STUDY

Shoe Allergens: Retrospective Analysis of Cross-Sectional Data from the North American Contact Dermatitis Group, 2001–2004

Erin M. Warshaw, Sarah E. Schram, Donald V. Belsito, Vincent A. DeLeo, Joseph F. Fowler Jr, Howard I. Maibach, James G. Marks Jr, C.G. Toby Mathias, Melanie D. Pratt, Robert L. Rietschel, Denis Sasseville, Frances J. Storrs, James S. Taylor, and Kathryn A. Zug

Background: **Chemicals used in leather tanning, rubber processing, and/or adhesives are the most often-cited culprits in footwear dermatitis. Patch testing patients with suspected shoe dermatitis is essential for diagnosis and management.**

Objectives: **The four goals for this study were to (1) determine the frequency of allergens associated with a shoe source in North American Contact Dermatitis Group (NACDG) patients with footwear allergic contact dermatitis; (2) compare these results to allergen frequencies from other published studies; (3) quantify the number of shoe-related reactions that were not identified with the NACDG standard series; and (4) identify relevant allergens not included on the NACDG standard series, based on data from other published studies.**

Methods: **The NACDG patch-tested 10,061 patients between 2001 and 2004. Data were retrospectively analyzed by (1) allergen source coded as ''shoe,'' (2) site of dermatitis as ''feet,'' and (3) diagnosis of ''allergic contact dermatitis.''**

Results: **Among the 109 NACDG patients with allergic contact dermatitis (ACD) of the foot and a shoe source of allergens, p-tertiary butylphenol formaldehyde resin, an adhesive, was the most common allergen, accounting for 24.7% of positive patch-test results, followed by potassium dichromate (17.5%) and carba mix (11.7%). When the data were examined according to groups of allergens, rubber chemicals (40.4%) were the most frequent allergens, followed by adhesives (32.5%), and leather components (20.1%). When data from published studies were pooled, potassium dichromate (31.5%) was the most frequent allergen, followed by p-tertiary butylphenol formaldehyde resin (17.1%) and cobalt chloride (12.9%). NACDG patients were statistically more likely to have positive patch-test reactions to p-tertiary butylphenol formaldehyde resin and statistically less likely to have a positive patch-test reaction to potassium dichromate than patients represented in pooled data from past studies. Nineteen (17.4%) of the 109 NACDG patients with ACD of the foot and a shoe source of allergens were identified as having a shoe source of a relevant allergen not included in the NACDG standard series.**

Conclusions: **In NACDG patients, the most common individual shoe allergen was p-tertiary butylphenol formaldehyde resin. As a group, rubber chemicals were most common, a finding consistent with those of other studies.**

THE PREVALENCE OF SHOE DERMATITIS among patients with contact dermatitis has been estimated at 3.3 to 11.7%.[1,2] In children, the feet are one of the most common sites for contact dermatitis, and footwear is the second leading cause of contact dermatitis cited.[3] Disparities in the series of allergens tested, different methods of shoe manufacture, environmental factors, and varying social trends in footwear across the globe contribute to the difficulty of accurately characterizing the epidemiology of allergic contact dermatitis (ACD) from shoes.

The main components of shoe construction include uppers/straps, soles, insoles, and heel and toe counters (stiff elements that maintain shoe shape). Adhesives are used to attach these parts together.[4] (For a full review of shoe manufacturing, readers are referred to the excellent chapter ''Shoes'' in *Contact Dermatitis*.[4]) Chemicals associated with leather, rubber, and adhesives have long been recognized as potentially sensitizing agents.[5,6] The most common allergens associated with ACD of the feet vary among studies but are typically those involved in leather or rubber processing.[1,7–10] The warm moist environment and occlusion provided by shoes are thought to potentiate the development of ACD.[11]

ACD from shoes can be debilitating, and the causative agent may not be obvious. Patch testing patients with

From the Veterans Affairs Medical Center, Minneapolis, MN.

Reprints not available.

DOI 10.2310/6620.2007.06047

suspected shoe ACD is essential for identifying the responsible allergen and for guiding shoe selection. Freeman observed that after a mean of 2.9 years from patch testing, 87.5% of 55 patients with footwear dermatitis had improvement or resolution of their symptoms.[9]

Studies evaluating the frequency of allergens associated with dermatitis of the feet have been conducted in Europe,[7,8,12–17] the Middle East,[18,19] Asia,[2,20–23] Australia, [9] and regionally in North[1,10,24–26] and South America.[27] To our knowledge, the frequency of allergens associated specifically with a shoe source has not been investigated broadly in North America. The North American Contact Dermatitis Group (NACDG) has collected aggregated data from patients patch-tested across North America from 1971 to the present. Beginning in 2001, a specific three-digit allergen source was coded for each NACDG standard allergen as well as for other relevant allergens not included on the NACDG standard series. The four goals for this retrospective study were (1) to determine the frequency of allergens associated with a shoe source in NACDG patients with footwear ACD, (2) to compare these results to allergen frequencies from other published studies, (3) to quantify the number of shoe-related reactions that were not identified with the NACDG standard series, and (4) to identify relevant allergens not included on the NACDG standard series, based on data from other published studies.

