

**Table 5** Patch test results with single components of fragrance mix and fragrance mix II in patients with positive reactions to the mixes ( $n = 405$  and  $137$ , respectively). Vehicle was petrolatum

| Allergen           | Concentration | Negative | ?  | +   | ++  | +++ | Irritant | % positive |
|--------------------|---------------|----------|----|-----|-----|-----|----------|------------|
| Fragrance mix      | 8%            | 0        | 0  | 259 | 115 | 31  | 0        | 100.0      |
| Oakmoss absolute   | 1%            | 258      | 17 | 71  | 41  | 17  | 1        | 31.9       |
| Isoeugenol         | 1%            | 314      | 12 | 51  | 18  | 9   | 1        | 19.3       |
| Hydroxycitronellal | 1%            | 334      | 9  | 48  | 9   | 2   | 2        | 14.6       |
| Cinnamal           | 1%            | 341      | 13 | 38  | 9   | 4   | 0        | 12.6       |
| Cinnamyl alcohol   | 1%            | 349      | 11 | 35  | 8   | 2   | 0        | 11.1       |
| Eugenol            | 1%            | 358      | 8  | 29  | 7   | 3   | 0        | 9.6        |
| Geraniol           | 1%            | 360      | 15 | 25  | 4   | 1   | 0        | 7.4        |
| Amyl cinnamal      | 1%            | 377      | 10 | 16  | 1   | 1   | 0        | 4.4        |
| Fragrance mix II   | 14%           | 0        | 0  | 96  | 36  | 5   | 0        | 100.0      |
| HICC               | 5%            | 68       | 4  | 40  | 20  | 4   | 1        | 46.7       |
| Citral             | 2%            | 103      | 6  | 18  | 6   | 2   | 2        | 19.0       |
| Farnesol           | 5%            | 112      | 3  | 14  | 4   | 1   | 3        | 13.9       |
| Hexyl cinnamal     | 10%           | 118      | 8  | 9   | 1   | 0   | 1        | 7.3        |
| Citronellol        | 1%            | 122      | 5  | 8   | 0   | 0   | 2        | 5.8        |
| Coumarin           | 5%            | 127      | 3  | 6   | 0   | 0   | 1        | 4.4        |

baseline series are shown. Reactions to MCI/MI increased threefold, from 1.7% in 2006 to 5.2% in 2011. There was a slight increase in positive reactions to FM, rising from 7.4% in 2006 to 8.8 in 2011, while reactivity to FM II and HICC showed no uniform trend over the study period. Three substances from the DKG preservative series are depicted in Fig. 3. While there was slight reduction in positive reactions to Bronopol, from 1.8% in 2006 to 0.8% in 2011, there was no uniform trend with IPBC. However, age- and sex-standardized frequency of sensitization to MI rose from 1.2% in 2009, when it was introduced into the DKG preservative series, to 5.7% in 2011, which is an increase by the factor 4.75.

To get information on additional individual allergens, we analysed patch test reactions to selected current ingredients of leave-on cosmetics which are not part of the routine test series. Some of them were commercially available as patch test preparations, namely cetyl alcohol 5% pet., phenoxyethanol 1% pet., panthenol 5% pet. and titanium dioxide 0.1% pet., but most were individual preparations with differing test concentrations and vehicles tested in few patients only. By far most of these patch tests remained negative. A few positive reactions were seen with panthenol, one with *Calendula officinalis* extract and three with phenoxyethanol (Table 7). However, the latter occurred only in patients with several other positive reactions, and clinical relevance was doubted by the testing physicians.

## Discussion

A proportion of almost 15% cases with suspected cosmetic intolerance among all patch tested patients may seem quite a lot. However, a closer look reveals that almost half of these were patch tested to exclude contact allergy, and a final diagnosis of allergic contact dermatitis was made in only 26%. Hence, the

true proportion of contact allergy cases connected with cosmetics is much lower, probably around 4%. In this context, it is important to keep in mind that IVDK data are based on the skin hospital patients, and not from the general population. Partly, these data reflect the difference between assumed and proven frequency of contact allergy due to cosmetics mentioned in the introduction.<sup>1,2</sup> It has to be considered that patch testing alone may not pick up every case of cosmetic ingredient allergy. The skin of the face and around the eyes is thinner and more sensitive, so false-negative patch test reactions may occur on the thick skin of back. Moreover, due to the particular product composition, cosmetic ingredients may penetrate better into the skin than from a patch test preparation vehicle. Therefore, in some cases it may be necessary to do a strip patch test or to perform a use test (Repeated Open Application Test or Provocative Use Test). However, there are no reliable large-scale data on how many cases of cosmetic ingredient allergy remain undetected by limiting diagnostics to patch testing.

