

Trends and current spectrum of contact allergy in Central Europe: results of the Information Network of Departments of Dermatology (IVDK) 2007–2018*

W. Uter ¹, O. Gefeller ¹, V. Mahler² and J. Geier³

¹Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany

²Paul Ehrlich Institut, Langen, Germany

³Information Network of Departments of Dermatology, University Medical Center, Göttingen, Germany

Linked Comment: Schuttelaar. *Br J Dermatol* 2020; **183**:800–801.

Summary

Correspondence

Wolfgang Uter.

Email: wolfgang.uter@fau.de

Accepted for publication

11 February 2020

Funding sources

None.

Conflicts of interests

W.U. has accepted honoraria for presentations or travel reimbursement from cosmetic industry associations and received lecture fees from dermatology-related sponsors for educational lectures on contact allergy. The Information Network of Departments of Dermatology (IVDK), maintained by the IVDK e.V., of which J.G. is an employee, is sponsored by the cosmetic and fragrance industry (associations) and by public funds. V.M. declares membership in the executive committee of the German Contact Dermatitis research group (DKG) and European Society of Contact Dermatitis (ESCD), and has provided expert opinions for German statutory accident insurances and courts and (before the commencement of the current employment at the Paul Ehrlich Institut) received fees for lecture and training activities for SmartPractice Germany and German Statutory Accident Insurance for health and welfare.

*Plain language summary available online

DOI 10.1111/bjd.18946

Background Changing patterns of exposure lead to changes in the spectrum of contact allergy in the general population and in patients patch tested for suspected contact allergy. The main contact allergens (haptens) are assembled in the so-called 'baseline series'.

Objectives To present the current spectrum of contact allergy to baseline series allergens, and its temporal development over the last 12 years, based on data collected by the 56 active departments of the trinational Information Network of Departments of Dermatology (IVDK).

Methods Patch-test data, along with core demographic and clinical information, subdivided into 4-year periods for all patients patch tested with the baseline series in the IVDK, were analysed descriptively. Moreover, log-binomial regression analysis addressed temporal trends of specific contact allergies, adjusted for potentially confounding factors.

Results Among the 125 436 patients tested with the German baseline series, the most common allergens were nickel (14.7%), fragrance mix I (8.1%), Myroxylon pereirae resin (7.5%) and cobalt (5.2%), with no conclusive trend. The rise and fall of contact allergy to methylchloroisothiazolinone/methylisothiazolinone (MI), following (self-) regulation in the European Union, reflected the MI contact allergy epidemic. Propolis showed a marked upward trend with a prevalence of 3.94% during the period 2015–2018.

Conclusions Decreases in sensitization prevalence likely reflect reduced exposure, with some lag, as seen with hydroxyisohexyl 3-cyclohexene carboxaldehyde. If no (sufficient) decrease can be observed despite interventions, such as for nickel and chromium, affected subgroups should be identified and their causative exposures explored. Finally, increases such as that observed with propolis, certainly warrant targeted investigation of the exposures driving sensitization, and possibly intervention.

What is already known about this topic?

- Contact allergy is prevalent in the general population.
- Surveillance based on clinical data offers timely information on trends concerning certain allergens or subgroups at risk.

What does this study add?

- This analysis provides an update of the current contact allergy prevalence in Central Europe, including time trends.
- This study describes the demographic and clinical profile of patients tested from 2007 to 2018.
- This research identifies contact allergens that require (further) preventive efforts.

Contact allergy (contact sensitization) is a frequent condition occurring at the population level, as recently demonstrated by the results of the European Dermato-Epidemiology Network Fragrance Study.¹ Similarly to previous smaller population-based studies, certain exposures have been identified as risk factors for specific contact allergy, e.g. nickel² or *p*-phenylenediamine.³ However, as population-based patch-test studies are rarely performed, owing to considerable costs, the bulk of epidemiological surveillance is provided by patient-based research, i.e. clinical epidemiological studies. In this context, the baseline patch-test series, a collection of the most frequent or important contact allergens (haptens) applied nonselectively to all patients being patch tested, is perhaps the most important diagnostic tool.⁴ It offers a comparison between different subgroups of patients or patients over time, which is not distorted by differential selection for patch testing, compared with other allergens included in special series ('aimed testing'). Evidently, selection processes may differ between different countries and health systems. This needs to be considered when comparing results from different countries, e.g. from the European Surveillance System on Contact Allergies network.⁵

The Information Network of Departments of Dermatology (IVDK) is a trinational network of German-speaking countries (Germany, Austria and Switzerland) with stable participation during the past 12 years, thereby enabling a long-term comparison of the development of contact allergy prevalences. A comparison between these countries is deliberately not intended, as patch-testing standards and exposure conditions in the three countries involved are regarded as similar. The present analysis gives an overview of the overall pattern of sensitization to baseline series haptens observed during the last 12 years in addition to the sex- and age-specific pattern. Furthermore, time trends will be addressed concerning all baseline series allergens, adjusting for patient characteristics that could change during the study period, such as age and sex.

Materials and methods

The IVDK (<https://www.ivdk.org>) is a clinical surveillance network established in 1988.⁶ It comprises 60 departments, 56 of which are currently active, in three countries (two in Austria, five in Switzerland and the remainder from Germany). Data are collected continuously throughout the year and transmitted to the data centre in Göttingen twice a year in a pseudonymized fashion. Prior to being added to the IVDK database, all new data must pass a standardized quality control process.⁷

For the present analysis, data for all patients patch tested between 2007 and 2018 (both years inclusive) with the baseline series of the German Contact Dermatitis Research Group (DKG) (<https://dkg.ivdk.org>) were analysed. From a total of 141 762 patients consulting at least once, 125 436 (88.5%) patients were tested with the baseline series [in cases of multiple consultations involving the baseline series, observed in about 1.7% of patients, one of the two (or more) consultations was randomly chosen for analysis]. Many IVDK departments are tertiary referral centres where the baseline series is

not tested if an adequate test had been performed recently. Patch tests were read on day 3 or, if no day-3 reading was performed, on day 4 according to International Contact Dermatitis Research Group/European Society of Contact Dermatitis (ESCD) standards as summarized recently,⁸ partly refined by the DKG.⁹ Test preparations that changed over time were aggregated into one, including methyl dibromo glutaronitrile (increase of test concentration from 0.2% to 0.3%), different versions of Compositae mix, and use of 1% and, more often, 2% mercaptobenzothiazole. During the study period, Compositae mix from Chemotechnique Diagnostics (Vellinge, Sweden) was patch tested. Chemotechnique Diagnostics changed the composition and name of Compositae mix in 2011. The previous Compositae mix 5% in petrolatum (pet) included *Tanacetum vulgare* 1%, *Arnica montana* 0.5%, parthenolide 0.1%, *Chamomilla romana* 2.4% and *Achillea millefolium* 1%. Compositae mix II 5% pet, tested in the IVDK from October 2011 onwards, consists of *Anthemis nobilis* extract 1.2%, *Chamomilla recutita* extract 1.2%, *Achillea millefolium* extract 1%, *Tanacetum vulgare* extract 1%, *Arnica montana* extract 0.5% and parthenolide 0.1%.

In view of the long study period and time trends being of interest, the descriptive results are stratified into three 4-year intervals. This also concerns the patient population, which was described according to the MOAHLFA factors (Male, Occupational, Atopic, Hand, Leg, Face dermatitis, Age ≥ 40 years).¹⁰ Beyond the overall results, age- and sex-stratified results are also of interest; such crude prevalences are presented in the Supporting Information. All prevalences are accompanied by 95% confidence intervals (CIs).¹¹

In addition, a log-binomial regression analysis for each of the allergens was performed. A positive reaction (+ to +++) vs. a nonpositive reaction (negative, doubtful or irritant) was modelled as outcome. The following factors were used for adjustment to account for differences in potentially relevant characteristics of the patient populations: (i) sex, (ii) current or previous atopic eczema, (iii) age and (iv) department, in view of a (partly) changing contribution or other potentially confounding effects from different departments. Log-binomial regression analysis yields the (adjusted) prevalence ratio as risk estimate with accompanying CIs. For data management at the Göttingen data centre, SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used. For data analysis, R statistical software version 3.6 (<https://www.r-project.org>) was utilized.

Results

Demographic and clinical characteristics

In total, 125 436 patients were patch tested with the baseline series. Table 1 shows the MOAHLFA index of the patients patch tested during the three periods. During these three periods, the age and sex distribution of patients changed slightly, but significantly. The proportion of female patients increased from 62.3% to 64.2% in the most recent period (χ^2 -test, $P < 0.001$). In contrast, the proportion of patients aged 40 years

or above was largely stable. The proportion of patients with atopic eczema increased from 19.6% to 25.2% in the most recent period (χ^2 -test, $P < 0.001$). In contrast, a less pronounced fluctuation in the proportion of patients with face dermatitis, and a slight increase in the proportion of patients with hand dermatitis and decrease in the proportion of patients with leg dermatitis can be observed.

Descriptive analyses of patch-test results

In Table 2, the crude patch-test results for the three periods are shown. Regarding the metals included in the baseline series, limited variation and a stable overall temporal pattern is evident. This can also be seen if reaction to 'any metal' (of the three) is pooled (Figure 1). Among the preservatives, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and of course MI alone reflect the epidemic of MI contact allergy in Central Europe to some extent; see also the analysis of temporal evolution in Table 3 and Table S1 (see Supporting Information), which illustrates year-by-year changes and thus better depicts the increase, peak and decline of this epidemic. The sensitization prevalence of formaldehyde is largely stable above 1% in the patients who were consecutively tested. Methylidibromo glutaronitrile was tested as part of the baseline series initially at 0.3% pet, but since mid-2008 0.2% pet was used until March 2016, and again at 0.3% pet from April 2016 onwards. The relative frequency of positive reactions with the increased concentration is clearly higher. Paraben mix caused few positive test reactions, with no observable trend. Overall, 2-bromo-2-nitro-1,3-propanediol (bronopol) and iodopropynyl butylcarbamate (IPBC) elicited positive reactions in around 1% of patients, i.e. more commonly than paraben mix.

Fragrances are represented in the baseline series with seven different allergen preparations. For a few years, the emulsifier sorbitan sesquioleate (SSO) 20% pet, which is used in fragrance mix (FM) I and some single constituents as an emulsifier, has also been included.¹² As it is possible, as a 'worst-case scenario', that all patients who have positive reactions to SSO and to FM I are, in fact, sensitized only to SSO, both results were cross-tabulated in those 26 640 patients where both allergens had been tested (SSO had been used by all

departments only towards the end of the study period). Of 1710 patients positive to FM I, only 83 (4.9%) were also positive to SSO. Conversely, among all 190 patients with positive patch-test reactions to SSO, the 83 patients above represented 43.7%. The odds ratio (OR) of association between both reactions was 11.8 ($P < 0.001$). Of note, 107 (56.3%) patients positive to SSO 20% pet did not react to the SSO 5% included in FM I. FM I results based on patients not reacting to SSO yielded a 'corrected' prevalence of 6.1%, (95% CI 5.8–6.4); 'uncorrected' for SSO reactivity, the crude prevalence estimate was 6.4% (95% CI 6.1–6.7).