Materials and Methods

Between January 1, 2001, and December 31, 2004, 10,061 patients were patch-tested with the NACDG standard series of 65 allergens.[28] The allergens (obtained from Chemotechnique Diagnostics, Vellinge, Sweden) included in the standard series from 2001 to 2002 were slightly different from those tested from 2003 to 2004 (Table 1).[28] Patch-testing methods, relevance of reactions, and final diagnoses were determined according to methods previously reported.[28] Relevance and source codes were linked to specific allergens whereas site codes (up to three codes) and final diagnosis (up to three codes) were linked to patients but not to specific allergens. Information on the source of relevant allergens not included on the NACDG standard series was recorded, but the name of the allergen itself was not recorded. At a central location, all data were manually entered into a computerized database using *Access* 2003 software (Microsoft Corporation, Redmond, WA) and checked for quality assurance. For this analysis, only those individuals with a shoe source of any allergen (standard or other relevant allergen not on the standard series) were included (Group A). Other sequential subgroups analyzed included those patients with a positive reaction to a NACDG standard allergen attributed to a shoe source (Group B), those with feet as a site of involvement (Group C), those with feet as the primary site of involvement (Group D), and those with a final primary diagnosis of ACD (Group E) (Fig 1). For simplicity, this report focuses on the most conservative subgroup (Group E). The number of patients for whom shoes were identified as a source of other relevant allergens not included in the NACDG standard series of patch tests was calculated for each group.

To search the existing literature on allergens associated with shoes and/or foot dermatitis, a PubMed search was conducted with the search terms ''shoe AND allergens,'' ''shoe AND patch test,'' ''shoe AND allergic contact dermatitis,'' ''foot dermatitis AND patch test,'' ''foot dermatitis AND allergens,'' and ''foot AND allergic contact dermatitis,'' with results limited to humans and English. Hand searching was also performed for publications predating PubMed. These studies are summarized in Tables 2 and 3, except for those by Vani and colleagues,[22] Chen and colleagues,[23] and Belsito.[26] Data from the investigation of hand and foot dermatitis by Vani and colleagues were excluded in summary tables because individual allergen frequencies were not reported for foot dermatitis separately from hand dermatitis.[22] Data from Chen and colleagues were excluded from summary tables because that investigation focused on rubber chemicals only.[23] Data from Belsito[26] were not included in summary tables because the patients included in that study were also reported in the study by Shackelford and Belsito,[1] represented in Tables 2 and 3 (Donald Belsito, June 15, 2006). In the study by Trattner and colleagues, allergen frequencies were reported separately for the shoe and standard series.[18] Some patients reacted to the same allergen in both series, but the exact numbers were not published. To avoid duplicating data points, Tables 2 and 3 include only Trattner and colleagues' results from the shoe series, which included many allergens from the standard series. When only percentages were reported in published studies, we calculated exact numbers; these are identified as ''calculated.'' Pooled prevalence rates of published studies were calculated by adding the number of positive reactions to each allergen (numerator) and dividing this number by the total number of positive reactions related to shoes. Analyses comparing pooled

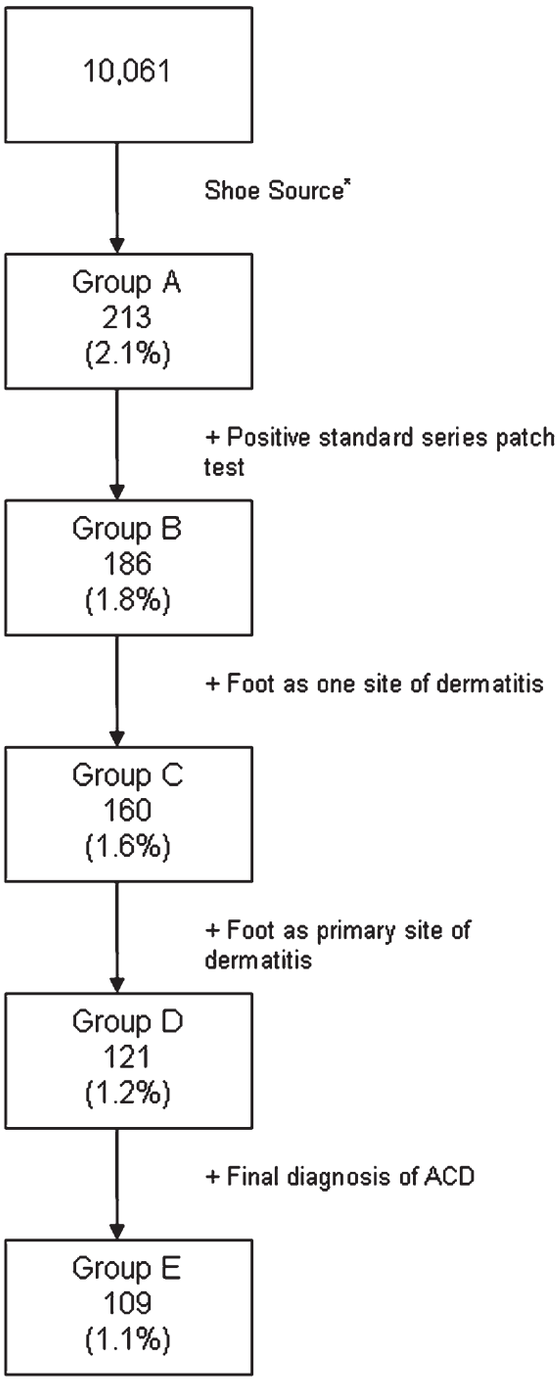

Figure 1. North American Contact Dermatitis Group patient selection criteria. (ACD = allergic contact dermatitis)

rates and NACDG data were performed with *SAS* software (Statistical Analysis System, SAS Institute Inc. Cary, NC). Pearson's chi square test was used to compare our results with published studies. Fisher's exact test (two tailed) was used when appropriate. A significance level of 0.05 was used for all analysis. Because this was an exploratory analysis, no adjustments for multiple comparisons were performed.

