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Patch test results in patients with suspected contact allergy to shoes: Retrospective IVDK data analysis 2009–2018

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Abstract

Background: Allergic contact dermatitis caused by shoes is common and new relevant allergens have been identified.

Objectives: To investigate the pattern of type IV sensitization in patients with suspected allergic contact dermatitis of the feet related to shoes as a presumed culprit trigger.

Methods: Retrospective analysis of data of the Information Network of Departments of Dermatology (IVDK), 2009-2018.

Results: Six hundred twenty-five patients with presumed shoe dermatitis were identified in a cohort of 119 417 patients. Compared to patients with suspected contact sensitization from other allergen sources (n = 118 792), study group patients were more frequently sensitized to potassium dichromate (10.8% vs 3.5%), colophony (7.2% vs 3.7%), mercaptobenzothiazole (MBT; 4.0% vs 0.6%), mercapto mix (4.6% vs 0.6%), and *p*-tert-butylphenol formaldehyde resin (1.6% vs 0.5%). Sensitizations to urea formaldehyde resin, melamine formaldehyde resin, glutaraldehyde, tricresyl phosphate, and phenyl glycidylether were rare. Moreover, reactions to compounds in the leather or textile dyes test series were scarce.

Conclusion: A distinct sensitization pattern was observed in patients with suspected allergy to shoe materials. Although substances with low sensitization rates should be removed from the leather and shoe patch test series, novel potential allergens should be added.

KEYWORDS

contact allergy, leather, mercaptobenzothiazole, patch testing, potassium dichromate, *p*-tert-butylphenol formaldehyde resin, shoe dermatitis

Abbreviations: BTMPS, Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate; Cr, chromium; D3, Day 3; DKG, German Contact Dermatitis Research Group/Deutsche Kontaktallergie-Gruppe; DMF, dimethyl fumarate; DMTBS, dimethylthio-carbamylbenzothiazole sulphide; DO3, Disperse orange 3; DPG, 1,3-diphenylguanidine; IPPD, N-isopropyl-N′-phenyl-p-phenylenediamine; IVDK, Information Network of Departments of Dermatology; MBT, mercaptobenzothiazole; MDA, 4,4′-diaminodiphenylmethane; OIT, octylisothiazolinone; PPD, P-phenylenediamine; PTBC, p-tert butyl catechol; PTBP-FR, *P*-tert-butylphenol formaldehyde resin; TBHQ, Tert-butylhydroquinone; TCMTB, 2-(thiocyanomethylthio)benzothiazole; ZDEC, zinc diethyldithiocarbamate.

The first evidence of human footwear can be tracked down to the late Pleistocene ~40 000 years ago based on the anatomy of feet.[1] At that time, shoes were worn for protection of the skin and against the cold, in the form of woven sandals, partially consisting of leather. Nowadays, the appearance aspect has become of greater importance and footwear consists of an abundance of different materials. Contact dermatitis of the feet caused by footwear, hereinafter referred to as "shoe dermatitis," represents ~10% of all patch testing cases.[2,3] Typically, the volar and dorsal aspects of the feet are affected, sparing the toes' flexural creases as well as the instep.[4] Whereas unilateral affection is possible, most cases present with a symmetrical manifestation.[5] The culprit agent causing the allergic contact dermatitis can often be found in leather (chromium salts, biocides, colorants), rubber, or adhesive components, in particular, *p*-tert-butylphenol formaldehyde resin (PTBP-FR).[6-11]

Various studies on the causative allergens in shoe dermatitis from different regions of the world, such as North America, Indonesia, Brazil, and India, have been published in recent years.[10,12-15] However, current large-scale studies on shoe dermatitis from Central Europe are missing. About 10 years ago, footwear dermatitis due to dimethyl fumarate (DMF) in leather was reported in parallel to the epidemic of "sofa dermatitis" due to DMF used as antimycotic substance at that time.[16-21] Recent case reports have shown that octylisothiazolinone,[22] dialkyl thioureas,[23] dimethylthio-carbamylbenzothiazole sulphide (DMTBS),[24,25] 2-(thiocyano-methylthio)benzothiazole (TCMTB),[26] acetophenone azine,[27,28] and Tinuvin 770 (bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate; BTMPS)[29] may also be important shoe allergens, yet may be overlooked as they are not tested routinely. Occasionally, secondary "contaminants" such as shoe refresher sprays or residues of antimycotics may cause shoe dermatitis, so taking a detailed history to identify further culprits is crucial.[30,31]

As far as data of the Information Network of Departments of Dermatology (IVDK) are concerned, two retrospective studies were conducted analyzing different aspects of foot and shoe contact dermatitis. In the early 1990s, we analyzed contact sensitizations in 85 patients who were occupationally exposed to shoes and leather. In addition to frequent sensitizations to potassium dichromate, we found a high proportion of positive reactions to glutardialdehyde, although the results may have been susceptible to false positives due to testing at 1% pet.[32] The second study focused on 2671 patients with foot dermatitis (irrespective of its cause) who were patch tested in IVDK departments from 2001 to 2010.[3] These patients reacted significantly more often to potassium dichromate (12.8% vs 4.1%), cobalt chloride (9.2% vs 6.2%), colophony (8.3% vs 4.0%), ammoniated mercury (5.7% vs 3.6%), PTBP-FR (3.6% vs 0.8%), mercapto mix (2.9% vs 0.5%), and mercaptobenzothiazole (2.5% vs 0.5%) than patients affected by eczema/dermatitis at other skin regions.[3]

Until now, there has been no retrospective IVDK data analysis explicitly focusing on patients with shoe dermatitis, that is, those with foot dermatitis *and* having shoes as the suspected allergen source. We therefore analyzed data of this particular subgroup of patients to describe a current corresponding sensitization pattern for the Central Europe region and provide patch test recommendations for the future.

