

DR SONJA CHRISTINE MOLIN (Orcid ID : 0000-0002-9383-034X)

Article type : Original Article

## **The frequency of specific contact allergies is reduced in psoriasis patients**

A. Claßen <sup>1</sup>\*, T. Buhl <sup>1</sup>\*, S. Schubert <sup>2</sup>, M. Worm <sup>3</sup>, A. Bauer <sup>4</sup>, J. Geier <sup>2</sup>, S. Molin <sup>5,6</sup> # for the  
IVDK study group +

<sup>1</sup> Department of Dermatology and Allergology, University Medical Center Goettingen, Germany

<sup>2</sup> Information Network of Departments of Dermatology (IVDK), University of Goettingen,  
Germany

<sup>3</sup> Department of Dermatology and Allergology, Allergy-Center-Charité, Charité -  
Universitaetsmedizin Berlin, Germany

<sup>4</sup> Department of Dermatology, University Hospital Carl Gustav Carus, Technical University  
Dresden, Germany

<sup>5</sup> Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany

<sup>6</sup> Division of Dermatology, Queen's University, Kingston, Canada

\* Equal contribution

### **Corresponding author:**

Sonja Molin

Division of Dermatology  
Queen's University  
166 Brock Street, C3-027

This article has been accepted for publication and undergone full peer review but has not been  
through the copyediting, typesetting, pagination and proofreading process, which may lead to  
differences between this version and the Version of Record. Please cite this article as doi:

10.1111/bjd.17080

This article is protected by copyright. All rights reserved.

Kingston, ON K7L 5G2  
Canada  
E-Mail: s.molin@queensu.ca

**Running head:** Allergic contact dermatitis in psoriasis

**Keywords:** psoriasis, allergic contact dermatitis, baseline series, patch testing, Th1, Th17

**Conflict of interest:** The authors declare not conflict of interest.

**Funding sources:** none

### **What's already known about this topic?**

Earlier studies suggested an inverse association between contact allergy and psoriasis, although the results have been inconsistent.

### **What does this study add?**

Our findings revealed a significantly lower overall risk for contact sensitization in individuals with psoriasis and lend further support to the potential role of allergen-specific immune polarization in contact dermatitis.

### **Abstract**

**Background:** Earlier studies suggested an inverse association between contact allergy and psoriasis, although the results of clinical studies have been inconsistent. Gene-expression studies in human contact allergy focusing on immune responses revealed nickel being an inducer of Th1/Th17 and some Th22 immune polarization, whereas fragrances were found to promote a Th2-dominated immune activation.

**Objectives:** To investigate (i) the epidemiological association between contact allergy and psoriasis in a large multicenter cohort and (ii) to analyze the sensitization profile to specific allergens in these patients.

**Patients and Methods:** Retrospective analysis of patch-tested patients from 56 departments of dermatology (1996-2015), including 2,387 patients with psoriasis, and 161,989 control patients. All patients with atopic dermatitis were excluded from both groups.

Results: The odds ratio (OR) for contact allergy was calculated to be 0.545 in psoriasis patients [95% confidence interval: 0.501-0.593]. Logistic regression analyses with several independent variables indicated a “protective effect” of having psoriasis for most allergens, independent of age, sex, affected body site, and patch test indication. Fragrance mix II (OR = 0.36) and lanolin alcohols (OR = 0.38) were found among the least common allergens in psoriatics. In contrast, the frequency of contact dermatitis to nickel was only marginally affected in patients with psoriasis compared to controls (OR=0.75).

Conclusions: The inverse association between psoriasis and allergic contact sensitization is likely to be not exclusively mediated by psoriasis itself. The polarization of the activated immune response by specific allergens may influence occurrence and significance of contact allergies in underlying immune-mediated diseases, eventually even beyond the skin.

## INTRODUCTION

Contact dermatitis is a complex yet common problem and a major challenge both for public health and immunology. An estimated 15-20% of the general population are affected by contact dermatitis, and regarding occupational diseases, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) range on top of these medical conditions <sup>1</sup>. Although an impressive amount of research has identified two distinct pathophysiological phases in the development of ACD, namely sensitization and elicitation phase, the complex immune mechanisms behind them are incompletely understood <sup>2,3</sup>.

Distinct hapten-specific polarizations of the murine immune system have been observed (reviewed in <sup>4</sup>), but attempts to translate and validate these findings to/in humans have been performed with rather low enthusiasm. Frequently expressed concerns comprise the lack of mounting allergic responses to clinically relevant allergens in mice (e.g. nickel), and the relevance of murine models for human ACD in general <sup>4</sup>. Only a few human ACD studies included skin analyses and most of them addressed either isolated specific markers or allergens or grouped immune responses to different allergens into a single concordant immune event <sup>5-7</sup>. Only recently, the analysis of shared and unique ACD transcriptomes, skin sections, and rtPCR data from human skin distinguished distinct polarizations of the immune response towards the three frequent allergens nickel, fragrance, and rubber: Nickel demonstrated induction of innate immunity and a Th1/Th17 signature, whereas fragrances and rubber polarized the immune response towards Th2, with smaller shares in Th22 and Th1/Th17 <sup>8</sup>.

We therefore became interested to investigate, whether ACD patients with a chronic immune-mediated disease would show different allergen-specific sensitization profiles than otherwise healthy ACD patients. Since psoriasis is one of the best characterized immune-mediated diseases with the interleukin-23/Th17 axis playing a major role in its immunopathology, we decided to analyze sensitization profiles in ACD patients with psoriasis versus otherwise healthy ACD patients. The availability of highly efficient antibodies successfully blocking this immune-mediated pathway in psoriasis underlines the homogenous immunopathology of this disease<sup>9,10</sup> thus making psoriasis an ideal clinical setting for investigating effects of systemic immune-deviation on ACD.

The development and frequencies of contact sensitization in psoriasis patients have been discussed controversially. Some former studies showed a significantly lower prevalence of contact allergies<sup>11-13</sup> whereas others reported an increase of positive patch tests in psoriasis patients<sup>14,15</sup>. To the best of our knowledge, no study has investigated the frequency of specific allergens in ACD patients with psoriasis in a sufficiently powered cohort. Therefore, we performed a retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK) regarding the prevalence of ACD in 2,387 patch-tested psoriasis patients from Germany, Austria and Switzerland, and compared the results to a control group of 161,989 patch-tested ACD patients without psoriasis.

## **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 procedures are described in detail elsewhere<sup>16</sup>. Briefly, patients' history, clinical data including a major and a minor diagnosis, and patch test results of all patients patch tested in the participating centers are recorded in local databases and, after anonymization, transmitted to the IVDK central office at the University of Göttingen twice a year. Data are subject to standardized quality control, added to the central IVDK database, and analyzed according to international standards<sup>17</sup>. This retrospective study has been reviewed and approved by the local ethics committee at the University Medical Center Göttingen.

For this data analysis, we selected data of the years 1996 to 2015 from the central database of the IVDK. Of the 207,050 patients patch tested in the IVDK during these years, we selected patients with major diagnosis "psoriasis". Among these patients, we limited our selection to those

without atopic dermatitis (study group: n = 2,387 patients). The control group consisted of patients without any diagnosis of psoriasis and, to ensure homogeneity between the groups, without any diagnosis of atopic dermatitis as well (n = 161,989). All IVDK members also are members of the German Contact Dermatitis Research Group (DKG). Patch testing and evaluation of reactions is performed according to DKG and ESCD guidelines<sup>18,19</sup>. For this data analysis, patch test reactions at day 3 (D3) were considered. In few exceptional cases, when a reading was done at D4 instead of D3, this reading was selected. Readings coded as +, ++ or +++, i.e. positive reactions with erythema, infiltration, papules and/or (coalescing) vesicles, according to scoring, were rated as positive in dichotomized analyses. Patch test preparations were purchased from Almirall Hermal, Reinbek, Germany, until 2013, and from SmartPractice Europe, Reinbek, Germany, from 2014 on. Patch test exposure time was 24 hours in 24%, and 48 hours in 76% of the patients. With a few (temporary) exceptions, Finn-Chambers-on-Scanpor (8 mm inner diameter) were used as test chambers. In recent years, we increasingly started to read patch test results also on day 7.