Table 1. NACDG Standard Series, 2001–2004

Allergens	*Allergens*
Benzocaine 5% pet	Benzophenone-3 3% pet
Mercaptobenzothiazole 1% pet	Chloroxylenol (PCMX) 1% pet
Colophony 20% pet	DMDM hydantoin 1% aq
p-Phenylenediamine 1% pet	Diazolidinyl urea 1% aq
Imidazolidinylurea 2% aq	Ethyleneurea melamine-formaldehyde 5% pet
Jasmine absolute 2% pet	Methyldibromoglutaronitrile/phenoxyethanol 2% pet
Lanolin alcohol 30% pet	Iodopropynyl butyl carbamate 0.1% pet
Carba mix 3% pet	DL-α-Tocopherol 100%
Neomycin sulfate 20% pet	Sodium gold thiosulfate 0.5% pet
Thiuram mix 1% pet	Ethyl acrylate 0.1% pet
Formaldehyde 1% aq	Glyceryl thioglycolate 1% pet
Ethylenediamine dihydrochloride 1% pet	Tosylamide formaldehyde resin 10% pet
Epoxy resin 1% pet	Methylmethacrylate 2% pet
Quaternium-15 2% pet	Cobalt chloride 1% pet
p-tert-Butylphenol formaldehyde resin 1% pet	Tixocortol-21-pivalate 1% pet
Mercapto mix 1% pet	Budesonide 0.1% pet
Black rubber mix 0.6% pet	Hydrocortisone-17-butyrate 1% pet
Potassium dichromate 0.25% pet	Disperse Blue 106 1% pet
Myroxilon pereirae 25% pet	Tetracaine 1% pet
Nickel sulfate 2.5% pet	Lidocaine 15% pet
Diazolidinylurea 1% pet	Dibucaine 2.5% pet
DMDM hydantoin 1% pet	Prilocaine 2.5% pet*
Imidazolidinylurea 2% pet	Clobetasol-17-propionate 1% pet†
Bacitracin 20% pet	Cocamidopropyl betaine 1% aq
Mixed dialkyl thioureas 1% pet	Phenoxyethanol 1% pet*
Methylchloroisothiazolinone/methylisothiazolinone 100 ppm aq	Bisphenol F 1% pet†
Paraben mix 12% pet	Benzalkonium chloride 0.1% aq*
Methyldibromoglutaronitrile 0.4% pet*	Triamcinolone acetonide 1% pet†
Cinnamic aldehyde 1% pet†	Dimethylol dihydroxyethyleneurea 4.5% aq
Fragrance mix 8% pet	Cocamide DEA 0.5% pet
Amidoamine 0.1% aq	Compositae mix 6% pet
2-bromo-2-nitropropane-1,3-diol 0.5% pet	Glutaral 1% pet
Sesquiterpene lactone mix 0.1% pet	DL-α-Tocopherol acetate 100%*
Budesonide 0.01% pet†	Tea tree oil, oxidized, 5% pet†
Thimerosal 0.1% pet*	Ylang ylang oil 2% pet
Propylene glycol 30% aq	

aq = aqueous; DEA = diethanolamine; DMDM = dimethylol dimethyl; PCMX = para-chloro-meta-xylenol; pet = petrolatum; ppm = parts per million.
*Only tested from 2001 to 2002.
†Only tested from 2003 to 2004.

Results

Demographics

Of the 10,061 patients who were patch-tested by the NACDG between 2001 and 2004, 213 patients had a shoe source identified as either (1) a source of a positive standard series patch-test allergen or (2) a source of a relevant allergen not included in the NACDG standard series (see Fig 1, Group A). Of these 213 patients, 186 had positive patch-test reactions to a standard series allergen attributed to a shoe source (Group B); 160 patients had feet listed as a site, and 121 of those had feet as the primary site of dermatitis involvement (Groups C and D, respectively). Last, 109 patients had a primary diagnosis of ACD with the feet as the primary site of involvement and a positive patch-test result attributed to a shoe source

Table 2. Putative Allergen Frequencies from Published Studies for Shoe Allergens on the NACDG Standard Series