Patients with past or present atopic dermatitis were over-represented in the study group, which may explain a part of the dermatitis cases erroneously attributed to cosmetic use. In particular, periorbital atopic dermatitis may mimic allergic contact dermatitis.<sup>19</sup>

As expected and reported from other investigations on contact allergy due to cosmetics,<sup>2,8–10,20,21</sup> fragrances and preservatives were the most prominent allergen groups among cosmetic ingredients. Positive reactions to FM, FM II and Balsam of Peru were significantly more frequent in the study group than in the control group, indicating an increased proportion of patients with contact allergy to fragrances. Over the years 2006–2011, there was a slight increase in positive reactions to FM, while reactivity to FM II and HICC showed no uniform trend over the

**Table 6** Patch test results with the DKG preservative series 'additional fragrances to be declared' and 'additional fragrances and essential oils'

| Test series/Allergen                     | Concentration | Patient count | Negative | ?  | +  | ++ | +++ | Irritant | % positive |
|------------------------------------------|---------------|---------------|----------|----|----|----|-----|----------|------------|
| Additional fragrances to be declared     |               |               |          |    |    |    |     |          |            |
| Tree moss                                | 1%            | 708           | 636      | 22 | 29 | 13 | 4   | 4        | 6.5        |
| Methyl 2-octynoate                       | 1%            | 708           | 691      | 11 | 5  | 1  | 0   | 0        | 0.8        |
| Amyl cinnamyl alcohol                    | 1%            | 708           | 687      | 9  | 3  | 2  | 0   | 7        | 0.7        |
| Limonene                                 | 2%            | 704           | 693      | 6  | 4  | 0  | 0   | 1        | 0.6        |
| Butylphenyl methylpropional              | 10%           | 707           | 696      | 6  | 4  | 0  | 0   | 1        | 0.6        |
| Benzyl cinnamate                         | 5%            | 708           | 699      | 5  | 3  | 0  | 0   | 1        | 0.4        |
| Benzyl salicylate                        | 1%            | 708           | 697      | 6  | 3  | 0  | 0   | 2        | 0.4        |
| Alpha-isomethyl ionone                   | 1%            | 708           | 698      | 4  | 3  | 0  | 0   | 3        | 0.4        |
| Linalool (stabilized)                    | 10%           | 708           | 697      | 4  | 3  | 0  | 0   | 4        | 0.4        |
| Benzyl alcohol                           | 1%            | 706           | 696      | 5  | 2  | 0  | 0   | 3        | 0.3        |
| Benzyl benzoate                          | 1%            | 708           | 693      | 7  | 1  | 0  | 0   | 7        | 0.1        |
| Anise alcohol                            | 1%            | 708           | 701      | 4  | 0  | 0  | 0   | 3        | 0.0        |
| Additional fragrances and essential oils |               |               |          |    |    |    |     |          |            |
| Ylang-ylang (I and II) oil*              | 10%           | 513           | 468      | 16 | 18 | 7  | 2   | 2        | 5.3        |
| Sandalwood oil*                          | 10%           | 514           | 480      | 14 | 13 | 2  | 2   | 3        | 3.3        |
| Jasmine absolute*                        | 5%            | 514           | 488      | 7  | 12 | 4  | 0   | 3        | 3.1        |
| Lemongrass oil                           | 2%            | 665           | 620      | 20 | 8  | 10 | 1   | 6        | 2.9        |
| Clove oil                                | 2%            | 665           | 642      | 6  | 11 | 2  | 0   | 4        | 2.0        |
| Majantol                                 | 5%            | 516           | 495      | 12 | 5  | 2  | 0   | 2        | 1.4        |
| Patchouli oil                            | 10%           | 512           | 501      | 4  | 5  | 1  | 0   | 1        | 1.2        |
| Orange oil                               | 2%            | 664           | 653      | 4  | 6  | 0  | 0   | 1        | 0.9        |
| Narcissus absolute                       | 2%            | 513           | 502      | 6  | 4  | 0  | 0   | 1        | 0.8        |
| Menthol                                  | 1%            | 663           | 650      | 6  | 5  | 0  | 0   | 2        | 0.8        |
| Neroli oil                               | 2%            | 665           | 653      | 4  | 4  | 1  | 0   | 3        | 0.8        |
| Lemon oil                                | 2%            | 665           | 654      | 4  | 5  | 0  | 0   | 2        | 0.8        |
| Salicyl aldehyde                         | 2%            | 665           | 654      | 3  | 4  | 0  | 0   | 4        | 0.6        |
| Cedar wood oil                           | 10%           | 665           | 648      | 7  | 2  | 2  | 0   | 6        | 0.6        |
| Laurus nobilis leaf oil                  | 2%            | 665           | 655      | 4  | 4  | 0  | 0   | 2        | 0.6        |
| Benzaldehyde                             | 5%            | 665           | 655      | 7  | 3  | 0  | 0   | 0        | 0.5        |
| Peppermint oil                           | 2%            | 665           | 656      | 4  | 3  | 0  | 0   | 2        | 0.5        |
| Vanillin                                 | 10%           | 664           | 662      | 0  | 2  | 0  | 0   | 0        | 0.3        |
| Eucalyptus spp. oil                      | 2%            | 665           | 662      | 1  | 1  | 0  | 0   | 1        | 0.2        |