In order to allow a comparison of sensitization frequencies of baseline series allergens, reaction rates were standardized for sex and age (32.5% women < 40 years of age, 32.5% women ≥ 40 years of age, 17.5% men < 40 years of age, 17.5% men ≥ 40 years of age) using previously published methods<sup>20,21</sup>. Statistical significance (p < 0.05) of differences in sensitization frequencies was determined by non-overlapping 95% confidence intervals (CI) of standardized reaction rates. CIs of reaction rates with zero positive reactions were calculated as published earlier<sup>22</sup>. Differences in proportions of population characteristics between the study group and the control group were tested for statistical significance with the Chi<sup>2</sup>-test. Data was managed and analyzed using the statistical analysis software SAS®, version 9.3 (SAS Institute, Cary, NC, USA).

Reaction frequencies to single allergens are influenced by distributions of age and sex<sup>21</sup> and in addition by a more or less liberal or directed indication for patch testing. All these factors are not distributed equally in the study group (psoriasis patients) and the control group. We performed logistic regression analyses with positive patch test reactions to baseline series allergens as target (dependent) variables, and seven dichotomized independent variables. These were “exclusion of contact allergy” as patch test indication, female sex, age of ≥ 40 years, affected body site “hand” / “face” / “leg”, and being a psoriasis patient (member of the study group) or not (member of the control group). Logistic regression analyses were performed with 100 as the maximal number of iterations. Results are presented as odds-ratio (OR) estimates with profile-

likelihood CIs. The model used was verified by the Hosmer and Lemeshow goodness-of-fit test ( $p > 0.05$ ). Our data analysis was limited to patch test results with those 19 allergen preparations which had been part of the DKG baseline series over the whole study period (1996 – 2015), with 2 exceptions: Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) was introduced into the DKG baseline series in 2002, and fragrance mix II in 2005.

## RESULTS

For a descriptive characterization and easier capture of the differences between patient groups with contact dermatitis, the MOAHLFA-index is a well-established instrument to describe factors potentially influencing the frequency of sensitization to particular allergens<sup>21</sup>. In brief, this index is used to display the proportion of male sex, occupational, atopic, hand, leg or face dermatitis, and age >40 years within patient groups. Our study group (psoriasis patients without atopic dermatitis, n=2,387 patients) and our control group (all other tested patients without atopic dermatitis, n=161,989 patients) differed significantly in all items of the MOAHLFA (Tab. 1). We found significantly more males and slightly higher percentages of patients with occupational dermatitis and age of 40 years and more in the study group. The majority (54.5%) of patch-tested psoriasis patients had hand dermatitis, whereas only a minority of control group patients showed hand involvement (23.6%). An affection of the face and legs was observed far more frequently in the control group (Tab. 1). A more detailed analysis of our data revealed important differences in indications for patch testing in the patient groups. Of the study group (psoriasis patients), 59.4% (n=1,418) were tested to exclude contact allergy, while this was the case in only 36.8% (n=59,683) of the control group patients ( $P < 0.001$ ).

We identified 2,294 patients (96.1%) in the study group and 146,873 patients in the control group (90.6%) who were patch tested with the DKG baseline series. 578 of 2,294 (25%) patients in the study group, and 57,155 of 146,873 (39%) patients in the control group showed at least one positive reaction to the baseline series allergens presented in this study. The difference was statistically significant ( $P < 0.001$ ). Patient numbers as well as age- and sex-standardized proportions of patients with positive reactions to the 19 baseline series allergens are listed in table 2. In accordance with the lower overall proportion of positive reactions in the study group, lower reaction frequencies were observed with all of these 19 allergen preparations. However, in 4 cases, statistical significance was not reached: cobalt chloride, methylchloroisothiazolinone / methylisothiazolinone (MCI/MI), mercapto mix, and paraben mix. One can expect sensitization frequencies to be lower in those subgroups of patients who are tested to exclude contact allergy

when compared to those tested because of suspected contact allergy. Therefore, we compared patch test results in these subgroups of patients, separately for the study and the control group (Tab. S1+S2). In the study group, only fragrance mix II showed a significantly reduced age- and sex-standardized percentage of positive reactions in the subgroup tested for exclusion of contact allergy (0.6% vs. 2.9%), while there was no significant difference with all other 18 of the 19 allergens. In contrast, reaction frequencies to all allergens were significantly reduced in the control group among those tested in order to exclude contact allergy. The detailed results of these subgroup analyses are displayed in the supplemental files.

Analyzing our large cohort of patch-tested patients with psoriasis (n=2,387) in comparison to all other tested individuals (n=161,989) from 56 allergy departments in Germany, Austria and Switzerland, we found a significantly lower risk for contact sensitization in psoriasis patients to the 19 baseline series allergens (listed in Tab. 2). The odds ratio for contact allergy was calculated to be 0.545 [95% CI: 0.501-0.593] in psoriasis patients, without any further consideration of allergens and circumstances.

As mentioned earlier, reaction frequencies to single allergens are influenced by distributions of age and sex<sup>21</sup> and in addition by a more or less liberal or directed indication for patch testing. Since all these factors are not distributed equally in the study group and control group, we consolidated our results by logistic regression analyses with several independent parameters. Results of these logistic regression analyses with positive patch test reactions to one of the 19 baseline series allergens as target variables, and the seven independent variables indication “exclusion of contact allergy”, sex, age  $\geq 40$  years, affected body site “hand” / “face” / “leg”, and being a psoriasis patient (member of the study group) or not (member of the control group) are presented in table 3. With two exceptions (paraben mix and mercapto mix), ORs for being a psoriasis patient were significantly below 1, indicating a “protective effect” concerning sensitization to these allergens, independent of age, sex, affected body site, and patch test indication. Interestingly, this effect was most convincingly found with thiuram mix (OR = 0.34), fragrance mix II (OR = 0.36), and lanolin alcohols (OR = 0.38). Although other allergens were calculated with even lower or equal ORs (zinc diethyldithiocarbamate OR = 0.29, IPPD OR = 0.37), they were found positive in only seven or less psoriasis patients, thus this data basis needs to be considered less solid. In contrast, the “protective effect” of being a psoriasis patient regarding nickel allergy was much less pronounced; the corresponding OR was still significantly reduced, but this was in fact the least affected allergen (OR = 0.75), closely followed by cobalt (OR = 0.70). Being female was associated with a more than fourfold increased risk of nickel

sensitization (OR = 4.70) and with an increased risk of fragrance allergy, but to a lesser extent. An age of 40 years or more posed a higher risk of fragrance allergy and sensitization to Balsam of Peru but had a “protective” effect concerning nickel and cobalt allergy. Indication “exclusion of contact allergy” significantly lowered the risk of sensitization to all allergens included in this analysis.

In addition to the baseline series allergens, we also analyzed our study group for sensitization to external drugs. Patch tests with ingredients of medical creams and ointments, mainly topical corticosteroids and topical vitamin D3 analogs, were performed in 102 of the 2,387 psoriasis patients. However, no positive reactions to any of the common topical psoriasis treatments were found (two questionable positive reactions to the irritant dithranol).