	Holden (2005)[7]	*Nardelli (2005)*[8]	*Onder (2004)*[20]	*Lazzarini (2004)*[27]	*Rani (2003)*[19]	*Trattner (2003)*[18]	*Shackelford (2002)*[1]	*Cockayne (1998)*[12]	*Freeman (1997)*[9]	*Saha (1993)*[3]	*Bajaj (1988)*[21]	*Romaguera (1987)*[16]
Country	UK	Belgium	Turkey	Brazil	Pakistan	Israel	USA	UK	Australia	India	India	Spain
Age range (yr)	NR	3–83	17–45	6–84	NR	5–86	0–80	NR	2–78	NR	NR	NR
Total reactions	91	978	5	90	148	94	86	68	96	68	86	178
Reactions to shoe allergens on NACDG series	44	821	4	57	116	67	40	36	88	59	48	69
Allergen*	No. of Positive Reactions											
PTBFR 1%	1	63	0	0	32	8	3	NR	11	1	0	14
Potassium dichromate 0.25%	9	253	2	5	20	25	5	4	13	13	37	52
Carba mix 3%	5	9	NT	3	5**	6**	3	1	NT	6**	3**	0
Thiuram mix 1%	6	40	1	7	1	0	5	9	15	4	1#	0
Colophony 20%	0	89	0	5	5	5	1	2	5	8	2	0
MBT 1%	0	47	0	NT	2	3	5++	7	20	7++	3	0
Mercapto mix 1%	8	58	0	10	0	0	5++	6	22	7++	2##	0
Mixed dialkyl thioureas 1%	3	8	NT	NT	0	2	2	NR	NT	2	NT	NT
PPD 1%	5	106	0	7	5	0	0	3	2	2	NT	0
Black rubber mix 0.6%	0+++	6	NT	NT	1+++	0	2+++	NR	NT	1+++	NT	NT
Nickel sulfate 2.5%	1	NR	1	10	27	11	4	NR	NR	1	NT	3
Cobalt chloride 1%	1	132	0	5	10	0	0	NR	NT	NT	NT	NT
Glutaraldehyde 1%	0	NR	NT	NT	0	0	2	NR	NT	3	NT	0
Formaldehyde 1%	1	NR	0	1	7	5	2	NR	NR	3	NT	0
Epoxy resin 1%	0	NR	NT	3	1	2	0	1	NR	1	NT	NT
Disperse Blue 106 1%	1***	10	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Ethylenediamine dihydrochloride 1%@@	3	NT	NT	1	NT	NT	1	3	NT	NT	NT	NT

(Group E). Patients who were eliminated on the basis of site often had hand or scattered generalized dermatitis, which in some cases was related to allergens from a nonshoe source. Demographic data for each of the subgroups are shown in Table 4. Because results for the following analyses did not differ greatly for Groups B to E, we present data from only the most restrictive subgroup, Group E ($n = 109$).

Frequencies of Allergens in the NACDG Standard Series

Allergen frequencies for all subsets of patients with positive NACDG standard series patch-test results were evaluated. Among the 109 patients in Group E, there were 154 positive patch-test results (Table 5); 150 (97.4%) were considered to be of definite (9.7%), probable (33.1%), or possible (54.5%) relevance. Four (2.6%) positive patch-test

Table 2. (continued)

	Correia (1986)[15]	*Lynde (1982)*[10]	*Angelini (1980)*[13]	*Dahl (1975)*[25]	*Varelzides (1974)*[17]	*Epstein (1969)*[24]	*Calnan (1959)*[14]	*Pooled Data No. of Reactions/n (%)*	*NACDG (Current Data)*	p-*Value from Chi-Square Test*
Country	Portugal	Canada	Italy	USA	Greece	USA	UK	—	USA and Canada	—
Age range	NR	NR	NR	NR	17–64	4–72	NR	—	6–74	—
Total reactions	1,010	45	166	65	60	58	144	3,536	154	—
Reactions to shoe allergens on NACDG series	649	33	128	40	35	13	34	2,381	154	—
Allergen*	No. of Positive Reactions									
PTBFR 1%	233	NT	9	NR^^	NT	NT	NT	375/2,190 (17.1)	38 (24.7)	.0174
Potassium dichromate 0.25%	224	3	49	9	16	2	9	750/2,381 (31.5)	27 (17.5)	.0003
Carba mix 3%	NT	3**	NT	2+	NT	1**	NT	47/1,443 (3.3)	18 (11.7)	< .0001
Thiuram mix 1%	19	5#	4#	9#	5#	1#	6^	138/2,381 (5.8)	16 (10.4)	.0207
Colophony 20%	NR	1	NT	NT	NT	NT	NT	123/1,482 (8.3)	11 (7.1)	.6183
MBT 1%	NR	9	8	13	6	4	19	153/1,675 (9.1)	9 (5.8)	.1691
Mercapto mix 1%	109	3##	NT	NT	NT	NT	NT	230/2,131 (10.8)	8 (5.2)	.0281
Mixed dialkyl thioureas 1%	NT	NT	NT	NT	NT	NT	NT	17/1,147 (1.5)	7 (4.6)	.0080
PPD 1%	36###	5	41	5	1	3	NR	221/2,299 (9.6)	5 (3.3)	0.0057^^^
Black rubber mix 0.6%	NT	NT	NT	NT	5	NT	NT	15/1,182 (1.3)	3 (2.0)	.4531^^^
Nickel sulfate 2.5%	28	NT	12	NT	NT	2	NT	100/1246 (8.0)	2 (1.3)	< .0001^^^
Cobalt chloride 1%	NR	NT	NT	NT	NT	NT	NT	148/1,149 (12.9)	2 (1.3)	< .0001^^^
Glutaraldehyde 1%	NT	1	NT	0	NT	NT	NT	6/468 (1.3)	2 (1.3)	1.0000^^^
Formaldehyde 1%	NR	3	0	2	0	NT	NT	24/692 (3.5)	2 (1.3)	.2015^^^
Epoxy resin 1%	NR	NT	NT	NT	2	NT	NT	10/454 (2.2)	1 (0.7)	.3058^^^
Disperse Blue 106 1%	NT	NT	NT	NT	NT	NT	NT	11/865 (1.3)	1 (0.7)	1.0000^^^
Ethylenediamine dihydrochloride 1%@@	NT	NT	5	NT	NT	NT	NT	13/305 (4.3)	0	.0060^^^

MBT = mercaptobenzothiazole; NACDG = North American Contact Dermatitis Group; NR = not reported; NT = not tested; PPD = para-phenylenediamine; PTBFR = p-tertiary-butylphenol formaldehyde resin.