\*Moved from this series to the baseline series in September 2010.

Differing patient counts result from adding or deleting single substances from the series during the study period. Vehicle was petrolatum.

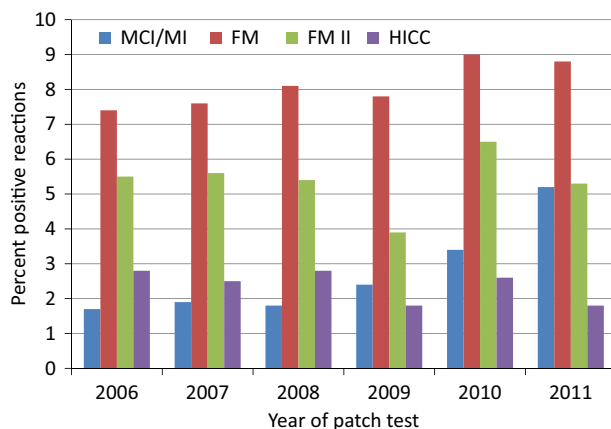
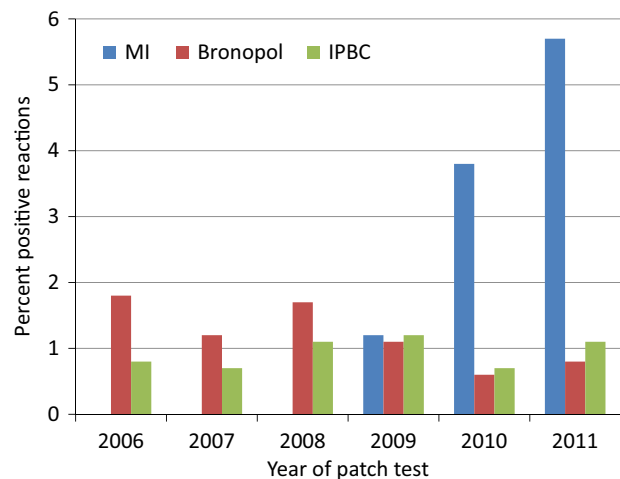
study period. The cause of the rising reactions to FM is still unclear. Analysing reactions in patients with positive FM reaction, oakmoss absolute is by far the leading allergen. This, and the following ranking of the other mix components is in line with former IVDK data analyses not focussed on 'cosmetic patients'.<sup>22,23</sup> Hence, nothing points to a changed fragrance exposure pattern in cosmetics which might explain the increasing reactions frequencies to FM. Reactions to the ingredients of FM II, with HICC as leading allergen, also are in accordance with former IVDK data analyses.<sup>24</sup> Concerning HICC, similar findings were also made in Belgium,<sup>25</sup> with frequent relevant reactions to HICC in patients tested due to suspected cosmetic intolerance. However, Nardelli and colleagues also found

frequent reactions to geraniol and limonene in skin care products.<sup>25</sup> In contrast, in our study group, geraniol was the least frequent allergen of the FM, and limonene elicited less than one per cent positive reactions. This difference may result from different habits of perfuming skin care products in Belgium and Germany. However, we have no reliable information on this topic. Generally, it has to be considered that patch testing with limonene and linalool does not detect all cases of contact allergy to these fragrances because the far more important allergens are their hydroperoxides which can be patch tested in addition or instead.<sup>26</sup> Of the other fragrances which must be declared, only tree moss elicited a considerable number of positive reactions, most of which were concomitant reactions with oak moss, due