1 | PATIENTS AND METHODS

The IVDK, founded in 1988, is a network of currently 58 dermatological departments in Germany, Switzerland, and Austria focusing on clinical epidemiology of contact allergy. The central IVDK database holds clinical data and patch test results of ~300 000 patients, with roughly 10 000 new data sets added every year. The routine operating procedures of the IVDK network are described in detail elsewhere.[33] Briefly, patients' histories, clinical data, and patch test results are recorded in local databases in the participating centers and, after pseudonymization, transmitted to the IVDK central office at the University Medical Centre of Göttingen twice a year. Data are subjected to a standardized quality control, added to the central IVDK database, and analyzed according to international standards.[34,35]

Patch testing was performed according to the guidelines of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe; DKG).[36-38] Test allergens were applied to the skin for 48 hours in 84.1% of the patients, and for 24 hours in 15.9%. Patch test reactions were classified as negative, doubtful (erythema or a few follicular papules only), positive (+, ++ or +++)—that is, reactions with erythema, infiltration, papules, and/or (coalescing) vesicles—or irritant. For the present data analysis, patch test reactions at day 3 (D3) were considered. In a few exceptional cases, when a patch test reading was performed at D4 instead of D3, this reading was selected. Patch test preparations were purchased from Almirall Hermal, Reinbek, Germany (until 2013); SmartPractice Europe, Greven, Germany (from 2014 on); or Chemotechnique, Vellinge, Sweden.

Age- and sex-standardizations of reaction frequencies were conducted according to published methods.[39] For comparisons, percentages of proportions of anamnestic items or reaction frequencies in disjunct groups of patients are presented together with exact 95% confidence intervals (CIs) in this study. Statistical significance of differences on a 5% level was concluded from non-overlapping 95% CIs. Data were managed and analyzed using the statistical analysis software SAS, version 9.4 (SAS Institute, Cary, NC, USA).

2 | RESULTS

We analyzed data from 2009 to 2018 taken from the central IVDK database. In these years, 119 417 patients were patch tested in the departments of dermatology that make up the IVDK. In 1057 patients (0.9%), shoes and boots were suspected as allergen sources relevant to the patients' dermatitis. Six hundred twenty-five (59.1%) of these patients exhibited dermatitis localized primarily to the feet. These 625 patients were considered as the study group.

Of the study group, 357 patients (57.1%) were men, 155 (24.8%) had a history of or had current atopic dermatitis, and 77 (12.3%) patients had occupational dermatitis. Ages ranged from 7 to 88 years (median 45 years). Age distribution is depicted in Figure 1. For comparison, the age distribution is provided of all other patients who were patch tested in the IVDK in the same time period. Patients of the study group were slightly younger than the overall tested patients,

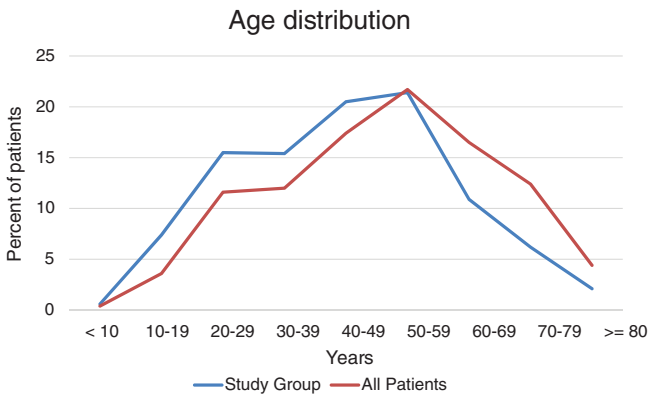

FIGURE 1 Age distribution of the patients in the study group compared to all patients who were patch tested in the IVDK (2009-2018)

TABLE 1 Distribution of the localization of dermatitis in the study group (625 patients with "shoe dermatitis")

Localization	n	%
Feet (no details given)	329	52.6
Soles	142	22.7
Arches	91	14.6
Toes	13	2.1
Ankles	6	1.0
Lower legs	44	7.0

but with a similar distribution pattern. Allergic contact dermatitis (ACD) was finally diagnosed in 203 patients (32.5%); the remainder had other forms of eczema. In 168 ACD patients (82.8% of 203), ACD was the only diagnosis. Ten patients (4.9%) additionally had atopic dermatitis, six (3.0%) from chronic irritant contact dermatitis, three (1.5%) from dyshidrotic eczema, and 16 (7.9%) from other dermatoses. Distribution of the localizations of dermatitis is presented in Table 1. Patients in whom the soles were primarily affected (n = 142) were significantly more often diagnosed with dyshidrotic eczema (29.6% vs 12.0%; $P < .0001$) and less frequently with allergic contact dermatitis (24.6% vs 34.8%; $P = .02$) than the remaining patients with foot dermatitis (n = 483). In 579 patients (92.6%), the DKG baseline series was tested; the DKG leather and shoes series was patch tested in 475 patients (76.0%), and the DKG leather and textile dye series in 329 patients (52.6%).

Positive reactions to allergens of the DKG baseline series are listed in Table 2. Most frequently, patients reacted to nickel sulfate (14.3%), potassium dichromate (9.8%), colophony (6.5%), and cobalt chloride (6.2%). Twenty-eight patients (4.8%) reacted to mercaptobenzothiazole (MBT) or its derivatives contained in the mercapto mix.