@Calculated.

@@Many authors do not consider this a relevant shoe allergen; however, it has been reported as a rubber stabilizer[12]

*In petrolatum, except for formaldehyde, which was in aqueous solution.

**Reported only N,N-diphenylguanidine, one component of the carba mix.

***Reported a Disperse Blue 106/124 mix.

+Reported N,N-diphenylguanidine and zinc diethyl-dithiocarbamate, two components of the carba mix.

++MBT and/or mercapto mix.

+++Reported only N-isopropyl-N-phenyl-4-phenylenediamine, one component of rubber mix.

#Reported only tetramethylthiuramdisulfide, one component of thiuram mix.

##Reported only N-cyclohexyl-2-benzothiazolesulfenamide, one component of mercapto mix.

###Reported PPD mix.

^Reported only tetramethylthiuram monosulfide, one component of thiuram mix.

^^PTBFR was tested but not reported separately.

^^^*p*-Value is from Fisher exact test (two tailed).

Table 3. Relevant Shoe Allergens Not in the NACDG Standard Series, from Published Studies

Allergen	*Shoe Source*	*No. of Positive Reactions**
Dithiodimorpholine[1,12]	Rubber	8
Hydroquinone monobenzylether [2,10,18]	Rubber, adhesive	8
Diphenylthiourea[18]	Rubber	4
2,2,4-trimethyl-1,2-dihydroquinoline[1,12]	Rubber	2
4-aminoazobenzene[2,7,8,10,15,18,19]	Dye	82
Disperse Orange 3[2,7,8,12,15]	Dye	56
Disperse Yellow 3[7,15]	Dye	30
Disperse Red 1[7,15]	Dye	16
Bismark Brown[10,15]	Dye	4
Disperse Blue 35[8]	Dye	3
Dodecylmercaptan[2,8,10,19]	Adhesive	84
p-tertiary-Butyl-catechol[8]	Cross reacts with PTBFR	20
Desmodur R (Bayer MaterialScience, Leverkusen, Germany)[16]	Adhesive	15
Benzoylperoxide[8]	Adhesive	11
Dimethylaminoethylether[1]	Adhesive	3
Desmodur RF R (Bayer MaterialScience, Leverkusen, Germany)[16]	Adhesive	3
para-tertiary-Butylphenol [10]	Adhesive (intermediate of PTBFR)	2
Desmocoll 400 R (Bayer MaterialScience, Leverkusen, Germany)[16]	Polyurethane	13
Isophorone diisocyanate[1]	Polyurethane	3
Dioctyl gallate[7]	On BCDS shoe series	2
2-thiocyanomethyl benzothiazole[8]	Leather	35
2n-octyl-4-isthiazolin-3-one[7,12,18,19]	Leather	9
Patients own shoes[2,9,17,20,24]	—	71
Leather[14,21]	Leather	94
Rubber[14,21,16]	Rubber	73
Plastic[21]	Plastic	8
Dye[14,25]	Dye	6

BCDS = British Contact Dermatitis Society; PTBFR = p-tertiary-butylphenol formaldehyde resin.
*Accounting for 1 reaction each: 2-methylthiazolidine-2-thion,[12] N-(cyclohexylthio)phthalimide,[1] butyl hydroxytoluene,[7] butyl hydroxyanisole,[7] toluenesulfonamide formaldehyde resin,[7] 2-monomethylol phenol,[7] dibutyl phthalate,[8] toluene diisocyanate.[1]

results were considered to be occupationally relevant. In this group of patients, p-tertiary butylphenol formaldehyde resin was the most frequent allergen, followed by potassium dichromate.

Literature Review

Data from past studies on allergens associated with suspected foot and/or footwear dermatitis are summarized in Tables 2 and 3. Table 2 includes (1) allergens that were also on the NACDG standard series, (2) pooled data for these allergens, and (3) the NACDG results for comparison. Table 3 lists relevant allergens from other studies and that were not on the NACDG standard series. Topical medications, ointments, and creams that have been reported to cause foot dermatitis were excluded from these tables.

Comparison of Allergen Frequencies

p-tertiary Butylphenol Formaldehyde Resin

p-tertiary Butylphenol formaldehyde resin (PTBFR) has been used as an additive in rubber glues since the 1950s.[29] Currently it is found as a component of neoprene adhesives used to attach shoe linings and insoles.[30] In this study, PTBFR accounted for 24.7% of positive patch-test results related to shoes. In the study of 119 patients with suspected shoe dermatitis in Pakistan by Rani and