Regarding topical medicaments and excipients, bufexamac had been patch tested until the end of 2013, when it was still on the market in Germany and Austria.¹³ Lanolin alcohol yielded a relatively stable prevalence of ~2–2.5% positive test reactions, while cetearyl alcohol, added to the DKG baseline series about 25 years ago, is a relatively rare allergen. Concerning the overlap of positive reactions with lanolin alcohols, 241 patients reacted to both; this equates to 23.2% of the 1037 patients with positive reactions to cetearyl alcohol and 8.5% of the 2839 patients positive to lanolin alcohol.

The prevalence of contact allergy to thiuram mix was constantly above 2%, while that of zinc diethyldithiocarbamate (ZDEC), as one representative of dithiocarbamates tested, was around one-quarter of this prevalence. In the 124 512 patients tested with both allergens, 499 reacted to both thiuram mix and ZDEC, corresponding to 78.3% of all patients positive to ZDEC and 18.4% of those positive to thiuram mix (OR 198.9, $P < 0.001$). All other markers, benzothiazole accelerators or the *p*-phenylenediamine derivative used as an antioxidant, are well below 1% prevalence in consecutively tested patients. Of the two resin components tested in the study period, epoxy resin (diglycidylether of bisphenol A) yielded ~1.5% positive reactions.

Differences between male (36.7% overall) and female patients regarding reactions to the baseline series are shown in Table S2 (see Supporting Information). The age of patients was considered by stratifying into a 'young' age group (up to age 30 years), a 'medium' age group (age 31–65 years) and an 'old' age group (66 years and above) (Table S3; see Supporting Information). A sensitivity analysis excluding departments using 24-h patch-test application is presented in Table S4 (see Supporting Information).

Table 1 The MOAHLFA index¹⁰ of patients patch tested with the baseline series during the three periods

Characteristic	2007–2010	2011–2014	2015–2018	All patients
Male	16 303 (37.7)	16 356 (36.5)	13 382 (35.8)	46 041 (36.7)
Occupational	6647 (15.4)	7578 (16.9)	6871 (18.4)	21 096 (16.8)
Atopic dermatitis	8501 (19.6)	10 450 (23.3)	9426 (25.2)	28 377 (22.6)
Hand dermatitis	11 996 (27.7)	13 382 (29.9)	12 245 (32.8)	37 623 (30)
Leg dermatitis	5194 (12)	4892 (10.9)	3626 (9.7)	13 712 (10.9)
Face dermatitis	6856 (15.8)	7398 (16.5)	5908 (15.8)	20 162 (16.1)
Age ≥ 40 years	31 127 (71.9)	32 606 (72.8)	26 748 (71.6)	90 481 (72.1)

Data are provided as n (%). MOAHLFA, Male, Occupational, Atopic, Hand, Leg, Face dermatitis, Age ≥ 40 years. For comparison, the MOAHLFA index of all patients consulting, including those not tested with the baseline series, is shown in the rightmost column.

Table 2 Patch-test results with the baseline series during the three periods, tested in 125 436 patients

		2007–2010			2011–2014			2015–2018		
Allergen	Conc.	N	Positive tests (%)	95% CI	N	Positive tests (%)	95% CI	N	Positive tests (%)	95% CI
Metals										
Nickel sulfate	5	42 545	14	13.67–14.34	43 801	14.43	14.1–14.76	36 491	16	15.62–16.38
Potassium dichromate	0.5	42 987	4.17	3.98–4.36	44 328	3.28	3.11–3.45	37 048	4.46	4.26–4.68
Cobalt chloride	1	42 906	5.27	5.06–5.49	44 213	4.84	4.64–5.04	36 918	5.52	5.29–5.76
Preservatives										
MCI/MI (aq.)	0.01	43 032	2.42	2.28–2.57	44 332	4.74	4.54–4.94	36 890	3.67	3.48–3.87
MI (aq.)	0.05				8620	5.96	5.47–6.48	36 581	4.15	3.95–4.36
Formaldehyde (aq.)	1	43 033	0.98	0.89–1.07	44 378	1.16	1.07–1.27	37 006	1.25	1.14–1.37
Methyldibromo glutaronitrile	0.2	24 171	2.54	2.34–2.74	44 069	2.63	2.48–2.78	13 959	2.01	1.79–2.26
Methyldibromo glutaronitrile	0.3	18 755	3.62	3.36–3.9				23 077	4.72	4.45–5
Paraben mix	16	43 029	0.93	0.85–1.03	44 366	0.64	0.57–0.72	36 983	0.79	0.71–0.89
2-Bromo-2-nitro-1,3-propanediol	0.5	42 929	1.16	1.06–1.27	35 790	0.68	0.6–0.77			
Iodopropynyl butylcarbamate	0.2				8595	1.29	1.06–1.55	36 780	0.95	0.85–1.05
Fragrances										
Fragrance mix I	8	42 832	7.56	7.31–7.82	44 096	9.52	9.25–9.8	35 873	7	6.74–7.27
Fragrance mix II	14	42 798	4.87	4.67–5.08	44 214	5.14	4.94–5.35	36 929	4.27	4.07–4.48
HICC	5	43 054	2.08	1.95–2.22	44 390	2.08	1.95–2.21	37 033	1.72	1.59–1.86
Myroxylon pereirae	25	42 943	7.4	7.15–7.65	44 255	8.21	7.96–8.47	37 010	6.63	6.37–6.88
Sorbitan sesquioleate ^a	20							27 452	0.7	0.61–0.81
Santalum album	10	1957	1.38	0.91–2	43 002	1.26	1.16–1.37	37 154	1.18	1.07–1.3
Jasminum spp.	5	1952	1.33	0.87–1.95	43 012	1.47	1.36–1.59	37 142	1.28	1.17–1.4
Cananga odorata	10	1956	1.79	1.25–2.48	42 993	2.47	2.33–2.63	37 155	2.23	2.08–2.38
Plants (other)										
Colophonium	20	42 984	3.87	3.69–4.06	44 308	3.85	3.67–4.03	37 060	3.67	3.48–3.87
Propolis	10	43 033	2.35	2.21–2.5	44 330	3.6	3.43–3.78	37 058	3.94	3.75–4.15
Oil of turpentine	10	43 008	2.16	2.03–2.3	44 378	1.18	1.08–1.28	36 992	0.74	0.65–0.83
Compositae mix	5	41 923	1.37	1.26–1.49	12 956	1.78	1.56–2.03			
Compositae mix II	5				31 458	1.48	1.35–1.62	36 953	1.36	1.25–1.49
Medicaments, topical										
Bufoexamac	5	42 990	1.02	0.93–1.12	35 772	0.76	0.68–0.86			
Cetearyl alcohol	20	43 056	0.84	0.75–0.93	44 385	1.03	0.93–1.12	37 076	0.61	0.53–0.69
Lanolin alcohol	30	43 039	2.28	2.14–2.42	44 360	2.56	2.42–2.71	37 030	1.96	1.82–2.11
Rubber additives										
Thiuram mix	1	42 999	2.12	1.99–2.26	44 300	2.14	2.01–2.28	36 931	2.32	2.17–2.48
Zinc diethyl dithiocarbamate	1	43 062	0.59	0.52–0.67	44 386	0.45	0.39–0.51	37 118	0.54	0.47–0.62
Mercapto mix (CBS, MBT, MOR)	1	43 059	0.64	0.57–0.72	44 361	0.66	0.59–0.75	36 853	0.5	0.43–0.58
Mercaptobenzothiazole	1							16 313	0.47	0.37–0.58
Mercaptobenzothiazole	2	43 025	0.65	0.58–0.73	44 378	0.55	0.49–0.63	20 609	0.59	0.49–0.71
IPPD	0.1	43 059	0.69	0.61–0.77	44 376	0.77	0.69–0.86	37 109	0.75	0.67–0.85
Resins/glues										
PTBFR	1	43 052	0.59	0.52–0.67	35 777	0.5	0.43–0.58			
Epoxy resin (DGEBA)	1	42 651	1.55	1.43–1.67	44 121	1.66	1.54–1.78	36 575	1.57	1.44–1.7

Conc., concentration tested in petrolatum, except where otherwise indicated; CI, confidence interval; aq., aqua; CBS, N-cyclohexyl-2-benzothiazyl sulfenamide; DGEBA, diglycidyl ether of bisphenol A; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, N-isopropyl-N-phenyl-p-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOR, morpholinylmercaptobenzothiazole; PTBFR, p-tert-butylphenol formaldehyde resin. ^aNot a fragrance allergen, but is listed here as it is used as an emulsifier in fragrance mix I. Allergens tested in less than 1000 patients overall have been omitted altogether. If less than 1000 patients were tested in one period, the results for that period were omitted. During the 12 years, some allergens were withdrawn and others added, resulting in varying numbers tested within one 4-year period.

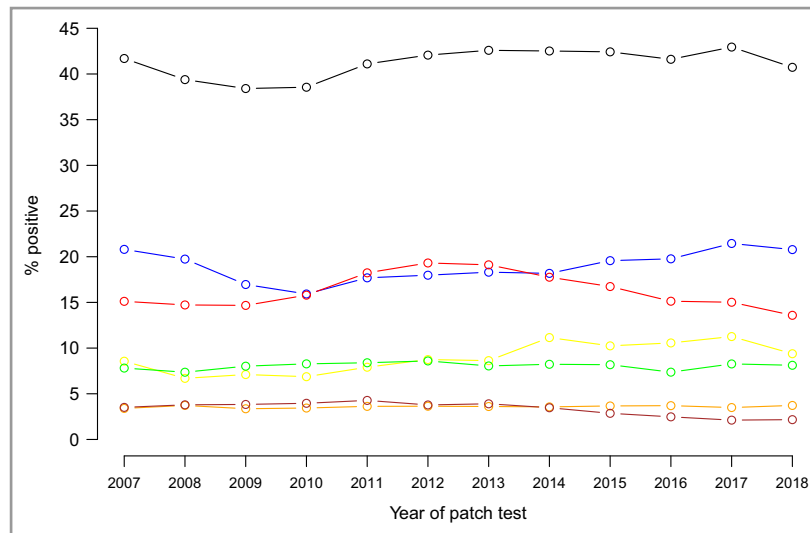


Figure 1 Time trend of groups of allergens. Metals (blue), fragrances (red), preservatives (yellow), plant-based materials (green), rubber (orange), and the overall yield in terms of the percentage of patients positive to any allergen(s) of the baseline series (black). The groups of allergens correspond to the categorization used in Tables 2 and 3. Resins/glues have not been aggregated as they comprised only two allergens (but are included in the overall yield).

Multifactorial analysis of time trends

In a methodologically more elaborate attempt to quantify changes in sensitization prevalence over time, a multifactorial, mutually adjusted log-binomial regression analysis was performed for each allergen (Table 3 and Table S1; see Supporting Information). Time trends are barely noticeable for nickel, while chromium and cobalt show similar U-shaped patterns. Concerning MI, a halved risk of sensitization was observed when tested in 2018 compared with 2014, when it was included in the baseline series. In contrast, MCI/MI had been tested throughout, and thus also reflects the MI-related increase by a 2.5-fold increased risk compared with baseline in 2013, and a sharp decline almost to baseline levels thereafter. The time course of 2-bromo-2-nitro-1,3-propanediol sensitization showed a marked decline.