**Table 7** Patch test results with additional cosmetic ingredients

| Category/<br>Substance                                 | Concentration,<br>vehicle | Number of<br>patients<br>tested | Test<br>results                         |
|--------------------------------------------------------|---------------------------|---------------------------------|-----------------------------------------|
| Ointment bases, emulsifiers, stabilizers, antioxidants |                           |                                 |                                         |
| Behenyl alcohol                                        | 5% pet.                   | 1                               | Neg.                                    |
| <i>Butyrospermum parkii</i><br>butter (sheabutter)     | Various                   | 12                              | Neg.                                    |
| Carbomer                                               | Various                   | 9                               | Neg.                                    |
| Cetyl alcohol                                          | 5% pet.                   | 311                             | 310 Neg.; 1 ?                           |
| Cyclopentasiloxane                                     | As is                     | 1                               | Neg.                                    |
| Cyclohexasiloxane                                      | As is                     | 1                               | Neg.                                    |
| Dimethicone                                            | Various                   | 4                               | Neg.                                    |
| Glycerol                                               | As is                     | 29                              | Neg.                                    |
| Glyceryl stearate                                      | 30% pet.                  | 7                               | Neg.                                    |
| Mineral oil                                            | As is                     | 3                               | Neg.                                    |
| Paraffinum liquidum                                    | As is                     | 3                               | Neg.                                    |
| Sodium carbomer                                        | Various                   | 9                               | Neg.                                    |
| Squalane                                               | Various                   | 3                               | Neg.                                    |
| Tocopherol                                             | Various                   | 8                               | Neg.                                    |
| Preservatives                                          |                           |                                 |                                         |
| Phenoxyethanol                                         | 1% pet.                   | 277                             | 269 Neg.;<br>5 ?; 3 +                   |
| Others                                                 |                           |                                 |                                         |
| Bisabolol                                              | Various                   | 2                               | Neg.                                    |
| <i>Calendula officinalis</i><br>extract                | Various                   | 4                               | 2 Neg.; 1 + ;<br>1 ir.                  |
| Ethylhexylglycerin                                     | Various                   | 2                               | Neg.                                    |
| Octocrylene                                            | 10% pet.                  | 3                               | Neg.                                    |
| Panthenol                                              | 5% pet.                   | 771                             | 761 Neg.;<br>3 ?; 4 + ;<br>2 + +; 1 ir. |
| Titanium dioxide                                       | 0.1% pet.                 | 54                              | Neg.                                    |
| Xanthan gum                                            | Various                   | 4                               | Neg.                                    |

Neg., Negative; ir., Irritant

**Figure 2** Time trend of age- and sex-standardized reaction frequencies to four allergen preparations from the DKG baseline series.**Figure 3** Time trend of age- and sex-standardized reaction frequencies to three allergen preparations from the DKG preservative series. MI was not part of the series before 2009.

to common ingredients. Among the additional fragrances and essential oils, Ylang-ylang oil, sandalwood oil and jasmine absolute were the most prominent allergens, which is not a cosmetic-specific finding. Due to their high frequency of sensitization, the DKG has included them in the baseline series in 2010. Hence, from our data, we cannot derive a special fragrance allergy pattern, which would point to particularly problematic fragrance materials in leave-on cosmetics or body care products. In addition, one has to be aware of the limitation that only a very small proportion of the patients was tested with single fragrance materials.

Of the preservatives, MI is currently in the dermatologists' and allergists' focus, with dramatically increasing incidence of contact sensitization, to a great extent caused by cosmetic exposure.<sup>27–30</sup> The suitable patch test concentrations for MI and MCI/MI are a matter of debate. Higher concentrations than the DKG used are recommended by the EECDRG.<sup>31,32</sup> Hence, we cannot exclude that some cases of contact allergy to these preservatives were missed, and the frequencies of sensitization were even higher. In cosmetics, MI was used in a fixed combination together with MCI, at a concentration of 15 ppm MCI/MI, leading to a final MI concentration of 3.75 ppm. In recent years, MI has been increasingly used without MCI at concentrations up to 100 ppm in the finished product. Obviously, to prevent contact sensitization, this limit has to be lowered considerably.<sup>27,30</sup> Increasing frequency of sensitization to MI is also probably the cause of the recent increase in contact sensitization to MCI/MI by cross-reactivity of MI-sensitized patients to MCI.<sup>33</sup> An increase in sensitization to MCI/MI in patients with suspected cosmetic intolerance has also recently been reported from Korea, however, without investigating cross-reactivity with MI.<sup>34</sup>