## DISCUSSION

The aim of our study was to analyze the specific contact sensitization profiles of psoriasis patients. We therefore compared the patch-test results and detailed clinical features of a large cohort of patients with psoriasis (n = 2,387) and a large cohort of non-psoriatic individuals (n = 161,989), both without atopic background, from 56 allergy departments in Germany, Austria and Switzerland. This resulted in a comprehensive data set that allowed us to rule out many possible confounders by logistic regression analysis. Our findings revealed a significantly lower overall risk for contact sensitization in individuals with psoriasis (OR 0.545).

The prevalence of contact sensitization in psoriasis patients has been discussed controversially before. Some studies showed a significantly lower prevalence of contact allergies in psoriatics compared to healthy individuals, with odds ratios of 0.58 respectively 0.64 compared to other patients, adjusted for age and sex<sup>11-13</sup>. These studies are in line with our data. Other studies lead to contradictory results, describing 42.7% or 68% psoriasis patients with positive patch tests to baseline series allergens<sup>14,15</sup>. The two last cohorts, however, were from monocenter studies and included only 110 and 47 patients that were tested with the local standard series. Another recent monocentric study did not find a significant difference in sensitization to allergens from an extended European baseline series in 2,349 psoriasis patients and 39,910 non-psoriasis patch-test patients<sup>23</sup>. However, results were not adjusted for age or sex or other confounding factors like in our study and included patients with atopic background (remarkably, 30% of patients in both groups were reported with coexisting atopic dermatitis). Previous analyses have shown similar results for patients with atopic eczema<sup>24</sup>. Therefore, the atopic predisposition in the latter study

must be considered a significant confounding factor and might explain the difference in results compared to our non-atopic study cohort.

Several other factors may also have contributed to the apparently contradictory findings from different studies on contact sensitization in psoriasis, such as ongoing treatment with UV-light, topical immunomodulators or systemic immune suppressants. Diagnostic criteria for psoriasis may differ as well as may the exact patch testing protocols.

Still, to the best of our knowledge, our study population is largest cohort ever investigated on this question, and our results on the lower frequency match almost perfectly the only earlier Danish study on a larger population outside a single medical center <sup>13</sup>.

Many factors might influence the allergic sensitization rates in a cohort of patients, including sex, age, but also indication for patch testing or localization of the allergic contact dermatitis. For example, a larger percentage of patients in our study group (59.4%) were patch tested to specifically exclude contact allergies (compared to only 36.8% in the control group) because the clinicians did not suspect an underlying contact allergy. This could make a higher percentage of positive reactions more likely among the control group and might influence the overall outcome. Also for example the frequency of hand dermatitis was higher among the study group compared to the control group. Like hand dermatitis, psoriatic inflammation of the hands is associated with epidermal barrier dysfunction <sup>25</sup>. One might therefore expect an increased frequency of contact allergies due to the elevated allergen penetration among those patients.

To rule out these confounders we performed a logistic regression analysis including these items as independent variables. With two exceptions (paraben mix and mercapto mix), being a psoriasis patient was associated with a “protective effect” on sensitization to the allergens from the baseline series, independent of age, sex, affected body site, and also patch test indication.

In addition, the results of our logistic regression analysis replicated well-known associations, e.g. between hand dermatitis and glove allergens (thiuram mix, OR 3.58), females and nickel sensitization (OR 4.70), higher age and balsam of Peru sensitization (OR 2.50) or leg dermatitis and lanolin alcohols (OR 4.45), underlining the trustworthiness of our results <sup>26-29</sup>.

An important aim of our study was the comprehensive analysis of the allergen-specific sensitization profile of psoriasis patients. With this we wanted to gain detailed insight into the influence of systemic IL23/Th17-polarized inflammation in psoriasis on different contact allergens. By focusing our analysis on the contact allergens of the baseline series, we again

found a consistently lower frequency of reactions in the psoriasis group. This effect was most pronounced with thiuram mix (OR = 0.34), fragrance mix II (OR = 0.36) and lanolin alcohols (OR = 0.38). Of note, the immune response triggered by these allergens differs significantly from the inflammatory cytokines involved in psoriasis<sup>8</sup>. Interestingly, former studies showed elevated sensitization rates of these allergens in atopic dermatitis, a chronic inflammatory skin disease leaning towards a Th2-polarized immune response<sup>24</sup>. Suffering from psoriasis would thus result in lower sensitization respectively “protection” to Th2-inducing allergens. As expected, we observed in our study almost the opposite effect of sensitization rates with the Th1/Th17-polarizing haptens nickel and cobalt. These two haptens resulted in only slightly reduced positive patch test results in psoriasis patients (ORs 0.75 and 0.70).

Potential limitations of our study are that we do not have any information on the history and duration of psoriasis or concomitant diseases in the individual patients as well as we do not have late readings in all patch test patients. Both, disease duration of psoriasis and date of patch test reading might be of interest when comparing reaction profiles of psoriasis patients and healthy controls. In previous reports, psoriasis patients with longer disease duration were found to have a higher rate of patch test positivity to topical drugs, nickel, and fragrances compared to newly diagnosed psoriasis patients<sup>30</sup>. In addition, it was only recently reported that patch test reactions to nickel reach their maximum 2-3 days later in psoriasis patients compared to non-psoriatic patients<sup>7</sup>, suggesting a benefit of late readings at day 7.

Taking together, psoriasis and contact dermatitis both involve complex immune processes that make it difficult to understand what happens in case of their co-occurrence. Our findings provide evidence from a large cohort of patch test patients with and without psoriasis, lending further support to the potential role of allergen-specific immune polarization in contact dermatitis.

## ACKNOWLEDGEMENTS

We thank the colleagues from the 70 co-operation partner clinics of the IVDK who contributed data to this analysis.

+ Members of the IVDK study group:

Ulrike Beiteke, Department of Dermatology, Dortmund Hospital, Dortmund, Germany;  
ulrike.beiteke@klinikumdo.de

This article is protected by copyright. All rights reserved.

Joachim Dissemmond, Department of Dermatology, University Hospital, Essen, Germany;  
Joachim.Dissemmond@uk-essen.de

Timo Buhl, Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany; timo.buhl@med.uni-goettingen.de

Knut Schäkel, Department of Dermatology, Ruprecht Karls University, Heidelberg, Germany;  
Knut.Schaekel@med.uni-heidelberg.de

Claudia Pföhler, Department of Dermatology, Saarland University Medical School, Homburg, Germany; claudia.pfoehler@uks.eu

Jochen Brasch, Department of Dermatology, University Hospitals of Schleswig-Holstein, Campus Kiel, Kiel, Germany; jbrasch@dermatology.uni-kiel.de

Margitta Worm, Allergy Unit, Department of Dermatology and Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany; margitta.worm@charite.de

Andrea Bauer, Clinic and Policlinic for Dermatology, Medical Faculty Carl Gustav Carus, TU Dresden, Dresden, Germany; Andrea.Bauer@uniklinikum-dresden.de

Burkhard Kreft, Department of Dermatology and Venereology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; burkhard.kreft@uk-halle.de

Sibylle Schliemann, Department of Dermatology, Jena University Hospital, Jena, Germany;  
Schliemann@derma-jena.de

Ulf Darsow, Department of Dermatology and Allergology, Technical University Munich, Munich, Germany; ulf.darsow@tum.de

Detlef Becker, Department of Dermatology, University of Mainz, Mainz, Germany;  
detlef.becker@unimedizin-mainz.de

Jörg Fischer, Department of Dermatology and Allergology, University Medical Center Tübingen, Tübingen, Germany; joerg.fischer@med.uni-tuebingen.de

Karin Hartmann, Department of Dermatology, University of Luebeck, Luebeck, Germany;  
Karin.Hartmann@uksh.de