FM I displayed an increased probability of sensitization by approximately 40% in 2012 compared with 2007. Surprisingly, both the increase and the later decrease are absolutely steady. FM II and, more or less in parallel, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), show a considerable downward trend only in the last 2 years of the study. The trend for *Myroxylon pereirae* resin (MPR) mostly parallels that seen for FM I, while for the three essential oils no significant change can be seen as these began to be tested in 2011. In contrast to colophonium, which does not display a detectable trend, the sensitization prevalence of propolis started to increase significantly by more than 80% since 2007. Oil of turpentine displays a significant increase in the first few years, compared with the reference year, but exhibits a sharp decline from the year 2012 onwards. In contrast, the yield of positive reactions to test allergens of the Compositae mixes, despite the change of test preparations in 2011, has been largely stable.

The two emulsifiers, lanolin and cetearyl alcohol, do not show a conclusive temporal pattern in this analysis. Thiuram mix similarly shows a stable probability of sensitization over the years, as does ZDEC, if the curious offset in risk from the reference year 2007 is disregarded. The same holds true for the remaining rubber additives, notwithstanding some fluctuation of risk, which deviates significantly in some of the years from that found in the reference year. Regarding the two resin components included, neither showed a notable time trend.

Discussion

This analysis of long-term contact allergy surveillance data from the IVDK primarily provides an overview of the current prevalence of contact sensitization to the most important allergens (assembled in the baseline series). Moreover, the development of contact allergy frequencies over time was subject to an in-depth analysis adjusting for age and sex as a minimum requirement¹¹ and also for atopic eczema. These factors are considered to be true patient characteristics. In contrast, the anatomical site of dermatitis, such as hand, face and leg as used in the MOAHLFA index, can be viewed as exposure surrogates. Hence, to avoid overadjustment, the analysis of temporal patterns was deliberately not adjusted for anatomical site. The impact of interdepartmental variation is well known in such large networks,^{10,14} but was of lesser interest here, and treated merely as an adjustment factor.

The crude prevalences in the three 4-year periods (Table 2) provide a first impression of increasing or decreasing sensitization frequencies and, of course, of the proportion of positive reactions in general. However, in view of 11 departments joining the IVDK network over the course of the study period and seven dropping out during the final years of the study, on

Table 3 Results of multifactorial analyses (one for each allergen) quantifying the risk of sensitization associated with the year of patch testing using the prevalence ratio

Allergen	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Metals											
Nickel sulfate	1.01	0.90	0.89	0.93	0.93	0.97	0.98	1.01	1.04	1.10	1.01
Potassium dichromate	0.83	0.55	0.42	0.55	0.53	0.50	0.54	0.69	0.63	0.79	0.76
Cobalt chloride	0.94	0.71	0.58	0.69	0.74	0.73	0.69	0.76	0.70	0.87	0.93
Preservatives											
MCI/MI (aq.)	1.00	1.07	1.55	1.71	2.10	2.52	2.49	1.99	1.72	1.64	1.26
MI (aq.)							1.00	0.86	0.74	0.63	0.50
Formaldehyde (aq.)	0.81	0.81	0.79	0.79	1.03	1.06	1.11	1.22	1.08	0.99	0.88
Methyldibromo glutaronitrile	0.55	0.62	0.52	0.61	0.62	0.46	0.51	0.41	0.76	1.06	0.91
Paraben mix	0.85	0.96	0.39	0.58	0.75	0.39	0.44	0.71	0.49	0.77	0.71
2-Bromo-2-nitro-1,3-propanediol	1.20	0.91	0.41	0.67	0.51	0.34					
Iodopropynyl butylcarbamate							1.00	0.71	0.86	0.92	0.65
Fragrances											
Fragrance mix I	1.02	1.05	1.15	1.23	1.42	1.35	1.22	1.14	0.99	0.86	0.79
Fragrance mix II	0.93	0.87	1.01	0.91	0.99	1.03	0.99	0.88	0.92	0.79	0.70
HICC	0.98	0.82	0.85	0.91	0.82	0.96	0.79	0.81	0.70	0.73	0.62
Myroxylon pereirae	0.97	0.96	0.91	1.04	1.13	1.13	1.03	0.91	0.89	0.95	0.82
Sorbitan sesquioleate ^a								1.00	1.40	1.72	1.19
Santalum album				1.00	0.90	0.93	0.73	0.85	0.87	1.23	0.88
Jasminum spp.				1.00	0.95	0.94	0.87	0.82	0.82	0.97	0.91
Cananga odorata				1.00	1.06	0.98	1.05	1.02	0.93	1.02	0.92
Plants (other)											
Colophonium	0.97	1.04	0.95	1.01	1.00	0.90	0.98	0.99	0.89	0.97	0.92
Propolis	1.01	0.86	0.84	1.19	1.69	1.44	1.47	1.59	1.39	1.79	1.82
Oil of turpentine	0.66	1.25	1.60	0.92	0.37	0.45	0.69	0.62	0.45	0.26	0.16
Compositae mix	1.02	1.00	1.05	1.21	1.13	1.27	1.00	0.95	1.05	1.07	1.04
Medicaments, topical											
Bufexamac	1.09	1.02	1.02	0.85	0.68	0.77					
Cetearyl alcohol	0.80	0.90	1.00	1.38	1.42	0.99	0.98	0.60	0.64	0.90	0.90
Lanolin alcohol	1.13	1.20	1.28	1.33	1.16	1.41	1.41	1.34	1.22	0.85	0.87
Rubber additives											
Thiuram mix	1.12	1.00	1.04	0.98	0.95	0.97	1.03	1.02	1.18	0.97	1.04
Zinc diethyl dithiocarbamate	0.60	0.48	0.52	0.47	0.41	0.46	0.46	0.51	0.48	0.61	0.53
Mercapto mix (CBS, MBT, MOR)	1.08	0.97	0.90	0.92	0.92	1.12	0.83	0.81	0.85	0.66	0.64
Mercaptobenzothiazole	0.85	0.78	0.75	0.70	0.68	0.71	0.53	0.76	0.55	0.61	0.64
IPPD	1.27	1.30	1.19	1.39	1.48	1.07	1.14	1.17	1.17	1.39	1.36
Resins/glues											
PTBFR	0.87	0.68	0.70	0.74	0.71	0.65	0.75				
Epoxy resin (DGEBA)	1.25	1.13	0.96	1.09	1.00	1.24	1.12	1.22	1.07	1.00	1.05

aq., aqua; CBS, N-cyclohexyl-2-benzothiazyl sulfenamide; DGEBA, diglycidyl ether of bisphenol A; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, N-isopropyl-N-phenyl-p-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOR, morpholinylmercaptobenzothiazole; PTBFR, p-tert-butylphenol formaldehyde resin. ^aNot a fragrance allergen, but is listed here as it is used as an emulsifier in fragrance mix I. The reference year is 2007, except if allergens were included in the baseline series in later years. In this case, the first year of use is taken as reference. Results are additionally adjusted for contributing department, sex, atopic eczema and age (dichotomized). Detailed results including confidence intervals are provided in Table S1 (see Supporting Information). Significant risk estimates are provided in bold.

the one hand, and the well-known impact of department-related factors on the spectrum of contact allergy diagnosis, on the other, adjustment for department also seemed mandatory in the final analytical approach.

On the global scale of all patients who were patch tested, no trend whatsoever can be seen concerning the three metals present in the baseline series. However, the recent (albeit limited)¹⁵ success of nickel regulation will be reflected only in the younger patients, as demonstrated by a stratified analysis of

IVDK data.¹⁶ Older patients who acquired nickel allergy before regulation will contribute to a high global nickel allergy prevalence, and the peak of age-related nickel allergy will move towards higher age in the sense of a cohort effect. Conversely, chromium allergy has markedly declined compared with the reference year 2007, probably owing to chromium regulation in cement (2003/53/EC) coming into force in the European Union (EU) in 2005.¹⁷ Thereafter, it remained at a relatively steady lower level and started to increase again in 2015, which

is difficult to interpret. A second main source of chromium allergy, namely dichromate tanned leather, has been tackled by another EU regulation (EU 301/2014), limiting content to $< 3 \text{ mg kg}^{-1}$ [Annex XVII of regulation 1907/2006 (REACH)], which came into force in May 2015. Hence, a further decline would be expected, and the present slight increase must be investigated carefully. The broad availability of a cobalt spot test¹⁸ has increased knowledge of exposure to cobalt-releasing metal items; nevertheless, the clinical relevance of cobalt contact allergy is often difficult to determine.¹⁹

The MCI/MI and MI trends are easily explained by the MI contact allergy epidemic, which had its peak in Europe around 2013–2014.²⁰ MCI/MI can serve as a long-term indicator for MI contact allergy.²¹ In 2018, the pre-epidemic level of MCI/MI had almost been reached, which can be regarded as a success of the preventive measures implemented at the time,²⁰ which began with the industry recommendation in autumn 2013 not to use MI in leave-on cosmetics, and ended with a ban of MI in leave-on cosmetics and a restriction of up to 15 parts per million in rinse-off products by the Cosmetics Regulation. Nevertheless, MI and other isothiazolinones are still important contact allergens, and exposure and sensitization trends warrant close surveillance.²² While 2-bromo-2-nitro-1,3-propanediol was phased out of the baseline series in 2013–2014, IPBC had been added, yielding positive reactions in about 1% of the patients tested. Concerning patch testing with formaldehyde in the IVDK, it should be noted that formaldehyde is still tested at 1% aqua and not 2% aqua as recommended in the European baseline series.^{23,24} However, this recommendation refers to using a micropipette to dose the allergen solution correctly (e.g. 15 μL for a small Finn Chamber).⁸ As this type of dosing is not usually employed in the IVDK (and many other departments for that matter), overdosing by a factor of approximately two (with large variation) may occur when the usual 'drop technique' is applied.²⁵ Consequently, the average dose/area applied, even in IVDK departments, may thus be at least close to the target dose/area. A similar consideration puts the low test concentration used in the case of MI, namely, 500 parts per million (0.05%) aqua, rather than the recommended 2000 parts per million aqua, into perspective; also in this case, owing to the likelihood of overdosing, the actual dose/area might rather correspond to 1000 parts per million when micropipette dosing is used, although this would still not equate to the recommended 2000 parts per million.²⁶ Nevertheless, the lack of standardization by use of a micropipette when dosing water-based allergen preparations is a limitation of the present data and analysis.