Table 4. Demographics of Patient Groups

Data Subset	n	*Irritant Reactions*	*Unknown or Negative Reactions*	*Final Diagnosis of ACD*	*Sex (M/F)*	*Age < 18 yr*	*Age Range (yr)*	*Average Age (yr, M/F)*	*Ethnicity (C/B/A/H/O)*	*Atopic Patients**
Any shoe source (Group A)	213	N/A	N/A	201 (94.4%)	116/97	13	6-82	39.0/42.8	190/12/5/4/2	87 (40.8%)
Any site and any diagnosis (Group B)	186	0	6	177 (95.2%)	97/89	10	6-82	39.5/42.2	165/11/4/4/2	75 (40.3%)
Feet (Group C)	160	0	4	154 (96.3%)	84/76	8	6-79	39.0/41.2	142/11/2/4/1	66 (41.3%)
Feet as primary site (Group D)	121	0	2	119 (98.4%)	60/61	8	6-74	37.9/40.7	108/8/1/3/1	48 (39.7%)
Feet as primary site and ACD as primary diagnosis (Group E)	109	0	1	109 (100%)	55/54	6	6-74	38.3/41.2	97/7/1/3/1	40 (36.7)

A = Asian; ACD = allergic contact dermatitis; B = black; C = Caucasian; F = female; H = Hispanic; M = male; n = sample size; N/A = not applicable; O = other.
*Atopic patients defined as one or more of the following: hay fever, asthma, atopic eczema.

colleagues, PTBFR was also the most frequent allergen, accounting for 21.6% of positive reactions.[19] This was also the case in the Portuguese study by Correia and Brandão, who found that 23.1% of 539 patients with suspected footwear and/or stocking dermatitis were patch test positive to PTBFR.[15] In contrast, the studies from Kansas,[1] Canada,[10] Brazil,[27] and Britain[7] of patients with suspected footwear dermatitis found PTBFR to represent

Table 5. Frequency of Positive Patch-Test Reactions to NACDG Standard Series Allergens Attributed to a Shoe Source, with Feet As Primary Site of Involvement, and Primary Diagnosis of ACD (Group E).

*Allergen**	*Shoe Material*	*Positive Patch-Tests Reactions*[†‡] *(n = 151)*	*Definite, Probable, or Possible*	*Past Relevance*	*Unknown Relevance*	*Occupation Related*
PTBFR 1%	Adhesive	38 (24.68%)	38	0	0	1
Potassium dichromate 0.25%	Leather	27 (17.53%)	26	0	1	0
Carba mix 3%	Rubber	18 (11.69%)	18	0	0	1
Thiuram mix 1%	Rubber	16 (10.39%)	16	0	0	1
Colophony 20%	Adhesive	11 (7.14%)	11	0	0	0
MBT 1%	Rubber	9 (5.84%)	9	0	0	0
Mercapto mix 1%	Rubber	8 (5.19%)	8	0	0	0
Mixed dialkyl thioureas 1%	Rubber	7 (4.55%)	7	0	0	1
PPD 1%	Dye	5 (3.25%)	5	0	0	0
Black rubber mix 0.6%	Rubber	3 (1.95%)	3	0	0	0
Nickel sulfate 2.5%	Metal	2 (1.30%)	1	0	1	0
Cobalt chloride 1%	Metal	2 (1.30%)	1	0	1	0
Glutaraldehyde 1%	Leather	2 (1.30%)	1	0	1	0
Formaldehyde 1%	Leather	2 (1.30%)	2	0	0	0
Epoxy resin 1%	Adhesive	1 (0.65%)	1	0	0	0
Disperse Blue 106 1%	Dye	1 (0.65)	1	0	0	0

MBT = mercaptobenzothiazole; PPD = p-phenylenediamine; PTBFR = p-tertiary-butylphenol formaldehyde resin.
*In petrolatum, except for formaldehyde, which was tested in aqueous solution.
[†]Percentages shown represent percent of total number of positive patch-test results for this subset.
[‡]Tea tree oil and neomycin each accounted for one positive reaction and were coded as having a shoe source although they may have been shoe contaminants.

only up to 4.4% of relevant shoe-related allergens. It is unclear why studies occurring largely over similar time periods and geographic regions have found such varying rates of allergy to PTBFR. However, the inclusion criteria for these studies varied, and this may have affected allergen frequencies. Some studies selected patients on the basis of suspected footwear dermatitis. [10,15,19] whereas others included all patients with dermatitis of the feet.[17,27] When data from published studies were pooled, PTBFR represented 17.1% of positive reactions. NACDG patients were 1.44 times more likely than patients in past studies to have a positive reaction to PTBFR (95% confidence interval [CI], 1.08–1.93; $p = .0174$).

Potassium Dichromate

Chromium salts are used to tan leather. Although trivalent salts are typically used for tanning, hexavalent potassium dichromate is considered more reliable for patch testing.[11] An increased risk of foot dermatitis has been reported in patients with positive reactions to both trivalent and hexavalent salts as compared to patients with negative reactions to trivalent and positive reactions to hexavalent salts.[31] In this study of NACDG patients, only hexavalent potassium dichromate was tested and was found to be the second most frequent shoe-related allergen, accounting for 17.5% of positive reactions. European,[7,8,13,17] Mediterranean,[18] and Indian[2,21] studies of patients with foot dermatitis found potassium dichromate to be the most frequent allergen, accounting for 10.0 to 43.0% of relevant positive reactions. When the data from published studies were pooled, potassium dichromate was the most frequent individual allergen, accounting for 31.5% of reactions. Patients in past studies were 1.80 times more likely than NACDG patients to have a positive reaction to potassium dichromate (95% CI, 1.27–2.54; $p = .0003$).