We compared age- and sex-standardized frequencies of sensitizations to baseline series allergens of the study group to all other patients tested in the IVDK from 2009 to 2018 (Table S1 in the online supplement). Patients with shoe dermatitis reacted significantly more often to potassium dichromate (10.8% vs 3.5%), colophony (7.2% vs 3.7%), MBT (4.0% vs 0.6%), and mercapto mix (4.6% vs 0.6%). Reactions to PTBP-FR were also noted more frequently in the study group (1.6% vs 0.5%), although significance was borderline. Frequencies of sensitizations to nickel, cobalt, thiurams, preservatives (including formaldehyde), and fragrances were not increased in the study group.

Only 5 of the 14 allergens of the DKG leather and shoes series elicited positive reactions in more than 1% of the patients tested (Table 3). These allergens were 1,3-diphenylguanidine (DPG), mercury(II)amidochloride, 4,4′-diaminodiphenylmethane (MDA), 1,2-benzisothiazolin-3-one sodium salt, and PTBP-FR. In 226 patients tested with MDA, p-phenylenediamine (PPD) was tested in parallel. Four of these patients reacted to MDA, and each of these four patients also reacted to PPD. No patients reacted to chloroacetamide or chlorocresol.

In Table 4, positive reactions to the DKG leather and textile dyes series are listed. Only two allergens elicited positive reactions in more than 1% of the patients tested: PPD and disperse orange 3 (DO3). Both allergens were tested in parallel in 219 patients. Eleven of these patients reacted positively to PPD, and 7 to DO3. All of the DO3-positive patients also reacted to PPD. No positive reactions were noted to disperse blue 3, disperse red 11, or disperse yellow 3.

The DKG rubber series was patch tested in 240 patients. Results are presented in Table 5 in the online supplement. Positive reactions to MBT and its derivatives (components of the mercapto mix), DPG, and N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD) were most frequently noted, followed by zinc diethyldithiocarbamate (ZDEC) and thiurams. Four of 237 patients (1.7%) had a positive patch test reaction to p-tert butyl catechol 0.25% petrolatum (pet.) (PTBC). In 235 patients, PTBC and PTBP-FR were patch tested in parallel. Of these, two had a strong (++) positive reaction to PTBP-FR, and four a weak (+) positive reaction to PTBC. No patient reacted to both substances.

Tert-butylhydroquinone (TBHQ) 1% pet. was tested in 394 patients, 7 (1.8%) of whom reacted positively. Only one patient reacted to both PTBC and TBHQ.

Octylisothiazolinone 0.025% pet. (OIT) was patch tested in 49 patients only; no positive reactions were observed.

Dimethyl fumarate (DMF) was patch tested in 65 patients at test concentrations ranging from 0.001% (= 10 ppm) to 1% in water, and at 0.1% in pet. One patient showed a weak positive reaction to DMF 1% aq. but did not react to 0.1% or 0.01% aq. All other tests remained negative.

Material from the patients' own shoes were patch tested in 135 patients. Twenty-nine tests were performed with leather parts, 28 with textile parts, seven with foam material, and six with rubber parts. In the majority of tests (n = 80), the material was not specified. Body care products for the feet were tested in 16 patients. There were 17 positive reactions to materials not specified (9 +, 7 ++, 1+++), 4 reactions to leather samples (2+, 1

TABLE 2 Patch test reactions to allergens of the DKG baseline series in the study group. Some allergens were added to the baseline series during the course of the study period. Others were removed, resulting in reduced test frequencies

Allergen	Test concentration	Number of patients tested	% positive
Nickel sulfate	5%	568	14.3
Potassium dichromate	0.5%	569	9.8
Colophony	20%	571	6.5
Cobalt chloride	1%	568	6.2
Balsam of Peru (*Myroxylon pereirae*)	25%	567	5.6
Fragrance Mix I	8%	570	5.6
Mercapto Mix (CBS, MBTS, MOR)	1%	571	4.6
Fragrance Mix II	14%	571	4.4
Mercaptobenzothiazole (MBT)[a]	2%	490	3.7
Methyldibromo glutaronitrile (MDBGN)[b]	0.3%	125	3.2
Propolis	10%	569	3.2
Methyldibromo glutaronitrile (MDBGN)[b]	0.2%	444	3.2
Lanolin alcohols	30%	569	3.0
Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (aq.)	0.01%	569	2.5
Mercaptobenzothiazole (MBT) [a]	1%	82	2.4
Thiuram mix	1%	571	2.3
Oil of turpentine	10%	564	2.0
p-Tert-butylphenol formaldehyde resin (PTBP-FR)	1%	514	1.9
N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD)	0.1%	569	1.8
Methylisothiazolinone (aq.)	0.05%	461	1.5
Zinc diethyldithiocarbamate (ZDEC)	1%	570	1.2
Jasmine absolute	5%	497	1.0
Sandalwood oil	10%	497	1.0
Epoxy resin	1%	566	0.9
Cetearyl alcohol	20%	569	0.9
Iodopropynyl butylcarbamate (IPBC)	0.2%	462	0.9
Ylang Ylang (I + II) oil	10%	497	0.8
Formaldehyde (aq.)	1%	569	0.7
Paraben Mix	16%	569	0.7
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)	5%	569	0.7
Compositae Mix II[c]	5%	349	0.6
Compositae Mix I[c]	5%	218	0.5
2-Bromo-2-nitropropane-1,3-diol	0.5%	489	0.2

Note: Vehicle is petrolatum (pet.) unless water (aq.) is specified.
Abbreviations: CBS, *N*-cyclohexyl-2-benzothiazyl sulfenamide; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole.
[a]MBT was patch tested at 1% pet. in 2016/2017 and at 2% pet. in all other periods.
[b]MDBGN was patch tested at 0.2% pet. until March 2016 and at 0.3% pet. from April 2016 on.
[c]There was a switch from Compositae Mix I to Compositae Mix II in 2011.