The (adjusted) time trend of FM I reactions is peculiar. We have noted an increase in sensitization prevalences to cinnamal and cinnamyl alcohol among patients who tested positive to FM I from 2008–2009 to 2012–2013,²⁷ which is possibly an indication of changing exposures. However, no conclusive explanation is currently available, except perhaps for an effect of a pre-emptive withdrawal of *Evernia prunastri* (oak moss) extract by industry, even before a ban of (chlor)atranol-

containing fragrance ingredients [i.e. this extract and also *Evernia furfuracea* extract (tree moss)]. This was based on the 2012 Fragrance Opinion of the The Scientific Committee on Consumer Safety (SCCS/1459/11)²⁸ and will come into effect in August 2019 concerning newly launched products and in August 2021 concerning products sold. The third substance to be banned according to this timeline is HICC, and a similar explanation may hold true in terms of pre-emptive withdrawal. In the present trend analysis, the decline from 2007 became consistently significant in 2014, and in 2018 amounted to a 38% reduction of HICC sensitization risk compared with 2007. This trend is mostly mirrored in the FM II trend, of which HICC is the single most important constituent. A recent review of the chemistry and epidemiology of MPR has demonstrated that traditional sources of exposure and sensitization have now vanished in most countries.²⁹ Therefore, the clinical relevance of MPR contact allergy is notoriously difficult to explain, particularly to the sensitized patient. As only a small proportion of patients positive to FM I are, at the same time, positive to SSO, the prevalence estimate for FM I contact allergy is hardly affected by considering SSO or not. However, in individual patient management, a false diagnosis of fragrance allergy (specifically contact allergy to one or more FM I ingredients) as a result of interfering SSO sensitization should certainly be avoided.¹² Three essential oils have been added to the German baseline series in 2011, showing sensitization prevalences of around 1%. However, only extended labelling will enable assessment of clinical relevance, and avoidance of future contact for the patient. Propolis has been tested in the German baseline series for a long time and has recently found its way into the European baseline series,²³ which seems warranted in view of a considerable sensitization prevalence.

Adhesives applied to human skin may still contain colophonium and derivatives, as recently seen in some medical devices.^{30,31} In contrast to a steady prevalence of colophonium allergy, positive reactions to oil of turpentine are dwindling; however, this is a high-volume raw material in fragrance production.²⁸ Compositae mix yielded a moderate number of positive reactions. The poor standardization of this mix, together with some concerns regarding active sensitization,³² warrant research into alternative strategies for investigating this plant allergen family.

The importance of thiuram mix is steady over time, although thiurams have increasingly been replaced by other accelerators, including dithiocarbamates. As thiurams and corresponding dithiocarbamates constitute a redox pair, thiuram mix is also regarded as a good marker for dithiocarbamate contact allergy.³³ In the context of consecutive patch testing, the other rubber allergens yielded a much lower prevalence of positive reactions. An additional 'rubber series' should be tested regularly, especially in an occupational context.^{34,35} Epoxy resins, including other resins, hardeners and reactive diluents to be tested in a special series, continue to be an important, mostly occupational, contact allergen, e.g. in the construction industry.^{17,36}

A strength of the present study is the size of the database analysed, enabling adjustment for multiple potential

confounders. Moreover, the patch-test allergens are derived from a homogeneous source, and the IVDK regularly meets for standardization purposes. With respect to limitations of the present multicentre routine data,³⁷ day-7 readings are recommended in the ESCD patch-test guideline, because overall, approximately 10–15% of positive reactions would otherwise be missed.⁸ Hence, the prevalences in the present analysis may underestimate true morbidity. However, as the reading strategy did not change during the study period, the temporal analysis is not biased. Another limitation of this study is the inability to link an allergic reaction to information that is collected on a case-wise basis (and not allergen-wise basis), such as the anatomical site of dermatitis, in the documentation system currently used. We are hopeful that a new concept regarding the final evaluation of patients who undergo patch testing and the documentation of clinical relevance of allergic patch-test reactions that has recently been suggested will be adopted at some stage, thereby enabling better individual documentation and detailed epidemiological analysis.³⁸

Acknowledgments

The members of the IVDK who contributed data are gratefully acknowledged in Table S5 (see Supporting Information).

References

- Diepgen TL, Ofenloch RF, Bruze M *et al.* Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol* 2016; **174**:319–29.
- Schüttelaar MLA, Ofenloch RF, Bruze M *et al.* Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: The EDEN Fragrance Study. *Contact Dermatitis* 2018; **79**:1–9.
- Diepgen TL, Naldi L, Bruze M *et al.* Prevalence of contact allergy to p-phenylenediamine in the European general population. *J Invest Dermatol* 2016; **136**:409–15.
- Bruze M, Condé-Salazar L, Goossens A *et al.* Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999; **41**:241–50.
- Uter W, Amario-Hita JC, Balato A *et al.* European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. *J Eur Acad Dermatol Venereol* 2017; **31**:1516–25.
- 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.
- Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes 'Informationsverbund Dermatologischer Kliniken' (IVDK). *Dermatol Beruf Umwelt* 2005; **53**:107–14 (in German).
- 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.
- Mahler V, Nast A, Bauer A *et al.* S3-Leitlinie Durchführung des Epikutantests mit Kontakallergenen und Arzneimitteln, Teil 1. *J Dtsch Dermatol Ges* 2019; **17**:1075–93 (in German).
- 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.
- Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**:47–56.
- de Groot A, Gilissen L, Geier J *et al.* Adding sorbitan sesquioleate to the European baseline series: necessary, reasonable, or unavoidable? *Contact Dermatitis* 2019; **81**:221–5.
- Uter W, Schnuch A. EMA revokes marketing authorization for buprenorphine. *Contact Dermatitis* 2011; **64**:235–6.
- Uter W, Gefeller O, Giménez-Arnau A *et al.* Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009–2012. *Contact Dermatitis* 2015; **73**:82–90.
- Ahlström MG, Thyssen JP, Menné T, Johansen JD. Prevalence of nickel allergy in Europe following the EU Nickel Directive – a review. *Contact Dermatitis* 2017; **77**:193–200.
- Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. *Contact Dermatitis* 2013; **69**:253–6.
- Geier J, Krauthelm A, Uter W *et al.* Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health* 2011; **84**:403–11.
- Midander K, Julander A, Skare L *et al.* The cobalt spot test—further insights into its performance and use. *Contact Dermatitis* 2013; **69**:280–7.
- Alinaghi F, Zachariae C, Thyssen JP, Johansen JD. Causative exposures and temporal development of cobalt allergy in Denmark between 2002 and 2017. *Contact Dermatitis* 2019; **81**:242–8.
- Methylisothiazolinone, quo vadis? *Contact Dermatitis* 2016; **75**:263–4.
- Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; **67**:334–41.
- Uter W, Aalto-Korte K, Agner T *et al.* The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. *J Eur Acad Dermatol Venereol* 2020; **34**:333–9.
- Wilkinson M, Gonçalo M, Aerts O *et al.* The European baseline series and recommended additions: 2019. *Contact Dermatitis* 2019; **80**:1–4.
- Hauksson I, Pontén A, Gruvberger B *et al.* Clinically relevant contact allergy to formaldehyde may be missed by testing with formaldehyde 1.0%. *Br J Dermatol* 2011; **164**:568–72.
- Frick-Engfeldt M, Gruvberger B, Isaksson M *et al.* Comparison of three different techniques for application of water solutions to Finn Chambers®. *Contact Dermatitis* 2010; **63**:284–8.
- Bruze M, Engfeldt M, Goncalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series—on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2013; **69**:263–70.
- Geier J, Uter W, Lessmann H, Schnuch A. Fragrance mix I and II: results of breakdown tests. *Flavour Frag J* 2015; **30**:264–74.
- Uter W, Johansen JD, Börje A *et al.* Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure-activity relationships. *Contact Dermatitis* 2013; **69**:196–230.
- de Groot AC. Myroxylon pereirae resin (balsam of Peru) – a critical review of the literature and assessment of the significance of positive patch test reactions and the usefulness of restrictive diets. *Contact Dermatitis* 2019; **80**:335–53.
- Passanisi S, Lombardo F, Barbalace A *et al.* Allergic contact dermatitis and diabetes medical devices: 2 clinical cases. *Contact Dermatitis* 2018; **79**:115–17.

- 31 Hyry HSI, Liippo JP, Virtanen HM. Allergic contact dermatitis from glucose sensors in type 1 diabetes patients. *Contact Dermatitis* 2019; **81**:161–6.
- 32 Bong JL, English JS, Wilkinson SM. Diluted Compositae mix versus sesquiterpene lactone mix as a screening agent for Compositae dermatitis: a multicentre study. *Contact Dermatitis* 2001; **45**:26–8.
- 33 Hansson C, Pontén A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. *Contact Dermatitis* 2014; **70**:300–8.
- 34 Uter W, Warburton K, Weisshaar E *et al.* Patch test results with rubber series in the European Surveillance System on Contact Allergies (ESSCA), 2013/14. *Contact Dermatitis* 2016; **75**:345–52.
- 35 Warburton KL, Uter W, Geier J *et al.* Patch testing with rubber series in Europe: a critical review and recommendation. *Contact Dermatitis* 2017; **76**:195–203.
- 36 Suuronen K, Bäck B, Aalto-Korte K *et al.* Skin exposure to epoxy chemicals in construction coating, assessed by observation, interviews, and measurements. *Contact Dermatitis* 2019; **80**:18–25.
- 37 Uter W, Rustemeyer T, Wilkinson M, Johansen JD. Quality in epidemiological surveillance of contact allergy. *Contact Dermatitis* 2016; **74**:175–80.
- 38 Uter W, Bauer A, Bensefa-Colas L *et al.* Pilot study on a new concept of documenting the clinical relevance of patch test results in contact dermatitis patients. *Contact Dermatitis* 2018; **79**:370–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Results of multifactorial analyses (one for each allergen) quantifying the risk of sensitization associated with the year of patch testing by the prevalence ratio, accompanied by 95% confidence intervals.

Table S2 Sex-stratified results in patients patch tested between 2007 and 2018 in 60 departments of the Information Network of Departments of Dermatology (IVDK) in terms of crude prevalences, accompanied by 95% confidence intervals.

Table S3 Patch-test results stratified for age groups in 125 436 patients patch tested between 2007 and 2018 in 60 departments of the Information Network of Departments of Dermatology (IVDK) in terms of crude prevalences, accompanied by 95% confidence intervals.

Table S4 Sensitivity analysis excluding departments using 24-h patch-test application.

Table S5 The members of the Information Network of Departments of Dermatology (IVDK) are gratefully acknowledged for contributing data.

Online supplemental table S1: Results of multifactorial analyses (one for each allergen) quantifying the risk of sensitisation associated with the year of patch testing by the prevalence ratio (PR), accompanied by 95% confidence intervals (CIs). The reference year is 2007, except if allergens were included in the baseline series in later years. In this case, the first year of use is taken as reference, see table. Results are additionally adjusted for contributing department, gender, atopic eczema and age (dichotomised).