Jana Witte, Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany; j.witte@uke.de

Wolfgang Pfützner, Clinical & Experimental Allergology, Department of Dermatology and Allergology, Philipps-University Marburg, Germany; wolfgang.pfuetzner@med.uni-marburg.de

Brigitte Coras-Stepanek, Department of Dermatology, Allergology and Environmental Medicine, Hospital Munich Schwabing, Munich, Germany; brigitte.coras@klinikum-muenchen.de

Christoph Skudlik, Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm) and Department of Dermatology, Environmental Medicine, and Health Theory, University of Osnabrück, Osnabrück, Germany; christoph.skudlik@uos.de

Nicola Wagner, Department of Dermatology, Erlangen University Hospital, Erlangen, Germany;  
nicola.wagner@uk-erlangen.de

Werner Aberer, Department of Dermatology and Venerology, Medical University of Graz, Austria; Werner.Aberer@medunigraz.at

Steffen Emmert, Department of Dermatology and Venereology, University Medicine Rostock, Rostock, Germany; steffen.emmert@med.uni-rostock.de

Jens Malte Baron, Department of Dermatology and Allergology, University Hospital of Aachen, Aachen, Germany; jbaron@ukaachen.de

Alika Ludwig, Department of Dermatology and Allergology, Klinikum Augsburg, Augsburg, Germany; Alika.Ludwig@klinikum-augsburg.de

Johannes Weiß, Department of Dermatology and Allergy, University of Ulm, Ulm, Germany; johannes.weiss@uniklinik-ulm.de

Vera Baur, Department of Dermatology, Paracelsus Medical University Nuremberg, Nürnberg, Germany; Vera.Baur@klinikum-nuernberg.de

Astrid Schmieder, Department of Dermatology, Venereology and Allergology, University Medical Center and Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; astrid.schmieder@umm.de

Elke Weisshaar, Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Medical Center, Heidelberg, Germany; Elke.Weisshaar@med.uni-heidelberg.de

Heidrun Grunwald-Delitz, Department of Dermatology, Wald Klinikum Gera, Gera, Germany; heidrun.grunwald-delitz@srh.de

Axel Trautmann, Department of Dermatology, Venereology, and Allergology, University Hospital Würzburg, Würzburg, Germany; Trautmann\_A@ukw.de

Andreas Bircher, University Hospital Basel, Department of Dermatology, Basel, Switzerland; Andreas.Bircher@unibas.ch

Christiane Szliska, Department of Dermatology, Bethesda Hospital, Freudenberg, Germany; christiane.szliska@diakonie-siegen.de

Isaak Effendy, Department of Dermatology, Bielefeld Medical Center, Bielefeld, Germany; Isaak.Effendy@sk-bielefeld.de

Michael Jünger, Department of Dermatology, University Medicine Greifswald, Greifswald, Germany; juenger@uni-greifswald.de

Randolf Brehler, Department of Dermatology, University Hospital Münster, Münster, Germany; r.brehler@uni-muenster.de

Sonja Molin, Department of Dermatology and Allergology, Ludwig-Maximilians-University, Munich, Germany; Sonja.Molin@med.uni-muenchen.de

Thomas Werfel, Department of Dermatology and Allergy, Division of Immunodermatology and Allergy Research, Hannover Medical School, Hannover, Germany; Werfel.Thomas@mh-hannover.de

Heinrich Dickel, Department of Dermatology, Venereology and Allergology, Ruhr University Bochum, Bochum, Germany; heinrich.dickel@rub.de

This article is protected by copyright. All rights reserved.

Juliane Rieker-Schwienbacher, Center for Dermatology, Phlebology and Allergology, Klinikum Stuttgart, Stuttgart, Germany; j.rieker-schwienbacher@klinikum-stuttgart.de

Dieter Vieluf, Department of Allergology, Photodermatology and Occupational dermatology, Dermatologikum Hamburg, Hamburg, Germany; d.vieluf@dermatologikum.de

Rudolf Stadler, Department of Dermatology, University Hospital, Johannes Wesling Klinikum, Minden, Germany; Rudolf.Stadler@klinikum-minden.de

Dagmar Simon, Department of Dermatology, Bern University Hospital, Bern, Switzerland; dagmar.simon@insel.ch

Manigé Fartasch, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany; fartasch@ipa-dguv.de

Alexander Navarini, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; Alexander.Navarini@usz.ch

Regina Treudler, Leipzig Interdisciplinary Allergy Center (LICA), Department of Dermatology, Venereology and Allergology, University Medical Center, Leipzig, Germany; regina.treudler@uniklinik-leipzig.de

Dirk Mechtel, Clinic for Skin Diseases and Allergology, Heinrich Braun Klinikum, Zwickau, Germany; dirk.mechtel@hbk-zwickau.de

Claudia Schröder-Kraft, Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm) of the University of Osnabrück and Dermatologic Center, BG Trauma Hospital Hamburg, Hamburg, Germany; c.schroeder-kraft@bgk-hamburg.de

Harald Löffler, Department of Dermatology, SLK Hospital Heilbronn, Heilbronn, Germany; Harald.Loefler@slk-kliniken.de

Matthias Fischer, BG Clinic Falkenstein of Occupational Diseases, Falkenstein, Germany; m.fischer@klinik-falkenstein.de

André Koch, Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; koch-ae@khdf.de

Ulrike Raap, Department of Dermatology, University of Oldenburg, Oldenburg, Germany; raap.ulrike@klinikum-oldenburg.de

Stefan Nestoris, Clinic for Dermatology, Klinikum Lippe-Detmold, Detmold, Germany, Stefan.Nestoris@klinikum-lippe.de

Jürgen Grabbe, Department of Dermatology, Cantonal Hospital Aarau, Aarau, Switzerland; Juergen.Grabbe@ksa.ch

Julie di Lucca, Department of Dermatology, University Hospital Center CHUV, Lausanne, Switzerland; julie.di-lucca@chuv.ch

Markus Zutt, Department of Dermatology and Allergology, Medical Center Bremen-Mitte, Bremen, Germany; markus.zutt@klinikum-bremen-mitte.de

Philipp Spring, Dermatological and Dermato-Surgical Center CEDDECC, Lausanne, Switzerland; springphil@hotmail.com

This article is protected by copyright. All rights reserved.