++, 1+++), 3 to rubber samples (2+, 1++), 3 to textile materials (2+, 1++), and 1 to foam material (+). Of those 22 patients who reacted to their own shoe material, 5 had no reaction to standardized patch test substances. The remaining 17 patients reacted to nickel sulfate (8 patients), colophony (8), MBT and MBT derivatives (6), fragrances (6), potassium dichromate (5), cobalt chloride (5), PTBP-FR (3), DPG (3), oil of turpentine (3), thiurams (2), iodopropynyl butylcarbamate (2), formaldehyde (1) melamine formaldehyde resin (1), dibutylthiourea (1), ethyleneglycol dimethacrylate (1), and dimethyl fumarate (1). However, we have no information whether these allergens were present in the culprit shoes.

TABLE 3 Patch test reactions to allergens of the DKG leather and shoes series in the study group

Allergen	Test concentration	Number of patients tested	% positive
1,3-Diphenylguanidine (DPG)	1%	467	2.6
Mercury(II)amidochloride	1%	467	2.6
4,4′-Diaminodiphenylmethane	0.5%	467	1.9
1,2-Benzisothiazolin-3-one, sodium salt	0.1%	466	1.7
p-Tert-butylphenol formaldehyde resin (PTBP-FR)	1%	441	1.6
Ethylenediamine dihydrochloride	1%	465	0.9
Phenol formaldehyde resin (Novolak)	5%	465	0.9
Urea formaldehyde resin	10%	466	0.4
Melamine formaldehyde resin	7%	466	0.4
Glutaraldehyde	0.3%	467	0.4
Tricresyl phosphate	5%	464	0.2
Phenyl glycidylether	0.25%	468	0.2
Chloroacetamide	0.2%	466	0.0
Chlorocresol	1%	467	0.0

Note: Vehicle is petrolatum throughout.

TABLE 4 Patch test reactions to allergens of the DKG leather and textile dyes series in the study group

Allergen	Test concentration	Number of patients tested	% positive
p-Phenylenediamine (PPD)[a]	1%	219	5.0
Disperse Orange 3 (CI 11005)	1%	323	2.8
Disperse Red 17 (CI 11210)	1%	323	0.9
Disperse Blue 124[b]	0.3%	251	0.8
Disperse Blue 106[b]	0.3%	251	0.8
Acid Yellow 36 (CI 13065)	1%	323	0.6
Bismarck Brown R	0.5%	322	0.3
Disperse Red 1 (CI 11110)	1%	323	0.3
Disperse Yellow 9 (CI 10375)	1%	323	0.3
Naphthol AS (CI 37505)	1%	323	0.3
Disperse Blue 3 (CI 61505)	1%	323	0.0
Disperse Red 11 (CI 62015)	1%	323	0.0
Disperse Yellow 3 (CI 11855)	1%	321	0.0

Note: Vehicle is petrolatum throughout.
[a]PPD was inserted in this test series in October 2011.
[b]Disperse Blue 106 and 124 were removed from this test series in April 2016 because they were no longer available at 0.3% pet.

3 | DISCUSSION

Foot dermatitis is a complex disease that may give rise to several differential diagnoses: allergic or irritant contact dermatitis; atopic, dyshidrotic, or hyperkeratotic eczema; psoriasis; tinea pedis; and, rarely, lichen planus. According to the literature, 1.5%-24% of patch tested patients have allergic contact dermatitis due to shoes.[2-4,40-42] This great variation is probably explained by differences in patient selection criteria and variable climate conditions leading to different shoe-wearing habits. In our study, the prevalence of shoe dermatitis was even lower (0.9%), possibly based on strict inclusion criteria. Although female gender was predominant in some studies,[40-43] supporting the theory of a higher risk of sensitization due to the absence of stockings in summer, an opposite gender distribution was shown in our study and that of others.[3,4,44,45] It can be hypothesized that men's tendency to increased sweating (28) may facilitate allergen penetration and thus contribute to sensitization. Sweating of the feet is most pronounced on the soles. We found allergic contact dermatitis to be low in our patients with affected soles, which was probably due to the thick stratum corneum in that region.

With our retrospective analysis of IVDK data of patients with shoe dermatitis, we are able to describe a sensitization pattern for a

TABLE 5 Patch test reactions to allergens of the DKG rubber series in the study group and reactions to MBT, IPPD and ZDEC in study group patients tested with the DKG rubber series

Allergen	Test concentration	Number of patients tested	% positive
Mercaptobenzothiazole (MBT)	2%	184	4.3
1,3-diphenylguanidine (DPG)	1%	238	4.2
Morpholinyl mercaptobenzothiazole (MOR)	0.5%	238	4.2
N-cyclohexyl-2-benzothiazyl sulfenamide (CBS)	1%	238	3.8
Dibenzothiazyl disulfide (MBTS)	1%	238	2.9
N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD)	0.1%	224	2.7
Tetramethylthiuram monosulfide (TMTM)	0.25%	238	2.1
p-tert-butylcatechol	0.25%	237	1.7
Zinc diethyldithiocarbamate (ZDEC)	1%	224	1.3
Dipentamethylenthiuram disulfide (DPTD)	0.25%	239	1.3
Tetramethylthiuram disulfide (TMTD)	0.25%	239	1.3
Tetraethylthiuram disulfide (TETD)	0.25%	239	1.3
Ethylenediamine dihydrochloride	1%	239	0.8
Zinc dibutyldithiocarbamate (ZDBC)	1%	236	0.4
Dibutylthiourea	1%	238	0.4
Diphenylthiourea	1%	238	0.4
Methenamine (Hexamethylene tetramine)	1%	238	0.4
Monobenzone	1%	238	0.4
N,N′-diphenyl-p-phenylenediamine (DPPD)	0.25%	238	0.4
Cyclohexylthiophthalimide	0.5%	238	0.4
Zinc dibenzyldithiocarbamate	1%	238	0.0

Note: Vehicle is petrolatum throughout.

region with moderate climate. Of the baseline series allergens, we observed increased frequencies of sensitizations to potassium dichromate, colophony, and MBT and its derivatives.