Allergen	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Metals											
Nickel sulfate	1.01 (0.95-1.07)	0.90 (0.84-0.96)	0.89 (0.83-0.94)	0.93 (0.87-0.99)	0.93 (0.87-0.99)	0.97 (0.91-1.04)	0.98 (0.92-1.04)	1.01 (0.95-1.08)	1.04 (0.97-1.11)	1.10 (1.03-1.17)	1.01 (0.94-1.08)
Potassium dichromate	0.83 (0.74-0.92)	0.55 (0.49-0.63)	0.42 (0.36-0.48)	0.55 (0.49-0.62)	0.53 (0.46-0.60)	0.50 (0.44-0.57)	0.54 (0.48-0.62)	0.69 (0.61-0.77)	0.63 (0.56-0.72)	0.79 (0.70-0.88)	0.76 (0.67-0.86)
Cobalt chloride	0.94 (0.85-1.04)	0.71 (0.64-0.80)	0.58 (0.51-0.65)	0.69 (0.62-0.77)	0.74 (0.67-0.83)	0.73 (0.65-0.81)	0.69 (0.61-0.77)	0.76 (0.68-0.85)	0.70 (0.63-0.79)	0.87 (0.78-0.97)	0.93 (0.83-1.04)
Preservatives											
MCI/MI (aq.)	1.00 (0.83-1.20)	1.07 (0.89-1.28)	1.55 (1.31-1.83)	1.71 (1.46-2.02)	2.10 (1.79-2.46)	2.52 (2.16-2.95)	2.49 (2.13-2.91)	1.99 (1.70-2.34)	1.72 (1.45-2.04)	1.64 (1.38-1.95)	1.26 (1.04-1.52)
MI (aq.)							1.00 (ref.)	0.86 (0.76-0.97)	0.74 (0.66-0.85)	0.63 (0.55-0.72)	0.50 (0.43-0.58)

Formaldehyde (aq.)	0.81 (0.62-1.06)	0.81 (0.62-1.05)	0.79 (0.61-1.03)	0.79 (0.61-1.03)	1.03 (0.80-1.32)	1.06 (0.83-1.35)	1.11 (0.87-1.42)	1.22 (0.95-1.55)	1.08 (0.83-1.39)	0.99 (0.76-1.28)	0.88 (0.66-1.16)
Methyldibromoglutaronitrile	0.55 (0.47-0.64)	0.62 (0.54-0.72)	0.52 (0.45-0.60)	0.61 (0.53-0.70)	0.62 (0.54-0.71)	0.46 (0.39-0.53)	0.51 (0.43-0.59)	0.41 (0.35-0.49)	0.76 (0.66-0.87)	1.06 (0.93-1.20)	0.91 (0.80-1.05)
Paraben mix	0.85 (0.65-1.10)	0.96 (0.75-1.24)	0.39 (0.28-0.54)	0.58 (0.44-0.77)	0.75 (0.57-0.98)	0.39 (0.28-0.54)	0.44 (0.32-0.61)	0.71 (0.54-0.94)	0.49 (0.36-0.68)	0.77 (0.58-1.02)	0.71 (0.53-0.96)
2-Bromo-2-nitro-1,3-propanediol	1.20 (0.95-1.50)	0.91 (0.72-1.16)	0.41 (0.30-0.55)	0.67 (0.52-0.87)	0.51 (0.38-0.67)	0.34 (0.24-0.47)					
Iodopropynyl butylcarbamate							1.00 (ref.)	0.71 (0.53-0.93)	0.86 (0.65-1.13)	0.92 (0.70-1.22)	0.65 (0.47-0.89)
Fragrances											
Fragrance mix I	1.02 (0.92-1.12)	1.05 (0.95-1.15)	1.15 (1.05-1.26)	1.23 (1.12-1.35)	1.42 (1.30-1.55)	1.35 (1.23-1.48)	1.22 (1.11-1.34)	1.14 (1.03-1.25)	0.99 (0.89-1.10)	0.86 (0.77-0.96)	0.79 (0.70-0.88)
Fragrance mix II	0.93 (0.83-1.05)	0.87 (0.77-0.99)	1.01 (0.90-1.14)	0.91 (0.81-1.02)	0.99 (0.88-1.11)	1.03 (0.92-1.16)	0.99 (0.88-1.11)	0.88 (0.78-1.00)	0.92 (0.81-1.04)	0.79 (0.69-0.90)	0.70 (0.60-0.80)

HICC	0.98 (0.81-1.17)	0.82 (0.68-0.99)	0.85 (0.71-1.02)	0.91 (0.76-1.09)	0.82 (0.68-0.99)	0.96 (1.15)	0.79 (0.66-0.96)	0.81 (0.67-0.97)	0.70 (0.57-0.85)	0.73 (0.59-0.89)	0.62 (0.50-0.78)
<i>Myroxylon pereirae</i>	0.97 (0.88-1.07)	0.96 (0.88-1.06)	0.91 (0.83-1.00)	1.04 (0.95-1.13)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.03 (0.94-1.13)	0.91 (0.82-1.00)	0.89 (0.80-0.98)	0.95 (0.86-1.05)	0.82 (0.73-0.91)
Sorbitan sesquioleate ^{a)}								1.00 (ref.)	1.40 (0.71-2.74)	1.72 (0.89-3.34)	1.19 (0.60-2.37)
<i>Santalum album</i>				1.00 (ref.)	0.90 (0.71-1.12)	0.93 (0.74-1.16)	0.73 (0.57-0.93)	0.85 (0.67-1.09)	0.87 (0.67-1.12)	1.23 (0.98-1.56)	0.88 (0.67-1.14)
<i>Jasminum</i> spp.				1.00 (ref.)	0.95 (0.77-1.18)	0.94 (0.76-1.17)	0.87 (0.70-1.09)	0.82 (0.65-1.03)	0.82 (0.65-1.05)	0.97 (0.77-1.23)	0.91 (0.71-1.16)
<i>Cananga odorata</i>				1.00 (ref.)	1.06 (0.90-1.26)	0.98 (0.83-1.16)	1.05 (0.89-1.24)	1.02 (0.86-1.21)	0.93 (0.78-1.12)	1.02 (0.85-1.22)	0.92 (0.76-1.12)
Plants (other)											
Colophonium	0.97 (0.85-1.12)	1.04 (0.91-1.18)	0.95 (0.83-1.09)	1.01 (0.89-1.15)	1.00 (0.88-1.14)	0.90 (0.78-1.03)	0.98 (0.85-1.12)	0.99 (0.86-1.13)	0.89 (0.77-1.03)	0.97 (0.84-1.12)	0.92 (0.79-1.07)

Propolis	1.01 (0.85-1.19)	0.86 (0.73-1.03)	0.84 (0.71-1.00)	1.19 (1.02-1.39)	1.69 (1.45-1.96)	1.44 (1.24-1.68)	1.47 (1.26-1.71)	1.59 (1.36-1.85)	1.39 (1.18-1.63)	1.79 (2.10)	1.82 (2.14)
Oil of turpentine	0.66 (0.53-0.83)	1.25 (1.04-1.50)	1.60 (1.34-1.90)	0.92 (0.75-1.12)	0.37 (0.29-0.48)	0.45 (0.36-0.58)	0.69 (0.56-0.86)	0.62 (0.50-0.78)	0.45 (0.34-0.58)	0.26 (0.19-0.36)	0.16 (0.10-0.24)
Compositae mix	1.02 (0.80-1.30)	1.00 (0.79-1.27)	1.05 (0.83-1.32)	1.21 (0.97-1.51)	1.13 (0.90-1.42)	1.27 (1.01-1.59)	1.00 (0.78-1.26)	0.95 (0.74-1.21)	1.05 (0.82-1.34)	1.07 (0.84-1.37)	1.04 (0.81-1.35)
Medicaments, topicals											
Bufexamac	1.09 (0.84-1.43)	1.02 (0.78-1.34)	1.02 (0.78-1.33)	0.85 (0.64-1.12)	0.68 (0.50-0.92)	0.77 (0.57-1.03)					
Cetearyl alcohol	0.80 (0.59-1.08)	0.90 (0.67-1.20)	1.00 (0.76-1.33)	1.38 (1.06-1.80)	1.42 (1.09-1.85)	0.99 (0.74-1.32)	0.98 (0.73-1.31)	0.60 (0.43-0.85)	0.64 (0.45-0.90)	0.90 (1.23)	0.90 (1.25)
Lanolin alcohol	1.13 (0.94-1.36)	1.20 (1.00-1.44)	1.28 (1.07-1.53)	1.33 (1.12-1.59)	1.16 (0.97-1.40)	1.41 (1.18-1.69)	1.41 (1.18-1.68)	1.34 (1.11-1.60)	1.22 (1.01-1.48)	0.85 (0.68-1.05)	0.87 (0.70-1.09)
Rubber additives											
Thiuram mix	1.12 (0.93-)	1.00 (0.83-)	1.04 (0.87-)	0.98 (0.81-)	0.95 (0.79-)	0.97 (0.81-)	1.03 (0.86-)	1.02 (0.85-)	1.18 (0.98-)	0.97 (0.80-)	1.04 (0.85-)

	1.35)	1.21)	1.25)	1.17)	1.15)	1.17)	1.24)	1.23)	1.43)	1.18)	1.27)
Zinc diethyl	0.60 (	0.48 (	0.52 (	0.47 (	0.41 (	0.46 (	0.46 (	0.51 (	0.48 (	0.61 (	0.53 (
dithiocarbamate	0.43-	0.34-	0.37-	0.33-	0.28-	0.33-	0.32-	0.36-	0.34-	0.44-	0.37-
	0.83)	0.67)	0.72)	0.66)	0.58)	0.65)	0.65)	0.71)	0.69)	0.86)	0.76)
Mercapto mix (CBS-	1.08 (	0.97 (	0.90 (	0.92 (	0.92 (	1.12 (	0.83 (	0.81 (	0.85 (	0.66 (	0.64 (
MBTS-MOR)	0.77-	0.69-	0.64-	0.66-	0.66-	0.81-	0.59-	0.57-	0.59-	0.44-	0.42-
	1.50)	1.36)	1.27)	1.29)	1.29)	1.55)	1.18)	1.15)	1.22)	0.98)	0.97)
Mercaptobenzothiazole	0.85 (	0.78 (	0.75 (	0.70 (	0.68 (	0.71 (	0.53 (	0.76 (	0.55 (	0.61 (	0.64 (
	0.62-	0.56-	0.54-	0.51-	0.48-	0.51-	0.37-	0.55-	0.38-	0.42-	0.44-
	1.18)	1.08)	1.03)	0.97)	0.95)	0.99)	0.76)	1.06)	0.81)	0.89)	0.94)
IPPD	1.27 (	1.30 (	1.19 (	1.39 (	1.48 (	1.07 (	1.14 (	1.17 (	1.17 (	1.39 (	1.36 (
	0.91-	0.93-	0.85-	1.00-	1.07-	0.76-	0.81-	0.83-	0.82-	0.98-	0.95-
	1.79)	1.81)	1.66)	1.91)	2.04)	1.51)	1.60)	1.65)	1.66)	1.95)	1.94)
Resins/glues											
PTBFR	0.87 (	0.68 (	0.70 (	0.74 (	0.71 (	0.65 (	0.75 (				
	0.62-	0.48-	0.50-	0.52-	0.50-	0.45-	0.36-				
	1.22)	0.97)	0.99)	1.04)	1.01)	0.94)	1.54)				
Epoxy resin (DGEBA)	1.25 (	1.13 (	0.96 (	1.09 (	1.00 (	1.24 (	1.12 (	1.22 (	1.07 (	1.00 (	1.05 (
	1.00-	0.91-	0.77-	0.87-	0.80-	1.00-	0.90-	0.98-	0.85-	0.79-	0.82-
	1.55)	1.41)	1.20)	1.35)	1.25)	1.53)	1.39)	1.52)	1.35)	1.26)	1.34)