## REFERENCES

- 1 Peiser M, Tralau T, Heidler J *et al.* Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. *Cell Mol Life Sci* 2012; **69**: 763-81.
- 2 Kaplan DH, Igyarto BZ, Gaspari AA. Early immune events in the induction of allergic contact dermatitis. *Nat Rev Immunol* 2012; **12**: 114-24.
- 3 Kostner L, Anzengruber F, Guilloid C *et al.* Allergic Contact Dermatitis. *Immunol Allergy Clin North Am* 2017; **37**: 141-52.
- 4 Honda T, Egawa G, Grabbe S *et al.* Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. *J Invest Dermatol* 2013; **133**: 303-15.
- 5 Larsen JM, Bonefeld CM, Poulsen SS *et al.* IL-23 and T(H)17-mediated inflammation in human allergic contact dermatitis. *J Allergy Clin Immunol* 2009; **123**: 486-92.
- 6 Pennino D, Eyerich K, Scarponi C *et al.* IL-17 amplifies human contact hypersensitivity by licensing hapten nonspecific Th1 cells to kill autologous keratinocytes. *J Immunol* 2010; **184**: 4880-8.
- 7 Quaranta M, Eyerich S, Knapp B *et al.* Allergic contact dermatitis in psoriasis patients: typical, delayed, and non-interacting. *PLoS One* 2014; **9**: e101814.
- 8 Dhingra N, Shemer A, Correa da Rosa J *et al.* Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol* 2014; **134**: 362-72.
- 9 Merola JF, Li T, Li WQ *et al.* Prevalence of psoriasis phenotypes among men and women in the USA. *Clin Exp Dermatol* 2016; **41**: 486-9.
- 10 Boehncke WH, Schon MP. Psoriasis. *Lancet* 2015; **386**: 983-94.
- 11 Barile M, Cozzani E, Anonide A *et al.* Is contact allergy rare in psoriatics? *Contact Dermatitis* 1996; **35**: 113-4.
- 12 Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995; **32**: 982-6.
- 13 Bangsgaard N, Engkilde K, Thyssen JP *et al.* Inverse relationship between contact allergy and psoriasis: results from a patient- and a population-based study. *Br J Dermatol* 2009; **161**: 1119-23.
- 14 Krupashankar DS, Manivasagam SR. Prevalence and relevance of secondary contact sensitizers in subjects with psoriasis. *Indian Dermatol Online J* 2012; **3**: 177-81.
- 15 Heule F, Tahapary GJ, Bello CR *et al.* Delayed-type hypersensitivity to contact allergens in psoriasis. A clinical evaluation. *Contact Dermatitis* 1998; **38**: 78-82.
- 16 Schnuch A, Geier J, Lessmann H *et al.* Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy* 2012; **67**: 847-57.
- 17 Uter W, Schnuch A, Gefeller O *et al.* Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47-56.
- 18 Schnuch A, Aberer W, Agathos M *et al.* [Performing patch testing with contact allergens]. *J Dtsch Dermatol Ges* 2008; **6**: 770-5.
- 19 Johansen JD, Aalto-Korte K, Agner T *et al.* European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195-221.
- 20 Schnuch A. PAFS: population-adjusted frequency of sensitization. (I) Influence of sex and age. *Contact Dermatitis* 1996; **34**: 377-82.

- 21 Schnuch A, Geier J, Uter W *et al.* National rates and regional differences in sensitization to  
allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in  
40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200-9.
- 22 Gefeller O, Pfahlberg AB, Uter W. What can be learnt from nothing? - A statistical perspective.  
*Contact Dermatitis* 2013; **69**: 350-4.
- 23 Alwan W, Lynch M, McFadden J *et al.* Patch testing in patients with psoriasis: results of a 30-year  
retrospective study. *Br J Dermatol* 2017.
- 24 Heine G, Schnuch A, Uter W *et al.* Type-IV sensitization profile of individuals with atopic eczema:  
results from the Information Network of Departments of Dermatology (IVDK) and the German  
Contact Dermatitis Research Group (DKG). *Allergy* 2006; **61**: 611-6.
- 25 Schmuth M, Blunder S, Dubrac S *et al.* Epidermal barrier in hereditary ichthyoses, atopic  
dermatitis, and psoriasis. *J Dtsch Dermatol Ges* 2015; **13**: 1119-23.
- 26 Uter W, Hegewald J, Pfahlberg A *et al.* Contact allergy to thiurams: multifactorial analysis of  
clinical surveillance data collected by the IVDK network. *Int Arch Occup Environ Health* 2010; **83**:  
675-81.
- 27 Uter W, Pfahlberg A, Gefeller O *et al.* Risk factors for contact allergy to nickel - results of a  
multifactorial analysis. *Contact Dermatitis* 2003; **48**: 33-8.
- 28 Uter W, Geier J, Pfahlberg A *et al.* The spectrum of contact allergy in elderly patients with and  
without lower leg dermatitis. *Dermatology* 2002; **204**: 266-72.
- 29 Erfurt-Berge C, Geier J, Mahler V. The current spectrum of contact sensitization in patients with  
chronic leg ulcers or stasis dermatitis - new data from the Information Network of Departments  
of Dermatology (IVDK). *Contact Dermatitis* 2017; **77**: 151-8.
- 30 Malhotra V, Kaur I, Saraswat A *et al.* Frequency of patch-test positivity in patients with psoriasis:  
a prospective controlled study. *Acta Derm Venereol* 2002; **82**: 432-5.

## TABLES

**Tab. 1: MOAHLFA-indices of the study and the control group.**

| MOAHLFA-index           |   | Study group<br>(n= 2,387) |         | Control group<br>(n= 161,989) |         | Significance               |
|-------------------------|---|---------------------------|---------|-------------------------------|---------|----------------------------|
|                         |   | count                     | percent | count                         | percent | p-value of chi-square test |
| Male                    | M | 1,061                     | 44.4    | 60,399                        | 37.3    | <0.0001                    |
| Occupational dermatitis | O | 355                       | 14.9    | 21,196                        | 13.1    | 0.0102                     |
| Atopic dermatitis       | A | 0*                        | 0.0     | 0*                            | 0.0     | -                          |
| Hand dermatitis         | H | 1,300                     | 54.5    | 38,158                        | 23.6    | <0.0001                    |
| Leg dermatitis          | L | 101                       | 4.2     | 20,632                        | 12.7    | <0.0001                    |
| Face dermatitis         | F | 47                        | 2.0     | 24,018                        | 14.8    | <0.0001                    |
| Age ≥ 40 years          | A | 1,852                     | 77.6    | 119,307                       | 73.7    | <0.0001                    |

\* Atopic dermatitis patients were excluded, according to the study design.

**Tab. 2: Patch testing with 19 allergens from the DKG baseline series, 1996-2015. Vehicle was petrolatum unless otherwise indicated.**

**Significant differences in age- and sex-standardized proportions of patients with positive reactions are marked in bold print.**

| Substance                                                     | Test concentration | Study group (n=2,294)     |                                  |                                               | Control group (n=146,873) |                                  |                                               |
|---------------------------------------------------------------|--------------------|---------------------------|----------------------------------|-----------------------------------------------|---------------------------|----------------------------------|-----------------------------------------------|
|                                                               |                    | Number of patients tested | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] | Number of patients tested | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] |
| <b>Nickel sulfate</b>                                         | <b>5 %</b>         | <b>2,214</b>              | <b>229</b>                       | <b>13.6 [11.7 - 15.6]</b>                     | <b>143,046</b>            | <b>20,265</b>                    | <b>16.9 [16.7 - 17.1]</b>                     |
| <b>Fragrance mix I</b>                                        | <b>8 %</b>         | <b>2,230</b>              | <b>96</b>                        | <b>4.5 [3.4 - 5.6]</b>                        | <b>143 835</b>            | <b>13 606</b>                    | <b>8.4 [8.2 - 8.5]</b>                        |
| Cobalt chloride                                               | 1 %                | 2,242                     | 84                               | 4.5 [3.4 - 5.7]                               | 143,927                   | 7330                             | 5.8 [5.7 - 6.0]                               |
| <b>Balsam of Peru (Myroxylon pereirae)</b>                    | <b>25 %</b>        | <b>2,239</b>              | <b>102</b>                       | <b>3.8 [2.9 - 4.6]</b>                        | <b>143,977</b>            | <b>13 169</b>                    | <b>7.6 [7.5 - 7.7]</b>                        |
| <b>Potassium dichromate</b>                                   | <b>0.5 %</b>       | <b>2,245</b>              | <b>57</b>                        | <b>2.2 [1.5 - 2.9]</b>                        | <b>144,093</b>            | <b>5702</b>                      | <b>3.7 [3.6 - 3.8]</b>                        |
| Methylchloroisothiazolinone / methylisothiazolinone (MCI/MI)  | 100 ppm aq.        | 2,239                     | 41                               | 2.0 [1.2 - 2.7]                               | 143,801                   | 4043                             | 2.7 [2.6 - 2.8]                               |
| <b>Fragrance mix II *</b>                                     | <b>14 %</b>        | <b>1,474</b>              | <b>26</b>                        | <b>1.7 [0.8 - 2.6]</b>                        | <b>85,466</b>             | <b>4322</b>                      | <b>4.5 [4.3 - 4.6]</b>                        |
| <b>Colophony</b>                                              | <b>20 %</b>        | <b>2,239</b>              | <b>36</b>                        | <b>1.2 [0.8 - 1.7]</b>                        | <b>144,103</b>            | <b>6054</b>                      | <b>4.1 [4.0 - 4.2]</b>                        |
| <b>Lanolin alcohols</b>                                       | <b>30 %</b>        | <b>2,241</b>              | <b>21</b>                        | <b>0.9 [0.4 - 1.3]</b>                        | <b>144,152</b>            | <b>4732</b>                      | <b>2.9 [2.8 - 3.0]</b>                        |
| <b>Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) **</b> | <b>5 %</b>         | <b>1,709</b>              | <b>15</b>                        | <b>0.9 [0.5 - 1.4]</b>                        | <b>105,132</b>            | <b>2167</b>                      | <b>1.9 [1.8 - 2.0]</b>                        |