Chromium (Cr) salts are used in more than 90% of leather for tanning.[46] The trivalent chromium salts used in this process can oxidize to the hexavalent Cr(VI), which may leach from the leather. Cr(VI) elicits dermatitis and patch test reactions at lower concentrations than Cr(III) in sensitized patients, largely because it penetrates the skin more easily.[6,47] Mostly, diagnostic patch testing is performed using potassium dichromate 0.5% pet., where chromium is in its hexavalent state. The sensitization rate in our study (9.8%) was in the same range as described in a similarly designed Brazilian study.[12] It is interesting to note that it was lower than described in a previous IVDK data analysis (2001-2010) of patients with foot dermatitis.[3] According to EU regulation No. 301/2014, leather articles or parts coming into contact with the skin may not contain more than 3 ppm Cr(VI) from 2015 onwards.[48] The preventive effect of this regulation is not reflected by our data, because most of the patients were tested before 2015. The influence of time can hardly be recognized in cohorts as small as ours with ~50 patients with suspected shoe dermatitis per year.

Colophony is a well-known shoe allergen in glues and finishes or as tackifier.[15,40,49] In our study group, the frequency of sensitization to colophony was about twice as high as in the control group and comparable to earlier IVDK data on patients with foot dermatitis,[3] confirming its persistent and particular importance as a shoe allergen.

Among the rubber ingredients patch tested in the baseline series, MBT and its derivatives, but not thiurams, ZDEC, or IPPD, elicited significantly more positive reactions in shoe dermatitis patients compared to the control group. Generally, rubber components are known to be relevant shoe allergens.[10,12-15,40] However, the leading role of MBT and its derivatives in this context has been described previously by only Freeman, Australia,[9] and Nardelli et al., Belgium.[40]

Remarkably, cobalt sensitization was only slightly and insignificantly increased in our study group. This is in contrast to our earlier data on foot dermatitis[3] and data on shoe dermatitis patients from Belgium,[40] but it is in line with some other studies on contact allergy due to shoes.[10,12] Cobalt has recently gained more attention as a relevant allergen in leather consumer goods.[50,51]

PTBP-FR is considered as the most prominent occupational allergen encountered by shoemakers and repairers,[6] but has also been described as a relevant contact allergen in patients with shoe dermatitis.[3,9,10,40] In our study, the prevalence of sensitizations to PTBP-FR was increased compared to the control group (1.6% vs 0.5%), but only with borderline significance. In 2014, the DKG moved PTBP-FR from the baseline series to the "leather and shoes" series due to its low reaction frequency and because it is only a relevant contact allergen in shoes.

PTBC is used as a stabilizer in synthetic rubber. Its possible role as a shoe allergen remains unclear. In two previous studies,[10,40] reactions to PTBC were regarded as cross-reactions to PTBP-FR. However, we did not find any concomitant reactions to both substances. TBHQ is a widely used antioxidant, for example, in skin care products, that is chemically similar to PTBC and thus may possibly cross-react. However, we identified only one patient reacting to both PTBC and TBHQ. This suggests that PTBC may act as an independent shoe allergen in most cases. However, it must be considered that PTBC is tested at 0.25% pet. only, whereas PTBP-FR and TBHQ are being tested at 1% pet. and that the PTBC reactions might therefore be missed. Increasing the PTBC test concentration is, however, not an option, because higher concentrations have been shown to induce active patch test sensitization.[52] It might be worthwhile adding PTBC and TBHQ to the leather and shoe series in order to get more data on this issue.

The diagnostic value of the two patch test series recommended for patients with shoe dermatitis is limited: Half of the substances of the "leather and shoes" series, such as urea formaldehyde resin, melamine formaldehyde resin, glutaraldehyde, tricresyl phosphate, phenyl glycidylether, chloroacetamide, and chlorocresol, elicited positive reactions in less than 0.5% of the patients tested. Furthermore, we did not identify any publication indicating that the two formaldehyde resins play a significant role as contact allergens in shoes. Glutaraldehyde is used in tanning,[6] but in agreement with other studies on shoe dermatitis,[10] we could not identify it as a significant contact allergen in this context. Tricresyl phosphate and phenyl glycidyl ether are used in the shoe industry as a flame retardant and a reactive diluent for epoxy resins, respectively, yet neither seems to play a role as a shoe allergen. Again, reports on sensitization in this context could not be found. According to information from the chemical industry, the use of chloroacetamide and chlorocresol as biocides is declining, and we did not find any case of sensitization in our study group. As part of the DKG preservative and biocides series, both elicited positive reactions in less than 0.5% in the IVDK cohort from 2009 to 2018 (data not shown in detail). On the other hand, octylisothiazolinone, which has been reported to be a relevant leather and shoe allergen,[22] has only occasionally been patch tested in patients with shoe dermatitis. Based on our results, we propose reducing the DKG "leather and shoes" series to the first seven allergens of Table 3, which elicited almost 1% positive reactions or more. The rubber allergen DPG seems to be as important as thiurams or MBT derivatives in patients with shoe dermatitis. Mercury compounds have been used as preservatives in leather,[6] and have also been described as contact allergens in rubber boots in the 1990s,[53] but we are not sure if they are still currently relevant. A positive patch test reaction to MDA may indicate contact allergy to diphenylmethane-4,4′-diisocyanate,[54] a basic compound of polyurethanes that may be present in shoes, or it may be a cross-reaction in patients primarily sensitized to PPD.[55] Among other areas of application, benzisothiazolinone is being reviewed for use as a biocide for leather.[56] Ethylenediamine is used as a stabilizer in rubber latex[57] and may hence be a relevant shoe contact allergen. Phenol formaldehyde resins may be contained in urethane adhesives.[6] In addition, we recommend adding octylisothiazolinone 0.025% pet. as it has been reported to be a relevant allergen in leather.[6,22]