^{a)} Not a fragrance allergen, but listed along these as SSO is used as emulsifier in fragrance mix I

Online supplemental table S2: Gender-stratified results in patients patch tested between 2007 and 2018 in 60 departments of the IVDK in terms of crude prevalences, accompanied by 95% confidence intervals (CIs).); Conc., concentration tested in petrolatum, except where otherwise indicated: aq., water

Allergen	Conc.	Male tested	Male pos.	%	(95% CI)	Female tested	Female pos.	%	(95% CI)
Metals									
Nickel sulfate	5	45481	2397	5.27	(5.07– 5.48)	77356	15716	20.32	(20.03– 20.6)
Potassium dichromate	0.5	45596	1993	4.37	(4.19– 4.56)	78767	2905	3.69	(3.56–3.82)
Cobalt chloride	1	45583	1632	3.58	(3.41– 3.75)	78454	4804	6.12	(5.96–6.29)
Preservatives									
MCI/MI (aq.)	0.01	45531	1503	3.3	(3.14– 3.47)	78723	2995	3.8	(3.67–3.94)
MI (aq.)	0.05	16251	674	4.15	(3.85– 4.47)	28950	1358	4.69	(4.45–4.94)
Formaldehyde (aq.)	1	45622	499	1.09	(1–1.19)	78795	901	1.14	(1.07–1.22)
Methyldibromo glutaronitrile	0.2	30103	808	2.68	(2.5–2.87)	52096	1245	2.39	(2.26–2.52)
Methyldibromo glutaronitrile	0.3	15466	713	4.61	(4.28– 4.95)	26658	1061	3.98	(3.75–4.22)
Paraben mix	16	45561	492	1.08	(0.99–	78817	490	0.62	(0.57–0.68)

					1.18)				
2-Bromo-2-nitro-1,3-propanediol	0.5	29290	301	1.03	(0.92–	49792	444	0.89	(0.81–0.98)
					1.15)				
Iodopropynyl butylcarbamate	0.2	16328	171	1.05	(0.9–1.22)	29047	289	0.99	(0.88–1.12)
Fragrances									
Fragrance mix I	8	45061	3090	6.86	(6.63–	77740	6857	8.82	(8.62–9.02)
					7.09)				
Fragrance mix II	14	45458	1911	4.2	(4.02–	78483	4027	5.13	(4.98–5.29)
					4.39)				
HICC	5	45625	694	1.52	(1.41–	78852	1762	2.23	(2.13–2.34)
					1.64)				
<i>Myroxylon pereirae</i>	25	45563	3203	7.03	(6.8–7.27)	78645	6060	7.71	(7.52–7.89)
Sorbitan sesquioleate ^{a)}	20	9895	79	0.8	(0.63–	17557	114	0.65	(0.54–0.78)
					0.99)				
<i>Santalum album</i>	10	29696	370	1.25	(1.12–	52417	639	1.22	(1.13–1.32)
					1.38)				
<i>Jasminum</i> spp.	5	29700	362	1.22	(1.1–1.35)	52406	772	1.47	(1.37–1.58)
<i>Cananga odorata</i>	10	29684	651	2.19	(2.03–	52420	1275	2.43	(2.3–2.57)
					2.37)				
Plants (other)									
Colophonium	20	45592	1581	3.47	(3.3–3.64)	78760	3148	4	(3.86–4.14)
Propolis	10	45611	1502	3.29	(3.13–	78810	2570	3.26	(3.14–3.39)

					3.46)				
Oil of turpentine	10	45586	591	1.3	(1.19–1.4)	78792	1133	1.44	(1.36–1.52)
Compositae mix	5	20397	291	1.43	(1.27–1.6)	34493	514	1.49	(1.36–1.62)
Compositae mix II	5	24772	361	1.46	(1.31–	43639	609	1.4	(1.29–1.51)
					1.61)				
Medicaments, topicals									
Bufexamac	5	29311	215	0.73	(0.64–	49814	497	1	(0.91–1.09)
					0.84)				
Cetearyl alcohol	20	45641	396	0.87	(0.78–	78876	646	0.82	(0.76–0.88)
					0.96)				
Lanolin alcohol	30	45615	959	2.1	(1.97–	78814	1885	2.39	(2.29–2.5)
					2.24)				
Rubber additives									
Thiuram mix	1	45538	975	2.14	(2.01–	78692	1744	2.22	(2.11–2.32)
					2.28)				
Zinc diethyl dithiocarbamate	1	45659	242	0.53	(0.47–0.6)	78907	412	0.52	(0.47–0.57)
Mercapto mix	1	45507	374	0.82	(0.74–	78766	383	0.49	(0.44–0.54)
(CBS,MBTS,MOR)					0.91)				
Mercaptobenzothiazole	1	5739	39	0.68	(0.48–	10574	37	0.35	(0.25–0.48)
					0.93)				
Mercaptobenzothiazole	2	39787	311	0.78	(0.7–0.87)	68225	337	0.49	(0.44–0.55)
IPPD	0.1	45642	432	0.95	(0.86–	78902	488	0.62	(0.56–0.68)

					1.04)				
Resins/glues									
PTBFR	1	29330	134	0.46	(0.38–0.54)	49862	301	0.6	(0.54–0.68)
Epoxy resin (DGEBA)	1	45327	1038	2.29	(2.15–2.43)	78020	927	1.19	(1.11–1.27)

^{a)} Not a fragrance allergen, but listed along these as SSO is used as emulsifier in fragrance mix I

Allergens tested in less than 1000 patients overall have been omitted.

CBS, *N*-cyclohexyl-2-benzothiazyl sulfenamide; DGEBA, diglycidyl ether of bisphenol A; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOR, morpholinylmercaptobenzothiazole; PTBFR, *p*-*tert*-butylphenol formaldehyde resin

Online supplemental table S3: Patch test results stratified for age groups in 125436 patients patch tested between 2007 and 2018 in 60 departments of the IVDK in terms of crude prevalences, accompanied by 95% confidence intervals (CIs). ‘Young’ age group (until age 30); ‘middle’ age group (age 31 to 65); ‘old’ age group (66 and above).); Conc., concentration tested in petrolatum, except where otherwise indicated: aq., water

Allergen	Conc.	Young			Middle			Old		
		tested	%	(95% CI)	tested	%	(95% CI)	tested	%	(95% CI)
Metals										
Nickel sulfate	5	20672	14.77	(14.29–15.26)	73712	17.82	(17.54–18.1)	28449	6.76	(6.47–7.06)
Potassium dichromate	0.5	20893	3.11	(2.88–3.36)	74911	4.29	(4.15–4.44)	28555	3.62	(3.41–3.84)
Cobalt chloride	1	20813	6.78	(6.45–7.13)	74666	5.6	(5.44–5.77)	28554	2.95	(2.75–3.15)
Preservatives										
MCI/MI (aq.)	0.01	20841	3.98	(3.72–4.26)	74880	3.69	(3.55–3.82)	28529	3.18	(2.98–3.39)
MI (aq.)	0.05	7541	4.28	(3.84–4.76)	27783	4.79	(4.54–5.04)	9874	3.84	(3.47–4.24)
Formaldehyde (aq.)	1	20879	1.06	(0.93–1.21)	74993	1.25	(1.17–1.33)	28541	0.84	(0.73–0.95)
Methyldibromo glutaronitrile	0.2	13731	1.57	(1.36–1.79)	49450	2.58	(2.44–2.72)	19016	2.96	(2.72–3.21)

Methyldibromo glutaronitrile	0.3	7127	1.99	(1.68– 2.34)	25481	4.56	(4.31–4.82)	9514	4.93	(4.5–5.38)
Paraben mix	16	20864	0.71	(0.6–0.83)	74973	0.77	(0.71–0.83)	28537	0.9	(0.8–1.02)
2-Bromo-2-nitro-1,3- propanediol	0.5	13321	0.49	(0.38– 0.62)	47110	0.98	(0.89–1.07)	18650	1.18	(1.03– 1.35)
Iodopropynyl butylcarbamate	0.2	7555	0.64	(0.47– 0.84)	27926	1.07	(0.95–1.19)	9891	1.15	(0.95– 1.38)
Fragrances										
Fragrance mix I	8	20644	4.66	(4.38– 4.96)	73923	8.07	(7.87–8.27)	28230	10.69	(10.34– 11.06)
Fragrance mix II	14	20816	2.53	(2.32– 2.75)	74661	5.11	(4.95–5.27)	28460	5.62	(5.35– 5.89)
HICC	5	20889	0.96	(0.83–1.1)	75036	2.36	(2.25–2.47)	28548	1.7	(1.55– 1.86)
<i>Myroxylon pereirae</i>	25	20882	3.37	(3.13– 3.63)	74887	7.14	(6.96–7.33)	28435	11.3	(10.93– 11.67)
Sorbitan sesquioleate ^{a)}	20	4541	0.68	(0.46– 0.97)	17017	0.63	(0.52–0.76)	5892	0.93	(0.7–1.21)
<i>Santalum album</i>	10	13694	1.08	(0.91– 1.27)	49934	1.2	(1.1–1.29)	18481	1.43	(1.26– 1.61)
<i>Jasminum</i> spp.	5	13688	0.91	(0.75– 1.08)	49932	1.25	(1.15–1.35)	18482	2.1	(1.9–2.32)

<i>Cananga odorata</i>	10	13692	1.75	(1.54– 1.99)	49928	2.27	(2.14–2.41)	18480	2.99	(2.75– 3.24)
Plants (other)										
Colophonium	20	20887	3.3	(3.07– 3.55)	74941	4	(3.86–4.14)	28520	3.65	(3.43– 3.87)
Propolis	10	20880	2.22	(2.03– 2.43)	75006	3.32	(3.19–3.45)	28531	3.93	(3.7–4.16)
Oil of turpentine	10	20875	0.78	(0.66–0.9)	74978	1.41	(1.33–1.5)	28521	1.77	(1.62– 1.93)
Compositae mix	5	9251	1.03	(0.83– 1.25)	32570	1.5	(1.37–1.64)	13069	1.69	(1.48– 1.93)
Compositae mix II	5	11458	0.77	(0.62– 0.95)	41806	1.5	(1.38–1.62)	15143	1.68	(1.49–1.9)
Medicaments, topicals										
Bufexamac	5	13334	0.86	(0.71– 1.03)	47144	0.88	(0.79–0.96)	18646	0.99	(0.85– 1.14)
Cetearyl alcohol	20	20895	0.36	(0.28– 0.45)	75068	0.68	(0.62–0.74)	28550	1.61	(1.47– 1.76)
Lanolin alcohol	30	20895	2.19	(1.99– 2.39)	74999	2.05	(1.95–2.16)	28531	2.97	(2.78– 3.18)
Rubber additives										
Thiuram mix	1	20856	2.22	(2.02–	74839	2.36	(2.25–2.47)	28531	1.72	(1.57–

				2.43)						1.88)
Zinc diethyl dithiocarbamate	1	20901	0.51	(0.42–0.62)	75085	0.52	(0.47–0.58)	28576	0.54	(0.46–0.63)
Mercapto mix (CBS,MBTS,MOR)	1	20837	0.8	(0.68–0.93)	74869	0.63	(0.58–0.69)	28563	0.41	(0.34–0.49)
Mercaptobenzothiazole	1	2763	0.58	(0.33–0.94)	9999	0.52	(0.39–0.68)	3549	0.23	(0.1–0.44)
Mercaptobenzothiazole	2	18092	0.87	(0.74–1.02)	64913	0.61	(0.55–0.67)	25005	0.38	(0.31–0.46)
IPPD	0.1	20895	0.96	(0.83–1.1)	75075	0.75	(0.69–0.82)	28570	0.54	(0.45–0.63)
Resins/glues										
PTBFR	1	13345	0.52	(0.41–0.66)	47171	0.58	(0.51–0.65)	18675	0.49	(0.4–0.6)
Epoxy resin (DGEBA)	1	20614	1.32	(1.17–1.48)	74159	1.81	(1.71–1.91)	28570	1.24	(1.11–1.37)

^{a)} Not a fragrance allergen, but listed along these as SSO is used as emulsifier in fragrance mix I

Allergens tested in less than 1000 patients overall have been omitted.