Remarkably, the frequency of sensitization to MDBGN is still relatively high (2.5% when tested at 0.2% pet.) although this preservative was banned from cosmetics and body care products in 2008.<sup>35</sup> Probably many of the MDBGN-positive patients in our study had been previously sensitized. In general, a decreasing time trend in MDBGN contact sensitization can be observed in Germany like in other European countries.<sup>36–38</sup> Bronopol and IPBC, which are widely used in cosmetics and body care products, were far less frequent sensitizers in our study group. With bronopol, a slight but not constant, decrease in sensitization frequency was seen over the years, while there was no time trend observed with IPBC. This is in accordance with findings from other European countries.<sup>39,40</sup> Positive test reactions to paraben mix were observed in only 1% of the patients. Keeping in mind that about half of the positive reactions to the paraben mix are false positive<sup>41</sup> and regarding the widespread use of parabens in cosmetics and body care products, one has to state that for this use, parabens are safe from the allergist's point of view. Other preservatives contained in the DKG preservative series were rare sensitizers. In case of the formaldehyde releasers such as imidazolidinyl urea, diazolidinyl urea and quaternium 15, this probably due to their less frequent use in Europe, in contrast to North America, where they are more widely used and frequency of sensitization is much higher.<sup>8,21,42–44</sup> Remarkably, benzyl alcohol, which is not only a preservative but also one of the 26 fragrances to be declared in the EU,<sup>45</sup> elicited positive reactions in only 0.3% of the tested patients, regardless whether it was tested in the preservative or fragrance series. Hence, we have our doubts if benzyl alcohol is really an important allergen.

Ointment bases, emulsifiers etc. are frequently suspected to cause allergic reactions. Most frequently, positive reactions to lanolin alcohols and Amerchol L 101 were seen in our study group, which is in line with findings from other studies on cosmetic-related contact allergy.<sup>8</sup> Amerchol L 101 contains lanolin alcohols, which explains the high proportion of concomitant reactions to both. It has been doubted whether positive reactions to one of these test preparations really reflect the true frequency of sensitization to lanolin alcohols, because false-negative as well as false-positive reactions do occur. In addition, some patients may react to lanolin alcohols from the test preparation but not to lanolin in their cosmetics, or vice versa, and some patients with allergic contact dermatitis due to lanolin located on the lower legs around venous ulcers do tolerate lanolin-containing body care products on other parts of the body.<sup>46–48</sup> Lastly, positive reactions to lanolin alcohols are poorly reproducible.<sup>49</sup> All these findings have been summarized under the 'lanolin paradox', which makes interpretation of patch test data with lanolin very difficult. Some of the ointment bases and emulsifiers elicit a considerable number of positive reactions on patch testing. However, one has to be aware that these compounds are particularly prone to irritate the skin when applied under occlusion for 48 h. This is reflected by negative RIs and high PRs of several

corresponding test preparations, e.g. cocamidopropyl betaine 1% aqu., octyl gallate 0.3% pet., propylene glycol 20% aqu. and sorbitan sesquioleate 20% pet.<sup>18,50</sup> Of course, this does not mean that all of the positive reactions to these allergens are false positive; but they certainly have a higher proportion of false-positive reaction than other allergen preparations. In contrast, reactions to tert-butyl hydroquinone often indicate true sensitization. In particular, this stabilizer has been described as contact allergen in lipsticks etc.<sup>51</sup>

As mentioned in the introduction, there are several cosmetic ingredients to which sensitization has been observed in single cases, but which are not routinely tested. Therefore, patch testing with the individual product ingredients should be performed. However, cosmetic ingredients beyond the established patch test series have been patch tested in a small minority of the patients only. No far-reaching conclusions can be drawn from the results. There were just three substances tested in a few hundred patients, i.e. cetyl alcohol, phenoxyethanol and panthenol. The latter has been described before as contact allergen in cosmetics.<sup>52</sup> Phenoxyethanol is extremely widely used as preservative in cosmetics, and it is an extremely rare sensitizer.<sup>53</sup> As mentioned above, it is doubtful whether the positive reactions seen in our study group really reflect contact sensitization; therefore our data are not disagreeing.

## Conclusion

From our data analysis, we can draw the following conclusions. True allergic reactions to cosmetic ingredients are rarer than generally assumed. Fragrances seem to be the most frequent sensitizers in cases of contact allergy due to cosmetics. We could not identify special fragrance allergens in leave-on cosmetics. Among the preservatives, MI is currently the most important allergen, urgently requiring measures of primary prevention (limitation of exposure). Increasing sensitization to MI is (partly) responsible for the increase in reactions to MCI/MI in patients with suspected cosmetic intolerance. Other widely used preservatives, such as parabens or phenoxyethanol, are safe from the allergological point of view.

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