The leather and textile dyes series (Table 4) does not seem to be appropriate for detecting contact sensitization to leather colorants used in shoes. Either other dyes are being used or leather dyes do not pose a great risk to the consumer. PPD (with occasional cross-reaction to DO3) was the only allergen of this series to elicit a reaction in more than 1% of the study group. It is not yet clear whether these reactions are relevant to shoe dermatitis, as patients may have become sensitized to PPD through different exposures, for example, hair dyes. A significantly increased risk of PPD sensitization among patients with shoe dermatitis was described in a Belgian study.[39] In accordance with other studies, the authors stated that shoe dermatitis from dyes is extremely rare, and they assumed that reactions to dyes from stockings may be a confounder.[5,40] Although the frequencies of reactions were low in our study group, we would not recommend shortening this series because it has its relevance in suspected textile dye allergy.[58]

Concentration of DMF has been limited to 0.1 mg/kg (= 1 ppm) in any consumer products (including shoes) in the EU since March 2010.[59,60] Accordingly, only one possible sensitization to DMF was detected. However, this reaction was only elicited by the highest test concentration (1% aq.), hence a false positive (irritant) reaction cannot be excluded. Routine patch testing with DMF is no longer necessary since relevant exposure is lacking.

From the practical point of view, in individual cases, patch testing with the patient's own shoe material might be helpful. Indeed, new shoe allergens such as DMTBS or acetophenone azine have been identified by investigations like these.[24,25,27] However, in most cases, information on the ingredients of the shoe parts is almost impossible to obtain. Hence, the prospective scientific value of these tests is limited when no analytical chemical laboratory is at hand. In our data, positive patch tests with various materials from the patients' own shoes were recorded in 22 patients, and 17 of these patients had positive reactions to standardized patch test preparations as well. The relevance of these reactions for the shoe dermatitis, however, remained largely unclear, because information on the composition of the shoe material is not present. A declaration of the shoe ingredients, at least of the known and frequent contact allergens, would be helpful for secondary prevention. But considering the shoe production process, this is probably illusory.

4 | CONCLUSION

Among patch test patients, allergic contact dermatitis to shoes, in particular due to dyes, remains rare. Our findings are in agreement with the list of the most frequent and relevant allergens, that is, Cr(VI), colophony, MBT and its derivatives, and PTBP-FR. Urea formaldehyde resin, melamine formaldehyde resin, glutaraldehyde, tricresyl phosphate, phenyl glycidylether, chloroacetamide, and chlorocresol no longer seem to be relevant allergens and should therefore be removed from the leather and shoes patch test series. Octylisothiazolinone

should be added because there is increasing evidence that it is a relevant allergen in leather and shoes, although we did not identify allergic patients in our small series of patients tested with this substance. To evaluate the role of PTBC and TBHQ as potential cross-reacting allergens in patients with shoe dermatitis, we propose adding these two substances to the leather and shoes patch test series.