CBS, *N*-cyclohexyl-2-benzothiazyl sulfenamide; DGEBA, diglycidyl ether of bisphenol A; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzothiazole; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOR, morpholinylmercaptobenzothiazole; PTBFR, *p*-*tert*-butylphenol formaldehyde resin

Online supplemental table S4: Sensitivity analysis: Patch test results with the baseline series in the three periods restricted to departments using 2-day patch test exposure (n=47 departments; n=102548 patients). The table corresponds to Table 2: Number tested; % positives; (exact 95% confidence interval) in the three periods; Conc., concentration tested in petrolatum, except where otherwise indicated: aq., water

Allergen	Conc.	2007	–	2010	2011	–	2014	2015	–	2018
Metals										
Nickel sulfate	5	34253	14.87	(14.5– 15.26)	36635	15.12	(14.75– 15.49)	30127	16.8	(16.37– 17.22)
Potassium dichromate	0.5	34538	4.35	(4.14–4.57)	36979	3.24	(3.06–3.42)	30474	4.44	(4.21–4.68)
Cobalt chloride	1	34488	5.5	(5.26–5.75)	36912	4.84	(4.62–5.06)	30399	5.53	(5.28–5.79)
Preservatives										
MCI/MI (aq.)	0.01	34571	2.41	(2.25–2.58)	36979	4.97	(4.75–5.19)	30300	3.76	(3.55–3.98)
MI (aq.)	0.05				7059	6.03	(5.49–6.62)	29966	4.14	(3.92–4.37)
Formaldehyde (aq.)	1	34580	1.05	(0.95–1.17)	37016	1.25	(1.14–1.37)	30406	1.32	(1.2–1.46)
Methyldibromo glutaronitrile	0.2	19455	2.47	(2.25–2.7)	36726	2.67	(2.51–2.84)	11315	2.04	(1.79–2.32)
Methyldibromo glutaronitrile	0.3	15018	3.58	(3.29–3.89)				19143	4.56	(4.27–4.87)
Paraben mix	16	34590	0.91	(0.82–1.02)	37025	0.65	(0.57–0.74)	30399	0.73	(0.64–0.83)
2-Bromo-2-nitro-1,3-propanediol	0.5	34478	1.1	(0.99–1.21)	29972	0.72	(0.62–0.82)			
Iodopropynyl butylcarbamate	0.2				7048	1.28	(1.03–1.57)	30157	0.84	(0.74–0.94)
Fragrances										
Fragrance mix I	8	34484	7.65	(7.37–7.94)	36867	9.68	(9.38–9.99)	29712	7	(6.71–7.3)
Fragrance mix II	14	34418	5.15	(4.92–5.39)	36936	5.3	(5.08–5.54)	30406	4.4	(4.17–4.64)

HICC	5	34606	2.13	(1.98–2.29)	37033	2.1	(1.96–2.25)	30440	1.72	(1.58–1.87)
<i>Myroxylon pereirae</i>	25	34500	7.47	(7.19–7.75)	36946	8.42	(8.14–8.71)	30429	6.56	(6.29–6.85)
Sorbitan sesquioleate ^{a)}	20							22815	0.71	(0.6–0.82)
<i>Santalum album</i>	10	1623	1.66	(1.1–2.41)	35592	1.29	(1.17–1.41)	30518	1.16	(1.05–1.29)
<i>Jasminum</i> spp.	5	1618	1.3	(0.81–1.98)	35597	1.47	(1.34–1.6)	30504	1.19	(1.07–1.32)
<i>Cananga odorata</i>	10	1622	2.03	(1.4–2.85)	35581	2.53	(2.37–2.7)	30521	2.26	(2.1–2.44)
Plants (other)										
Colophonium	20	34550	4.05	(3.85–4.27)	36965	3.82	(3.63–4.02)	30479	3.63	(3.42–3.84)
Propolis	10	34583	2.49	(2.33–2.66)	36991	3.68	(3.49–3.88)	30462	4.07	(3.85–4.3)
Oil of turpentine	10	34562	2.19	(2.04–2.35)	37018	1.21	(1.1–1.33)	30411	0.73	(0.64–0.84)
Compositae mix	5	33919	1.39	(1.27–1.52)	10871	1.79	(1.55–2.06)			
Compositae mix II	5				26153	1.51	(1.36–1.66)	30337	1.32	(1.19–1.45)
Medicaments, topicals										
Bufexamac	5	34601	1.08	(0.98–1.2)	29963	0.74	(0.64–0.84)			
Cetearyl alcohol	20	34607	0.82	(0.73–0.92)	37032	1.02	(0.92–1.13)	30475	0.57	(0.49–0.67)
Lanolin alcohol	30	34582	2.52	(2.36–2.69)	37007	2.8	(2.64–2.98)	30485	2.06	(1.91–2.23)
Rubber additives										
Thiuram mix	1	34580	2.12	(1.97–2.28)	36996	2.11	(1.97–2.26)	30374	2.25	(2.08–2.42)
Zinc diethyl dithiocarbamate	1	34602	0.58	(0.5–0.66)	37036	0.44	(0.38–0.51)	30518	0.55	(0.47–0.64)
Mercapto mix (CBS,MBTS,MOR)	1	34608	0.65	(0.57–0.74)	37015	0.66	(0.58–0.75)	30262	0.47	(0.4–0.56)
Mercaptobenzothiazole	1							13530	0.39	(0.29–0.51)

Mercaptobenzothiazole	2	34584	0.69	(0.6–0.78)	37027	0.54	(0.47–0.62)	16800	0.56	(0.45–0.68)
IPPD	0.1	34599	0.7	(0.62–0.8)	37022	0.75	(0.66–0.84)	30506	0.7	(0.61–0.81)
Resins/glues										
PTBFR	1	34610	0.6	(0.52–0.69)	29972	0.5	(0.42–0.59)			
Epoxy resin (DGEBA)	1	34604	1.63	(1.5–1.77)	37025	1.62	(1.49–1.75)	30459	1.53	(1.4–1.67)

^{a)} Not a fragrance allergen, but listed along these as SSO is used as emulsifier in fragrance mix I

List of collaborators for Medline metadata: see separate file “ivdk_collaborators_07-18.txt”

Dr. med. Ulrike Beiteke, Department of Dermatology, Dortmund Hospital, Dortmund, Germany (ulrike.beiteke@klinikumdo.de); Prof. Dr. med. Joachim Dissemond, Department of Dermatology, University Hospital, Essen, Germany (Joachim.Dissemond@uk-essen.de); Prof. Dr. med. Timo Buhl, Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany (timo.buhl@med.uni-goettingen.de); Prof. Dr. med. Knut Schäkel, Department of Dermatology, Ruprecht Karls University, Heidelberg, Germany (Knut.Schaekel@med.uni-heidelberg.de); Prof. Dr. med. Claudia Pföhler, Department of Dermatology, Saarland University Medical School, Homburg, Germany (claudia.pfoehler@uks.eu); Dr. med. Cecilia Dietrich, Department of Dermatology, University Hospitals of Schleswig-Holstein, Campus Kiel, Kiel, Germany (cdietrich@dermatology.uni-kiel.de); Prof. Dr. med. Margitta Worm, Allergy Unit, Department of Dermatology and Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany (margitta.worm@charite.de); Prof. Dr. med. Andrea Bauer, Clinic and Policlinic for Dermatology, Medical Faculty Carl Gustav Carus, TU Dresden, Dresden, Germany (Andrea.Bauer@uniklinikum-dresden.de); Dr. med. Burkhard Kreft, Department of Dermatology and Venereology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany (burkhard.kreft@uk-halle.de); Dr. med. Sibylle Schliemann, Department of Dermatology, Jena University Hospital, Jena, Germany (Schliemann@derma-jena.de); Prof. Dr. Knut Brockow, Department of Dermatology and Allergology, Technical University Munich, Munich, Germany (knut.brockow@tum.de); PD Dr. med. Detlef Becker, Department of Dermatology, University of Mainz, Mainz, Germany (detlef.becker@unimedizin-mainz.de); Dr. med. Stephan Forchhammer, Department of Dermatology and Allergology, University Medical Center Tübingen, Tübingen, Germany (stephan.forchhammer@med.uni-tuebingen.de); PD Dr. med. Andreas Recke, Department of Dermatology, University of Luebeck, Luebeck, Germany (Andreas.Recke@uksh.de); Dr. med. Jana Witte, Department of Dermatology and Venereology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany (j.witte@uke.de); Prof. Dr. med. Wolfgang Pfützner, Clinical & Experimental Allergology, Department of Dermatology and Allergology, Philipps-University Marburg, Germany (wolfgang.pfuetzner@med.uni-marburg.de); Dr. med. Brigitte Coras-Stepanek, Department of Dermatology, Allergology and Environmental Medicine, Hospital Munich Schwabing, Munich, Germany (brigitte.coras@klinikum-muenchen.de); Prof. Dr. med. 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); Dr. med. Nicola Wagner, Department of Dermatology, Erlangen University Hospital, Erlangen, Germany (nicola.wagner@uk-erlangen.de); Prof. Dr. med. Werner Aberer, Department of Dermatology and Venerology, Medical University of Graz, Austria (Werner.Aberer@medunigraz.at); Prof. Dr. med. Steffen Emmert, Department of Dermatology and Venereology, University Medicine Rostock, Rostock, Germany (steffen.emmert@med.uni-rostock.de); Prof. Dr. med. Jens Malte Baron, Department of Dermatology and Allergology, University Hospital of Aachen, Aachen, Germany (jbaron@ukaachen.de); Dr. med. Katharina Siedlecki, Department of Dermatology and Allergology, Klinikum Augsburg, Augsburg, Germany (Katharina.Siedlecki@klinikum-augsburg.de); Dr. med. Robert Vetter, University Clinic of Dermatology and Venereology, Otto-von-Guericke University, Magdeburg, Germany (robert.vetter@med.ovgu.de); Dr. med. Vera Baur, Department of Dermatology, Paracelsus Medical University Nuremberg, Nürnberg, Germany (Vera.Baur@klinikum-nuernberg.de); PD Dr. med. Astrid Schmieder, Department of Dermatology, Venereology and Allergology, University Medical Center and Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (astrid.schmieder@umm.de); Prof. Dr. med. Elke Weisshaar, Department of Dermatology, Occupational Dermatology, University Medical Center, Heidelberg, Germany (Elke.Weisshaar@med.uni-heidelberg.de); Dr. Heidrun Grunwald-Delitz, Department of Dermatology, Wald Klinikum Gera, Gera, Germany (heidrun.grunwald-delitz@srh.de); Prof. Dr. med. Axel Trautmann, Department of Dermatology, Venereology, and Allergology, University Hospital Würzburg, Würzburg, Germany (Trautmann_A@ukw.de); PD Dr. med. Kathrin Scherer Hofmeier, University Hospital Basel, Department of Dermatology, Basel, Switzerland (Kathrin.Scherer@usb.ch); Prof. Dr. med. Christiane Szliska, Department of Dermatology, Bethesda Hospital, Freudenberg, Germany (christiane.szliska@diakonie-siegen.de); Prof. Dr. med. Johannes Weiß, Department of Dermatology and Allergy, University of Ulm, Ulm, Germany (johannes.weiss@uniklinik-ulm.de); Prof. Dr. med. Isaak Effendy, Department of Dermatology, Bielefeld Medical Center, Bielefeld, Germany (Isaak.Effendy@sk-bielefeld.de); Prof. Dr. med. Michael Jünger, Department of Dermatology, University Medicine Greifswald, Greifswald, Germany (juenger@uni-greifswald.de); Prof. Dr. med. Randolph Brehler, Department of Dermatology, University Hospital Münster, Münster, Germany (r.brehler@uni-muenster.de); Prof. Dr. med. Franziska Rueff, Department of Dermatology and Allergology, Ludwig-Maximilians-University, Munich,