Rubber Additives

Although an individual rubber component was not the most frequent allergen in this NACDG study, rubber chemicals were the most frequent allergens when considered as a group including carba mix, thiuram mix, mercaptobenzothiazole (MBT), mercapto mix, mixed dialkyl thioureas, and black rubber mix. This finding is consistent with those of the other North American studies of foot dermatitis,[1,10] as well as those of investigations in Brazil,[27] Australia,[9] and Britain,[12] which have found rubber chemicals to be the most common shoe allergen category overall. This is consistent with pooled data from published studies. This trend was noted by Cronin, who documented a shift from leather to rubber as the most common shoe antigen group in Britain in the 1950s and 1960s.[6] Although pooled data demonstrated rubber allergens to be most common as a group, individual allergen frequencies differed. Reactions to carba mix, thiuram mix, and mixed dialkyl thioureas were significantly higher in our NACDG population ($p = .0001$, .0207, and .0080, respectively) whereas reactions to mercapto mix were significantly higher in pooled data ($p = .0281$). Reactions to MBT and black rubber mix were also more frequent in pooled data; however, this difference was not significant ($p = .1691$, and .4531, respectively).

Relevant Allergens Not on the NACDG Standard Series

The numbers of patients with shoes listed as a relevant source of allergens not included on the NACDG standard series for the data subsets are listed in Table 6. For patients for whom shoes were considered a relevant source of allergens (Group A), the NACDG standard series did not identify the specific shoe allergen in 12.7% of cases and was unable to identify all relevant shoe allergens in 24.9% of cases.

Allergens not on the NACDG standard series that were found to be relevant in other studies are summarized in Table 3. In one American investigation of foot dermatitis, dithiodimorpholine (DTDM), a rubber accelerator, was responsible for the largest proportion of relevant positive reactions,[1] and this point was highlighted by Belsito.[26] For this reason, DTDM was included in the 2005–2006 NACDG standard series. The NACDG standard series also contains few dyes; 4-aminoazobenzene, Disperse Orange 3, Disperse Yellow 3, and Disperse Red 1 were all responsible for a number of allergic reactions in other studies.[2,7,8,10,15,18,19] Dodecylmercaptan, an adhesive, accounted for 1.4 to 4.8% of relevant positive reactions in four studies of suspected footwear dermatitis.[2,8,10,19]

Diphenylthiourea, an accelerator used in the manufacture of neoprene, caused four positive reactions in the study by Trattner and colleagues.[18] This allergen is not included in the dialkyl thiourea mix. On the basis of differences in structure, it is felt that there is little cross-reactivity between thioureas,[32] and in Trattner and colleagues' study, at least two patients reacted to diphenylthiourea but not to the dialkyl thiourea mix. Hydroquinone monobenzylether, benzoyl peroxide, 2-thiocyanomethyl benzothiazole, 2n-octyl-4-isothiazolin-3-

Table 6. Patients with Shoes Identified as Relevant Source for an Allergen Not on the NACDG Standard Series

Group	n	*Patients with Shoes As Source of Non-NACDG Standard Allergen*	*Patients with Shoes As Source of Non-NACDG Standard Allergen and No Positive Standard Allergen Attributed to Shoes*
A (Shoe source)	213	53	27
B (Any site and any diagnosis)*	186	26	0
C (Feet)*	160	25	0
D (Feet primary site)*	121	19	0
E (Feet primary site and ACD primary diagnosis)*	109	19	0

ACD = allergic contact dermatitis; *n* = sample size; NACDG = North American Contact Dermatitis Group.
*With positive test reactions to NACDG standard series allergen attributed to a shoe source.

one, Desmocoll 400 (Bayer MaterialScience, Leverkusen, Germany), and Desmodur R (Bayer MaterialScience) each accounted for eight or more positive relevant patch-test results in pooled data from other studies.[1,2,7,8,10,12,18,19] There are also numerous published reports of reactions to samples of patients' own shoes.[2,9,14,16,17,20,21,24,25]

Discussion

In this retrospective analysis of NACDG data, shoe dermatitis affected men (50.5%) and women (49.5%) approximately equally and most commonly was not occupation related. PTBFR was the most frequent individual allergen, followed (in order) by potassium dichromate, carba mix, thiuram mix, colophony, MBT, mercapto mix, mixed dialkyl thioureas, p-phenylenediamine (PPD), and black rubber mix. Nickel sulfate, cobalt chloride, glutaraldehyde, formaldehyde, epoxy resin, and Disperse Blue 106 each accounted for two or fewer positive reactions. When the data were examined according to groups of allergens, rubber additives were most frequent (40.4%), followed by adhesives (32.5%) and leather components (20.1%). To our knowledge, this is the first study using aggregated patch-test data to explore the frequency of allergens identified as having a shoe source in North America.

NACDG patients in this study were statistically more likely to have a positive patch-test reaction to PTBFR, carba mix, thiuram mix, PPD, or black rubber mix and statistically less likely to have a positive patch-test reaction to potassium dichromate, mercapto mix, nickel sulfate, cobalt chloride, or ethylenediamine as compared to pooled data from past studies. There are several possible explanations for these differences. Shoe manufacturing processes and materials change over time and vary around the world. Different environments require appropriate footwear choices, and fashion trends can change quickly. Just as important as these factors is that the series of allergens tested among studies are not consistent and that many standard series may lack important relevant shoe allergens. Therefore, it is possible that these differences are due to variations in study design rather than definitive trends.