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Stephan Traidl: Conceptualization; data curation; writing-original draft; writing-review & editing. **Thomas Werfel:** Data curation; investigation; supervision; writing-original draft; writing-review & editing. **Franziska Ruëff:** Data curation; investigation; project administration; resources; writing-original draft; writing-review & editing. **Dagmar Simon:** Data curation; investigation; project administration; writing-original draft; writing-review & editing. **Claudia Lang:** Data curation; investigation; project administration; writing-original draft; writing-review & editing. **Johannes Geier:** Conceptualization; data curation; funding acquisition; methodology; resources; supervision; visualization; writing-original draft; writing-review & editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Kuttruff JT, DeHart SG, O'Brien MJ. 7500 years of prehistoric footwear from Arnold Research Cave, Missouri. *Science*. 1998;281(5373):72-75.
2. Holden CR, Gawkrodger DJ. 10 years' experience of patch testing with a shoe series in 230 patients: which allergens are important? *Contact Dermatitis*. 2005;53(1):37-39.
3. Landeck L, Uter W, John SM. Patch test characteristics of patients referred for suspected contact allergy of the feet—retrospective 10-year cross-sectional study of the IVDK data. *Contact Dermatitis*. 2012;66(5):271-278.
4. Shackelford KE, Belsito DV. The etiology of allergic-appearing foot dermatitis: a 5-year retrospective study. *J Am Acad Dermatol*. 2002;47(5):715-721.
5. Angelini G, Vena GA, Meneghini CL. Shoe contact dermatitis. *Contact Dermatitis*. 1980;6(4):279-283.
6. Geier J, Lessmann H. Leather and shoes. In: John SM, Johansen JD, Rustemeyer T, Elsner P, Maibach HI, eds. *Kanerva's occupational dermatology*. 3rd ed. Switzerland: Springer; 2020:877-885.
7. Matthys E, Zahir A, Ehrlich A. Shoe allergic contact dermatitis. *Dermatitis*. 2014;25(4):163-171.
8. Munk R, Sasseville D, Siegel PD, Law BF, Moreau L. Thiurams in shoe contact dermatitis – a case series. *Contact Dermatitis*. 2013;68(3):185-187.
9. Freeman S. Shoe dermatitis. *Contact Dermatitis*. 1997;36(5):247-251.
10. Warshaw EM, Schram SE, Belsito DV, et al. Shoe allergens: retrospective analysis of cross-sectional data from the north american contact dermatitis group, 2001-2004. *Dermatitis*. 2007;18(4):191-202.
11. Lecamwasam K, Latheef F, Walker B, Wilkinson M. Contact allergy to reactive dyes in footwear. *Contact Dermatitis*. 2017;76(6):370-371.
12. Lazzarini R, Mendonca RF, Hafner MFS. Allergic contact dermatitis to shoes: contribution of a specific series to the diagnosis. *An Bras Dermatol*. 2018;93(5):696-700.
13. Slodownik D, Reiss A, Mashiach Y, Ingber A, Sprecher E, Moshe S. Textile and shoe allergic contact dermatitis in military personnel. *Dermatitis*. 2018;29(4):196-199.
14. Garg T, Agarwal S, Rana S, Chander R. Patch testing in patients with suspected footwear dermatitis: a retrospective study. *Indian Dermatol Online J*. 2017;8(5):323-327.
15. Febriana SA, Soebono H, Coenraads PJ, Schuttelaar ML. Contact allergy in indonesian patients with foot eczema attributed to shoes. *J Eur Acad Dermatol Venereol*. 2015;29(8):1582-1589.
16. Toledo F, Silvestre JF, Cuesta L, Borrego L, Perez M. Correlation between lesion site and concentration of dimethyl fumarate in different parts of shoes in patients with contact dermatitis caused by dimethyl fumarate in footwear. *Contact Dermatitis*. 2011;65(2):92-95.
17. Silvestre JF, Toledo F, Mercader P, Gimenez-Arnau AM, Spanish Research Group of Allergic Contact Dermatitis due to Dimethyl Fumarate in Spain. A summary of shoe allergic contact dermatitis caused by dimethyl fumarate in Spain. *Contact Dermatitis*. 2011;65(2):122-123.