|                                                        |                |              |           |                        |                |             |                        |
|--------------------------------------------------------|----------------|--------------|-----------|------------------------|----------------|-------------|------------------------|
| <b>Oil of turpentine</b>                               | <b>10 %</b>    | <b>2,240</b> | <b>23</b> | <b>0.8 [0.4 - 1.2]</b> | <b>143,966</b> | <b>2952</b> | <b>1.9 [1.8 - 1.9]</b> |
| <b>Thiuram mix</b>                                     | <b>1 %</b>     | <b>2,237</b> | <b>22</b> | <b>0.8 [0.4 - 1.1]</b> | <b>144,118</b> | <b>3207</b> | <b>2.2 [2.1 - 2.3]</b> |
| <b>Epoxy resin</b>                                     | <b>1 %</b>     | <b>2,194</b> | <b>21</b> | <b>0.8 [0.4 - 1.3]</b> | <b>143,821</b> | <b>2266</b> | <b>1.5 [1.4 - 1.6]</b> |
| Paraben mix                                            | 16 %           | 2,243        | 17        | 0.8 [0.3 - 1.3]        | 143,875        | 1741        | 1.1 [1.0 - 1.1]        |
| <b>Formaldehyde</b>                                    | <b>1 % aq.</b> | <b>2,242</b> | <b>16</b> | <b>0.6 [0.2 - 0.9]</b> | <b>144,196</b> | <b>1974</b> | <b>1.4 [1.3 - 1.4]</b> |
| Mercapto mix (without MBT)                             | 1 %            | 2,242        | 11        | 0.5 [0.1 - 0.8]        | 143,738        | 900         | 0.6 [0.6 - 0.7]        |
| <b>N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)</b> | <b>0.1 %</b>   | <b>2,241</b> | <b>7</b>  | <b>0.3 [0.0 - 0.6]</b> | <b>144,221</b> | <b>1086</b> | <b>0.8 [0.7 - 0.8]</b> |
| <b>Cetearyl alcohol</b>                                | <b>20 %</b>    | <b>2,243</b> | <b>7</b>  | <b>0.3 [0.0 - 0.6]</b> | <b>144,217</b> | <b>1613</b> | <b>0.9 [0.8 - 0.9]</b> |
| <b>Zinc diethyldithio-carbamate</b>                    | <b>1 %</b>     | <b>2,244</b> | <b>4</b>  | <b>0.1 [0.0 - 0.3]</b> | <b>144,234</b> | <b>761</b>  | <b>0.5 [0.5 - 0.5]</b> |

\* Reduced number of patients tested since fragrance mix II was not part of the baseline series before 2005.

\*\* Reduced number of patients tested since HICC was not part of the baseline series before 2002.

**Tab. 3: Logistic regression analyses with positive patch test reactions to baseline series allergens as target** (dependent) variables, and seven dichotomized independent variables (female sex, age of  $\geq 40$  years, affected body site “hand” / “face” / “leg”, “exclusion of contact allergy” as patch test indication, and being a psoriasis patient or not). Results are presented as odds ratios (OR) with 95% confidence intervals (profile likelihood method). Significant effects are presented with **boldfaced numbers**. For clarity reasons, we italicized the insignificant results.

| Target variables     | Odds ratio [95% confidence interval] of independent variables |                                                 |                           |                           |                              |                              |                             |
|----------------------|---------------------------------------------------------------|-------------------------------------------------|---------------------------|---------------------------|------------------------------|------------------------------|-----------------------------|
|                      | Psoriasis patient                                             | Indication<br>„exclusion of<br>contact allergy“ | Female sex                | Age 40+ years             | Affected body site<br>“hand” | Affected body site<br>“face” | Affected body site<br>“leg” |
| Nickel sulfate       | <b>0.75 [0.65 – 0.86]</b>                                     | <b>0.84 [0.82 – 0.87]</b>                       | <b>4.70 [4.51 – 4.91]</b> | <b>0.54 [0.52 – 0.56]</b> | <b>1.16 [1.11 – 1.20]</b>    | <i>1.04 [1.00 – 1.09]</i>    | <b>0.59 [0.56 – 0.63]</b>   |
| Fragrance mix I      | <b>0.47 [0.38 – 0.58]</b>                                     | <b>0.73 [0.71 – 0.76]</b>                       | <b>1.27 [1.22 – 1.32]</b> | <b>1.85 [1.76 – 1.94]</b> | <b>1.12 [1.07 – 1.17]</b>    | <b>1.21 [1.15 – 1.27]</b>    | <b>1.55 [1.47 – 1.63]</b>   |
| Cobalt chloride      | <b>0.70 [0.56 – 0.87]</b>                                     | <b>0.76 [0.72 – 0.79]</b>                       | <b>1.93 [1.83 – 2.04]</b> | <b>0.68 [0.68 – 0.72]</b> | <b>1.46 [1.38 – 1.54]</b>    | <b>0.91 [0.85 – 0.98]</b>    | <b>0.69 [0.63 – 0.76]</b>   |
| Balsam of Peru       | <b>0.54 [0.44 – 0.66]</b>                                     | <b>0.79 [0.76 – 0.82]</b>                       | <b>1.14 [1.10 – 1.19]</b> | <b>2.50 [2.37 – 2.64]</b> | <b>0.90 [0.86 – 0.95]</b>    | <i>1.01 [0.96 – 1.07]</i>    | <b>1.83 [1.74 – 1.92]</b>   |
| Potassium dichromate | <b>0.56 [0.42 – 0.72]</b>                                     | <b>0.72 [0.68 – 0.76]</b>                       | <b>0.87 [0.82 – 0.92]</b> | <b>1.41 [1.32 – 1.50]</b> | <b>1.51 [1.42 – 1.60]</b>    | <b>0.75 [0.68 – 0.82]</b>    | <b>0.84 [0.76 – 0.91]</b>   |
| MCI/MI               | <b>0.60 [0.43 – 0.80]</b>                                     | <b>0.74 [0.69 – 0.79]</b>                       | <i>1.04 [0.98 – 1.11]</i> | <b>1.46 [1.35 – 1.57]</b> | <b>1.82 [1.68 – 1.96]</b>    | <b>1.57 [1.44 – 1.72]</b>    | <i>0.93 [0.83 – 1.03]</i>   |
| Fragrance mix II     | <b>0.36 [0.23 – 0.51]</b>                                     | <b>0.73 [0.68 – 0.78]</b>                       | <b>1.18 [1.10 – 1.26]</b> | <b>1.77 [1.62 – 1.93]</b> | <b>1.20 [1.11 – 1.30]</b>    | <b>1.25 [1.14 – 1.36]</b>    | <b>1.30 [1.19 – 1.42]</b>   |
| Colophony            | <b>0.40 [0.28 – 0.55]</b>                                     | <b>0.71 [0.67 – 0.75]</b>                       | <b>1.27 [1.20 – 1.34]</b> | <b>1.14 [1.07 – 1.22]</b> | <b>1.30 [1.21 – 1.39]</b>    | <i>1.08 [1.00 – 1.17]</i>    | <b>1.85 [1.72 – 1.98]</b>   |
| Lanolin alcohols     | <b>0.38 [0.24 – 0.57]</b>                                     | <b>0.66 [0.62 – 0.71]</b>                       | <b>1.18 [1.11 – 1.26]</b> | <b>1.44 [1.32 – 1.56]</b> | <i>1.05 [0.96 – 1.15]</i>    | <b>1.17 [1.06 – 1.29]</b>    | <b>4.45 [4.15 – 4.78]</b>   |
| HICC                 | <b>0.41 [0.24 – 0.66]</b>                                     | <b>0.72 [0.65 – 0.79]</b>                       | <b>1.38 [1.26 – 1.52]</b> | <b>1.64 [1.46 – 1.83]</b> | <b>1.38 [1.24 – 1.54]</b>    | <b>1.42 [1.26 – 1.59]</b>    | <b>0.64 [0.55 – 0.75]</b>   |
| Oil of turpentine    | <b>0.55 [0.35 – 0.81]</b>                                     | <b>0.72 [0.66 – 0.77]</b>                       | <b>1.13 [1.05 – 1.22]</b> | <b>1.50 [1.36 – 1.65]</b> | <i>1.10 [1.00 – 1.21]</i>    | <i>1.03 [0.92 – 1.15]</i>    | <b>1.68 [1.52 – 1.86]</b>   |
| Thiuram mix          | <b>0.34 [0.22 – 0.51]</b>                                     | <b>0.55 [0.51 – 0.60]</b>                       | <b>1.16 [1.08 – 1.25]</b> | <b>1.39 [1.28 – 1.52]</b> | <b>3.58 [3.29 – 3.89]</b>    | <i>0.92 [0.80 – 1.05]</i>    | <b>1.83 [1.63 – 2.05]</b>   |