Germany (Franziska.Rueff@med.uni-muenchen.de); Prof. Dr. med. Thomas Werfel, Department of Dermatology and Allergy, Division of Immunodermatology and Allergy Research, Hannover Medical School, Hannover, Germany (Werfel.Thomas@mh-hannover.de); PD Dr. med. Heinrich Dickel, Department of Dermatology, Venereology and Allergology, Ruhr University Bochum, Bochum, Germany (heinrich.dickel@rub.de); Juliane Rieker-Schwienbacher, Center for Dermatology, Phlebology and Allergology, Klinikum Stuttgart, Stuttgart, Germany (j.rieker-schwienbacher@klinikum-stuttgart.de); PD Dr. med. Dieter Vieluf, Department of Allergology, Photodermatology and Occupational dermatology, Dermatologikum Hamburg, Hamburg, Germany (d.vieluf@dermatologikum.de); Prof. Dr. med. Rudolf Stadler, Department of Dermatology, University Hospital, Johannes Wesling Klinikum, Minden, Germany (Rudolf.Stadler@klinikum-minden.de); Prof. Dr. med. Dagmar Simon, Department of Dermatology, Bern University Hospital, Bern, Switzerland (dagmar.simon@insel.ch); Prof. Dr. med. 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); Dr. med. Sara Micaletto, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland (Sara.Micaletto@usz.ch); PD Dr. med. Regina Treudler, Leipzig Interdisciplinary Allergy Center (LICA), Department of Dermatology, Venereology and Allergology, University Medical Center, Leipzig, Germany (regina.treudler@uniklinik-leipzig.de); Dr. med. Stefan Nestoris, Clinic for Dermatology, Klinikum Lippe-Detmold, Detmold, Germany (Stefan.Nestoris@klinikum-lippe.de); Dr. med. Dirk Mechtel, Clinic for Skin Diseases and Allergology, Heinrich Braun Klinikum, Zwickau, Germany (dirk.mechtelt@hbk-zwickau.de); Dr. med. 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); Prof. Dr. med. Harald Löffler, Department of Dermatology, SLK Hospital Heilbronn, Heilbronn, Germany (Harald.Loeffler@slk-kliniken.de); Dr. med. Michal Gina, BG Clinic Falkenstein of Occupational Diseases, Falkenstein, Germany (m.gina@klinik-falkenstein.de); Dr. med. André Koch, Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany (koch-ae@khdf.de); Prof. Dr. med. Ulrike Raap, Department of Dermatology, University of Oldenburg, Oldenburg (raap.ulrike@klinikum-oldenburg.de); Prof. Dr. med. Jürgen Grabbe, Department of Dermatology, Cantonal Hospital Aarau, Aarau, Switzerland (Juergen.Grabbe@ksa.ch); Dr. med. Philipp Spring, Dermatological and Dermato-

Surgical Center CEDDECC, Lausanne, Switzerland (springphil@hotmail.com); Dr. med. Welf Prager, Practice for Dermatology, Allergology and Phlebology Prager and Partner, Hamburg, Germany (welf.prager@icloud.com); Dr. med. Daniel Wilfinger, Department of occupational disease and occupational medicine, AUVA Rehabilitationsklinik, Tobelbad, Austria (Daniel.Wilfinger@auva.at);

Online supplemental table S5: The members of the Information Network of Departments of Dermatology (IVDK) are gratefully acknowledged for contributing data.

Country	City/Department	Staff
Austria	Graz	W. Aberer
Austria	Graz	B. Kränke
Germany	Aachen	J.M. Baron
Germany	Augsburg	A. Ludwig
Germany	Augsburg	K. Siedlecki
Germany	Berlin Charité	M. Worm
Germany	Bielefeld	I. Effendy
Germany	Bochum	H. Dickel
Germany	Bochum BGFA	M. Fartasch
Germany	Bremen	D. Meyersburg
Germany	Bremen	N. Patsinakidis
Germany	Bremen	M. Zutt
Germany	Buxtehude	P. Große-Hüttmann
Germany	Buxtehude	P. Hausenblas
Germany	Buxtehude	E. Wrage-Brors
Germany	Dermatologikum Hamburg	V. Martin
Germany	Dermatologikum Hamburg	K. Reich
Germany	Dermatologikum Hamburg	K. Breuer
Germany	Dermatologikum Hamburg	D. Vieluf
Germany	Dessau	A. Jung
Germany	Dessau	U. Lippert
Germany	Dortmund	B. Mydlach
Germany	Dortmund	P.J. Frosch
Germany	Dortmund	K. Kügler
Germany	Dortmund	U. Beiteke
Germany	Dresden	P. Spornraft-Ragaller
Germany	Dresden	A. Bauer
Germany	Dresden Friedrichst.	A. Koch
Germany	Erlangen	V. Mahler

Germany	Erlangen	N. Wagner
Germany	Essen	U. Hillen
Germany	Essen	J. Dissemond
Germany	Falkenstein	H. Schwantes
Germany	Falkenstein	D. Vieluf
Germany	Falkenstein	M. Fischer
Germany	Falkenstein	M. Gina
Germany	Freudenberg	Ch. Szliska
Germany	Geier Göttingen	J. Geier
Germany	Gera	J. Meyer
Germany	Gera	H. Grunwald-Delitz
Germany	Gera	M. Kaatz
Germany	Göttingen	Th. Fuchs
Germany	Göttingen	J. Geier
Germany	Göttingen	T. Buhl
Germany	Greifswald	M. Jünger
Germany	Halle	B. Kreft
Germany	Hamburg	E. Coors
Germany	Hamburg	J. Witte
Germany	Hamburg BUK	C. Schröder-Kraft
Germany	Hamburg BUK	K. Breuer
Germany	Hamburg BUK	U. Seemann
Germany	Hannover	T. Schaefer
Germany	Hannover	Th. Werfel
Germany	Hannover	A. Kapp
Germany	Heidelberg	M. Hartmann
Germany	Heidelberg	K. Schäkel
Germany	Heidelberg AKS	T.L. Diepgen
Germany	Heidelberg AKS	E. Weisshaar
Germany	Heilbronn	H. Löffler
Germany	Heilbronn	P. Amann
Germany	Homburg / Saar	C. Pföhler

Germany	Jena	S. Schliemann
Germany	Kiel	J. Brasch
Germany	Leipzig	R. Treudler
Germany	Lippe Detmold	St. Nestoris
Germany	Lübeck	J. Grabbe
Germany	Lübeck	I. Shimanovich
Germany	Lübeck	U. Jappe
Germany	Lübeck	À. Recke
Germany	Lübeck	K. Hartmann
Germany	Mainz	D. Becker
Germany	Mannheim	H. Kurzen
Germany	Mannheim	D. Booken
Germany	Mannheim	C.-D. Klemke
Germany	Mannheim	W. Ludwig-Peitsch
Germany	Mannheim	A. Schmieder
Germany	Marburg	M. Hertl
Germany	Marburg	W. Pfützner
Germany	Minden	J. Hoffmann
Germany	Minden	R. Stadler
Germany	München LMU	P. Thomas
Germany	München LMU	B. Przybilla
Germany	München LMU	R. Eben
Germany	München LMU	T. Schuh
Germany	München LMU	S. Molin
Germany	München LMU	F. Rueff
Germany	München Schwabing	M. Agathos
Germany	München Schwabing	M. Georgi
Germany	München Schwabing	G. Isbary
Germany	München Schwabing	K. Ramrath
Germany	München Schwabing	B. Coras-Stepanek
Germany	München TU	U. Darsow
Germany	München TU	T. Biedermann

Germany	München TU	K. Brockow
Germany	Münster	B. Hellweg
Germany	Münster	R. Brehler
Germany	Münster	M. Behring
Germany	Nürnberg	A. Bachtler
Germany	Nürnberg	K. Ertner
Germany	Nürnberg	V. Baur
Germany	Oldenburg	M. Padeken
Germany	Oldenburg	O. Kautz
Germany	Oldenburg	U. Raap
Germany	Osnabrück	S.M. John
Germany	Osnabrück	Ch. Skudlik
Germany	Prager und Partner	W. Prager
Germany	Prager und Partner	V. Martin
Germany	Rostock	J. Trcka
Germany	Rostock	D. Rothaupt
Germany	Rostock	S. Emmert
Germany	Stuttgart	G. Nist
Germany	Stuttgart	J. Rieker-Schwienbacher
Germany	Tobelbad	D. Wilfinger
Germany	Tübingen	T. Biedermann
Germany	Tübingen	J. Fischer
Germany	Tübingen	S. Forchhammer
Germany	Ulm Univ.-Klinik	R. Hinrichs
Germany	Ulm Univ.-Klinik	J. Weiss
Germany	Würzburg	A. Trautmann
Germany	Zwickau	D. Teubner
Germany	Zwickau	B. Knopf
Germany	Zwickau	D. Mechtel
Switzerland	Aarau	J. Grabbe
Switzerland	Basel	A. Bircher
Switzerland	Basel	K. Scherer

Switzerland	Bern	D. Simon
Switzerland	Lausanne	C. Curdin
Switzerland	Lausanne	P. Spring
Switzerland	Lausanne	J. di Lucca
Switzerland	Lausanne CEDDECC	P. Spring
Switzerland	Zürich	B. Ballmer-Weber
Switzerland	Zürich	A. Navarini