18. Švecová D, Šimaljakova M, Doležalová A. Footwear contact dermatitis from dimethyl fumarate. *Int J Dermatol*. 2013;52(7):803-807.
19. D'Erme AM, Bassi A, Lotti T, Gola M. Dimethyl fumarate contact dermatitis of the foot: an increasingly widespread disease. *Int J Dermatol*. 2012;51(1):42-45.
20. Hasan T, Zimerson E, Bruze M. Persistent shoe dermatitis caused by dimethyl fumarate. *Acta Derm Venereol*. 2010;90(5):553-554.
21. Giménez-Arnau A, Silvestre JF, Mercader P, et al. Shoe contact dermatitis from dimethyl fumarate: clinical manifestations, patch test results, chemical analysis, and source of exposure. *Contact Dermatitis*. 2009;61(5):249-260.
22. Aerts O, Meert H, Romaen E, et al. Octylisothiazolinone, an additional cause of allergic contact dermatitis caused by leather: case series and potential implications for the study of cross-reactivity with methylisothiazolinone. *Contact Dermatitis*. 2016;75(5):276-284.
23. Rundle CW, Funk T, Brockman RM, Schwarzenberger K. Foot allergic contact dermatitis to mixed dialkyl thioureas. *Pediatr Dermatol*. 2019;36(4):517-519.
24. Schuttelaar ML, Meijer JM, Engfeldt M, et al. Allergic contact dermatitis caused by dimethylthiocarbamylbenzothiazole sulfide (DMTBS) in canvas shoes: in search of the culprit allergen. *Contact Dermatitis*. 2018;78(1):7-11.
25. Hulstaert E, Bergendorff O, Persson C, et al. Contact dermatitis caused by a new rubber compound detected in canvas shoes. *Contact Dermatitis*. 2018;78(1):12-17.
26. Herman A, Goossens A, Tennstedt D, et al. The preservative 2-(thiocyanomethylthio)benzothiazole: a potential allergen in leather products. *Contact Dermatitis*. 2019;81(4):262-265.
27. De Fre C, Bergendorff O, Raison-Peyron N, et al. Acetophenone azine: a new shoe allergen causing severe foot dermatitis. *Contact Dermatitis*. 2017;77(6):416-417.
28. Raison-Peyron N, Bergendorff O, Du-Thanh A, Bourrain JL, Bruze M. Two new cases of severe allergic contact dermatitis caused by acetophenone azine. *Contact Dermatitis*. 2017;76(6):380-381.
29. Ota A, Takehara Y, Okawa T, Ikegami R, Sasaki K, Numata M. Contact allergy to tinuvin 770, a hindered amine light stabilizer in sandals contributing to hyperkeratotic foot dermatitis. *Contact Dermatitis*. 2019;81(4):288-290.
30. Mowitz M, Ponten A. Foot dermatitis caused by didecyldimethylammonium chloride in a shoe refresher spray. *Contact Dermatitis*. 2015;73(6):374-376.
31. Zirwas MJ. Allergy to imidazole antifungals retained in shoes. *Dermatitis*. 2009;20(3):172-173.
32. Koch P, Nickolaus G, Geier J. Kontaktallergien bei Lederherstellern, Lederverarbeitern und in der Schuhindustrie. Fünf-Jahres-Analyse auf der Grundlage von Daten des Informationsverbundes Dermatologischer Kliniken. *Derm Beruf Umwelt*. 1996;44(56):257-262.
33. Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the information network of departments of dermatology (IVDK). *Allergy*. 2012;67(7):847-857.
34. Uter W, Schnuch A, Gefeller O, ESCD working group: European Surveillance System on Contact Allergies. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis*. 2004;51(2):47-56.
35. Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes „Informationsverbund Dermatologischer Kliniken" (IVDK). *Dermatol Beruf Umwelt*. 2005;53:107-114.
36. 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(4):195-221.
37. Mahler V, Nast A, Bauer A, et al. S3-leitlinie: Durchführung des Epikutantests mit Kontaktallergenen und Arzneimitteln – Kurzfassung Teil 1. *J Dtsch Dermatol Ges*. 2019;17(10):1076-1093.
38. Mahler V, Nast A, Bauer A, et al. S3-leitlinie: Durchführung des Epikutantests mit Kontaktallergenen und Arzneimitteln – Kurzfassung Teil 2. *J Dtsch Dermatol Ges*. 2019;17(11):1187-1207.
39. Schnuch A. PAFS: Population-adjusted frequency of sensitization. (I) influence of sex and age. *Contact Dermatitis*. 1995;34:377-382.
40. Nardelli A, Taveirne M, Drieghe J, Carbonez A, Degreef H, Goossens A. The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study. *Contact Dermatitis*. 2005;53(4):201-206.
41. Chowdhuri S, Ghosh S. Epidemio-allergological study in 155 cases of footwear dermatitis. *Indian J Dermatol Venereol Leprol*. 2007;73(5):319-322.
42. Rani Z, Hussain I, Haroon TS. Common allergens in shoe dermatitis: our experience in Lahore, Pakistan. *Int J Dermatol*. 2003;42(8):605-607.
43. Rasool F, Sehgal VN, Srivastava G, Aggarwal A, Hassan I. Footwear contact dermatitis: a prospective cross-sectional study of 108 outpatients from Delhi, India. *Skinmed*. 2018;16(2):90-97.
44. Trattner A, Farchi Y, David M. Shoe contact dermatitis in Israel. *Am J Contact Dermat*. 2003;14(1):12-14.
45. Lazzarini R, Duarte I, Marzagao C. Contact dermatitis of the feet: a study of 53 cases. *Dermatitis*. 2004;15(3):125-130.
46. Hedberg YS, Liden C, Odnevall WI. Chromium released from leather - I: exposure conditions that govern the release of chromium(III) and chromium(VI). *Contact Dermatitis*. 2015;72(4):206-215.
47. Hansen MB, Johansen JD, Menne T. Chromium allergy: significance of both cr(III) and cr(VI). *Contact Dermatitis*. 2003;49(4):206-212.
48. The European Commission. Commission regulation (EU) no 301/2014. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0301&from=DE. Accessed March 14, 2020. Updated 2014.
49. Strauss RM, Wilkinson SM. Shoe dermatitis due to colophonium used as leather tanning or finishing agent in Portuguese shoes. *Contact Dermatitis*. 2002;47(1):59.
50. Thyssen JP, Johansen JD, Jellesen MS, et al. Consumer leather exposure: an unrecognized cause of cobalt sensitization. *Contact Dermatitis*. 2013;69(5):276-279.
51. Hamann D, Hamann CR, Kishi P, Menné T, Johansen JD, Thyssen JP. Leather contains cobalt and poses a risk of allergic contact dermatitis: cobalt indicator solution and X-ray florescence spectrometry as screening tests. *Dermatitis*. 2016;27(4):202-207.
52. Hillen U, Frosch PJ, Franckson T, Pirker C, Goos M. Optimizing the patch test concentration of para-tertiary-butylcatechol: results of a prospective study with a dilution series. *Contact Dermatitis*. 2003;48(3):140-143.
53. Koch P, Nickolaus G. Allergic contact dermatitis and mercury exanthem due to mercury chloride in plastic boots. *Contact Dermatitis*. 1996;34(6):405-409.
54. Frick-Engfeldt M, Isaksson M, Zimerson E, Bruze M. How to optimize patch testing with diphenylmethane diisocyanate. *Contact Dermatitis*. 2007;57(3):138-151.
55. Uter W, Lessmann H, Geier J, et al. The spectrum of allergic (cross-) sensitivity in clinical patch testing with 'para amino' compounds. *Allergy*. 2002;57(4):319-322.
56. European Chemicals Agency. 1,2-benzisothiazol-3(2H)-one. https://echa.europa.eu/substance-information/-/substanceinfo/100.018.292. Accessed April 9, 2021. Updated 2021.
57. Lepoittevin J-P, Le Coz CJ. Dictionary of contact allergens: chemical structures, sources, and references; 63.210 ethylenediamine. In: Johansen JD, Mahler V, Lepoittevin JP, Frosch PJ, eds. *Contact dermatitis*. 6th ed. Switzerland, Cham: Springer Nature; 2021:1402.
58. Heratizadeh A, Geier J, Molin S, Werfel T. Contact sensitization in patients with suspected textile allergy. Data of the information network of departments of dermatology (IVDK) 2007-2014. *Contact Dermatitis*. 2017;77(3):143-150.

59. The European Commission. Commission decision 2009/251/EC of 17 March 2009: requiring member states to ensure that products containing the biocide dimethylfumarate are not placed or made available on the market. *Off J Eur Union*. 2009;2020:L74/32-34. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:074:0032:0034:EN:PDF.
60. The European Commission. Commission regulation no. 412/2012 of 15 may 2012 amending annex XVII to regulation (EC) no 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). *Off J Eur Union*. 2012;L 128:L128/1-3. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:128:0001:0003:en:PDF.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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