|                             |                           |                           |                           |                           |                           |                           |                           |
|-----------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Epoxy resin                 | <b>0.60 [0.38 – 0.91]</b> | <b>0.51 [0.46 – 0.56]</b> | <b>0.47 [0.43 – 0.51]</b> | <b>1.18 [1.07 – 1.30]</b> | <b>1.55 [1.40 – 1.71]</b> | <b>1.73 [1.54 – 1.94]</b> | <b>0.81 [0.69 – 0.94]</b> |
| Paraben mix                 | <i>0.74 [0.44 – 1.16]</i> | <b>0.70 [0.63 – 0.77]</b> | <b>0.70 [0.64 – 0.77]</b> | <b>1.37 [1.21 – 1.56]</b> | <i>1.05 [0.92 – 1.19]</i> | <i>0.91 [0.77 – 1.07]</i> | <b>3.01 [2.68 – 3.38]</b> |
| Formaldehyde                | <b>0.48 [0.28 – 0.75]</b> | <b>0.75 [0.68 – 0.82]</b> | <i>1.00 [0.91 – 1.10]</i> | <b>1.15 [1.04 – 1.28]</b> | <b>1.64 [1.47 – 1.82]</b> | <i>0.98 [0.85 – 1.13]</i> | <b>1.19 [1.03 – 1.36]</b> |
| Mercapto mix (w/o MBT)      | <i>0.67 [0.34 – 1.15]</i> | <b>0.63 [0.54 – 0.72]</b> | <b>0.69 [0.60 – 0.79]</b> | <i>0.96 [0.83 – 1.11]</i> | <b>1.90 [1.64 – 2.21]</b> | <b>0.56 [0.42 – 0.73]</b> | <i>1.11 [0.89 – 1.37]</i> |
| IPPD                        | <b>0.37 [0.16 – 0.72]</b> | <b>0.53 [0.46 – 0.61]</b> | <b>0.73 [0.65 – 0.83]</b> | <i>1.07 [0.94 – 1.23]</i> | <b>1.87 [1.64 – 2.15]</b> | <i>0.90 [0.73 – 1.11]</i> | <i>0.93 [0.75 – 1.14]</i> |
| Cetearyl alcohol            | <b>0.40 [0.17 – 0.78]</b> | <b>0.69 [0.62 – 0.76]</b> | <b>1.19 [1.07 – 1.32]</b> | <b>2.35 [1.98 – 2.81]</b> | <i>0.94 [0.79 – 1.10]</i> | <i>0.83 [0.68 – 1.00]</i> | <b>5.48 [4.88 – 6.16]</b> |
| Zinc diethyldithiocarbamate | <b>0.29 [0.09 – 0.67]</b> | <b>0.53 [0.45 – 0.63]</b> | <i>1.14 [0.99 – 1.33]</i> | <b>1.53 [1.28 – 1.85]</b> | <b>3.41 [2.85 – 4.08]</b> | <i>0.80 [0.58 – 1.08]</i> | <b>3.08 [2.51 – 3.78]</b> |

|                                                             |                    | Subgroup I of study group:<br>Indication “Exclusion of contact allergy” |                                  |                                               | Subgroup II of study group:<br>All other indications than subgroup I |                                  |                                               |
|-------------------------------------------------------------|--------------------|-------------------------------------------------------------------------|----------------------------------|-----------------------------------------------|----------------------------------------------------------------------|----------------------------------|-----------------------------------------------|
| Substance                                                   | Test concentration | Number of patients tested                                               | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] | Number of patients tested                                            | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] |
| Nickel sulfate                                              | 5 % pet.           | 1,323                                                                   | 135                              | 13.2 [10.7 - 15.7]                            | 891                                                                  | 94                               | 14.2 [11.2 -17.3]                             |
| Fragrance mix I                                             | 8 % pet.           | 1,330                                                                   | 48                               | 3.9 [2.5 - 5.2]                               | 900                                                                  | 48                               | 5.4 [3.6 -7.1]                                |
| Cobalt chloride                                             | 1 % pet.           | 1,335                                                                   | 42                               | 3.7 [2.3 - 5.0]                               | 907                                                                  | 42                               | 5.7 [3.7 -7.7]                                |
| Balsam of Peru (Myroxylon pereirae)                         | 25 % pet.          | 1,333                                                                   | 54                               | 3.6 [2.4 - 4.7]                               | 906                                                                  | 48                               | 4.2 [3.0 -5.5]                                |
| Potassium dichromate                                        | 0.5 % pet.         | 1,334                                                                   | 29                               | 1.6 [0.9 - 2.3]                               | 911                                                                  | 28                               | 3.0 [1.7 -4.3]                                |
| Fragrance mix II *                                          | 14 % pet.          | 837                                                                     | 9                                | 0.6 [0.2 - 1.0]                               | 637                                                                  | 17                               | 2.9 [1.2 -4.7]                                |
| Colophony                                                   | 20 % pet.          | 1,335                                                                   | 19                               | 1.0 [0.5 - 1.5]                               | 904                                                                  | 17                               | 1.6 [0.7 -2.5]                                |
| Methylchlorisothiazolinone / methylisothiazolinone (MCI/MI) | 100 ppm aq.        | 1,332                                                                   | 20                               | 1.4 [0.6 - 2.2]                               | 907                                                                  | 21                               | 2.7 [1.3 -4.2]                                |
| Lanolin alcohols                                            | 30 % pet.          | 1,334                                                                   | 12                               | 1.0 [0.3 - 1.7]                               | 907                                                                  | 9                                | 0.7 [0.2 -1.1]                                |
| Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) **      | 5 % pet.           | 990                                                                     | 9                                | 0.8 [0.1 - 1.6]                               | 719                                                                  | 6                                | 0.8 [0.0 -1.7]                                |
| Thiuram mix                                                 | 1 % pet.           | 1,333                                                                   | 8                                | 0.5 [0.1 - 0.8]                               | 904                                                                  | 14                               | 1.3 [0.5 -2.0]                                |
| Oil of turpentine                                           | 10 % pet.          | 1,333                                                                   | 16                               | 1.0 [0.4 - 1.6]                               | 907                                                                  | 7                                | 0.5 [0.1 -0.9]                                |
| Epoxy resin                                                 | 1 % pet.           | 1,315                                                                   | 13                               | 0.8 [0.2 - 1.3]                               | 879                                                                  | 8                                | 0.9 [0.1 -1.7]                                |
| Formaldehyde                                                | 1 % aq.            | 1,333                                                                   | 9                                | 0.4 [0.1 - 0.7]                               | 909                                                                  | 7                                | 0.8 [0.1 -1.5]                                |
| Zinc diethyldithiocarbamate                                 | 1 % pet.           | 1,335                                                                   | 1                                | 0.1 [0.0 - 0.4]                               | 909                                                                  | 3                                | 0.2 [0.0 -0.3]                                |
| Mercapto mix (without MBT)                                  | 1 % pet.           | 1,335                                                                   | 3                                | 0.3 [0.0 - 0.7]                               | 907                                                                  | 8                                | 0.7 [0.2 -1.2]                                |
| N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)             | 0.1 % pet.         | 1,334                                                                   | 5                                | 0.4 [0.0 - 0.9]                               | 907                                                                  | 2                                | 0.1 [0.0 -0.3]                                |
| Paraben mix                                                 | 16 % pet.          | 1,335                                                                   | 10                               | 1.0 [0.2 - 1.7]                               | 908                                                                  | 7                                | 0.7 [0.0 -1.3]                                |
| Cetearyl alcohol                                            | 20 % pet.          | 1,335                                                                   | 3                                | 0.3 [0.0 - 0.8]                               | 908                                                                  | 4                                | 0.3 [0.0 -0.6]                                |

duced number of patients tested since fragrance mix II was not part of the baseline series before 2005.

duced number of patients tested since HICC was not part of the baseline series before 2002.

| Substance                                                    | Test concentration | Subgroup I of control group:<br>Indication “Exclusion of contact allergy” |                                  |                                               | Subgroup II of control group:<br>All other indications than subgroup I |                                  |                                               |
|--------------------------------------------------------------|--------------------|---------------------------------------------------------------------------|----------------------------------|-----------------------------------------------|------------------------------------------------------------------------|----------------------------------|-----------------------------------------------|
|                                                              |                    | Number of patients tested                                                 | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] | Number of patients tested                                              | Patients with positive reactions | Age- and sex-standardized % positive [95% CI] |
| Nickel sulfate                                               | 5 % pet.           | 54,202                                                                    | 6,785                            | 15.5 [15.1 - 15.8]                            | 88,844                                                                 | 13,480                           | 17.8 [17.5 -18.1]                             |
| Fragrance mix I                                              | 8 % pet.           | 54,462                                                                    | 4,325                            | 6.9 [6.7 - 7.1]                               | 89,374                                                                 | 9,281                            | 9.3 [9.1 -9.5]                                |
| Cobalt chloride                                              | 1 % pet.           | 54,464                                                                    | 2,240                            | 4.9 [4.7 - 5.1]                               | 89,464                                                                 | 5,090                            | 6.4 [6.2 -6.6]                                |
| Balsam of Peru (Myroxylon pereirae)                          | 25 % pet.          | 54,505                                                                    | 4,456                            | 6.6 [6.4 - 6.8]                               | 89,473                                                                 | 8,713                            | 8.2 [8.0 -8.4]                                |
| Potassium dichromate                                         | 0.5 % pet.         | 54,526                                                                    | 1,724                            | 3.0 [2.9 - 3.2]                               | 89,568                                                                 | 3,978                            | 4.2 [4.0 -4.3]                                |
| Fragrance mix II *                                           | 14 % pet.          | 31,281                                                                    | 1,292                            | 3.6 [3.3 - 3.8]                               | 54,186                                                                 | 3,030                            | 5.0 [4.8 -5.2]                                |
| Colophony                                                    | 20 % pet.          | 54,533                                                                    | 1,852                            | 3.2 [3.1 - 3.4]                               | 89,571                                                                 | 4,202                            | 4.6 [4.4 -4.7]                                |
| Methylchloroisothiazolinone / methylisothiazolinone (MCI/MI) | 100 ppm aq.        | 54,413                                                                    | 1,238                            | 2.1 [2.0 - 2.3]                               | 89,389                                                                 | 2,805                            | 3.0 [2.9 -3.1]                                |
| Lanolin alcohols                                             | 30 % pet.          | 54,541                                                                    | 1,453                            | 2.4 [2.2 - 2.5]                               | 89,612                                                                 | 3,279                            | 3.2 [3.1 -3.3]                                |
| Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) **       | 5 % pet.           | 39,196                                                                    | 633                              | 1.5 [1.4 - 1.7]                               | 65,937                                                                 | 1,534                            | 2.1 [2.0 -2.3]                                |
| Thiuram mix                                                  | 1 % pet.           | 54,550                                                                    | 783                              | 1.4 [1.3 - 1.5]                               | 89,569                                                                 | 2,424                            | 2.6 [2.5 -2.8]                                |
| Oil of turpentine                                            | 10 % pet.          | 54,458                                                                    | 901                              | 1.5 [1.4 - 1.6]                               | 89,509                                                                 | 2,051                            | 2.1 [2.0 -2.2]                                |
| Epoxy resin                                                  | 1 % pet.           | 54,435                                                                    | 525                              | 0.9 [0.8 - 1.0]                               | 89,387                                                                 | 1,741                            | 1.9 [1.8 -2.0]                                |
| Formaldehyde                                                 | 1 % aq.            | 54,549                                                                    | 604                              | 1.1 [1.0 - 1.2]                               | 89,648                                                                 | 1,370                            | 1.5 [1.4 -1.6]                                |
| Zinc diethyldithiocarbamate                                  | 1 % pet.           | 54,563                                                                    | 182                              | 0.3 [0.2 - 0.3]                               | 89,672                                                                 | 579                              | 0.6 [0.6 -0.7]                                |
| Mercapto mix (without MBT)                                   | 1 % pet.           | 54,432                                                                    | 247                              | 0.5 [0.4 - 0.5]                               | 89,307                                                                 | 653                              | 0.7 [0.7 -0.8]                                |
| N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)              | 0.1 % pet.         | 54,559                                                                    | 249                              | 0.4 [0.4 - 0.5]                               | 89,663                                                                 | 837                              | 1.0 [0.9 -1.0]                                |
| Paraben mix                                                  | 16 % pet.          | 54,436                                                                    | 537                              | 0.9 [0.8 - 0.9]                               | 89,440                                                                 | 1,204                            | 1.2 [1.1 -1.3]                                |
| Cetearyl alcohol                                             | 20 % pet.          | 54,574                                                                    | 511                              | 0.7 [0.7 - 0.8]                               | 89,644                                                                 | 1,102                            | 1.0 [0.9 -1.0]                                |

duced number of patients tested since fragrance mix II was not part of the baseline series before 2005.

duced number of patients tested since HICC was not part of the baseline series before 2002.