In 12.7% of patients, the NACDG standard series failed to identify any relevant allergens. This is consistent with the study by Freeman, who found that 14.5% of 55 patients reacted to samples of their own shoes but did not react to any tested shoe allergens in her series.[9] This implies that there may be important shoe allergens that were not included in the 2001–2004 NACDG series. Potentially relevant allergens identified in other studies include DTDM, a number of dyes, dodecylmercaptan, diphenylthiourea, and samples from patients' own shoes. DTDM, which was added to the 2005–2006 series, appears to be of uncertain relevance. Although the data have not yet been compiled, there have been anecdotal reports of numerous irritant reactions to DTDM and conflicting opinions regarding the usefulness of DTDM as a patch-test allergen (NACDG members, personal communications, June 2006). Although the NACDG standard series does not include many individual dyes, it does include PPD. Considerable cross-reactivity between PPD and 4-aminoazobenzene, Disperse Orange 3, and Disperse Yellow 3 has been demonstrated.[33,34] Therefore, PPD may identify allergy to many dyes not on the standard NACDG tray. Evidence for cross-reactivity between PPD and other red, blue, and brown dyes is less compelling.[34] Also, allergy to dodecylmercaptan and possibly to diphenylthiourea may be missed by the current NACDG standard series.

When patch-testing for allergic reactions to shoes, it is common to patch-test with samples of patients' own footwear. However, it is important to recognize that shoe

samples must be very thin to avoid pressure effects and false-positive results.[4] Samples should also be first soaked in water for 15 minutes before application[35] and left in place for 4 to 5 days to avoid false-negative results.[4,11] Finally, one must be assured that tinea pedis has been ruled out since it has been reported that testing with shoe samples can result in a false-positive patch-test reaction due to the transmission of a fungal infection.[36]

Podmore compiled an extensive list of potential shoe allergens[30] but concluded that the common allergens causing shoe ACD were already included in the standard series and did not recommend the inclusion of any other allergens in the standard series for the detection of shoe allergens (Patricia Podmore, personal communication [abstract presentation, 44th American Academy of Dermatology Annual Meeting], December 1985). Given the current understanding of the chemicals used to manufacture shoes, it would be impossible to include every potential shoe allergen on a standard series. When using a limited standard series such as the T.R.U.E. Test allergen system (Allerderm, Phoenix, AZ) series, the use of an additional shoe series may be helpful in patients with suspected footwear dermatitis. In circumstances in which the NACDG standard series fails to identify a relevant shoe allergen and footwear dermatitis is strongly suspected, testing with additional dyes, dodecyl mercaptan, other allergens from a shoe series, and/or samples of the patient's own shoes may aid in diagnosis.

This study has several limitations. First, the NACDG does not code the specific allergen name for other relevant allergens not in the standard series. Therefore we were only able to determine that there was a shoe source in these cases. Second, we were unable to determine whether these other relevant allergens came from other patch-test series (such as a supplemental shoe series) or from testing with pieces of the patient's own shoes. Third, the duration of follow-up for determination of relevance to a shoe source is not recorded, and the relevance is not always confirmed over time. Fourth, our data may not be directly comparable to those of other studies. Most published studies included patients on the basis of suspected foot and/or footwear dermatitis whereas our patient data were based on shoes coded as the allergen source. Therefore, other studies were probably more likely to find topical medications and other nonshoe allergens as relevant, decreasing the percentage of positive results attributed to structural shoe source allergens such as rubber, leather, or adhesive chemicals. We attempted to adjust for this by limiting statistical comparisons to only those allergens contained on the NACDG standard series.

Future studies of footwear dermatitis would be greatly enhanced by more complete chemical information from manufacturers. Because of globalization of markets, information on shoe allergens is almost always unavailable. Without this information, identification of new and emerging allergens is extremely complicated and management for patients is difficult. While some information on shoes is available (eg, from <www.contactderm.org/members/FootDermatitis.pdf>, available to members of the American Contact Dermatitis Society),[37] many sensitized patients must resort to plastic shoes (that lack any leather or rubber allergens) or expensive custom-made shoes. ACD from footwear is a constantly evolving problem and a challenge to both physicians and patients.

References

1. Shackelford KE, Belsito DV. The etiology of allergic–appearing foot dermatitis: a 5-year retrospective study. J Am Acad Dermatol 2002; 47:715–21.
2. Saha M, Srinivas CR, Shenoy SD, et al. Footwear dermatitis. Contact Dermatitis 1993;28:260–4.
3. Romaguera C, Vilaplana J. Contact dermatitis in children: 6 years experience (1992-1997). Contact Dermatitis 1998;39:277–80.
4. Taylor JS, Erkek E, Podmore P. Shoes. In: Frosch PJ, Menné T, Lepoittevin JP, editors. Contact dermatitis. 4th ed. Berlin: Springer; 2006. p. 703–16.
5. Gaul LE, Underwood GB. Primary irritants and sensitizers used in fabrication of footwear. Arch Dermatol 1949;17:705–13.
6. Cronin E. Shoe dermatitis. Br J Dermatol 1966;78:617–25.
7. Holden CR, Gawkrodger DJ. 10 years' experience of patch testing with a shoe series in 230 patients: which allergens are important? Contact Dermatitis 2005;53:37–9.
8. Nardelli A, Taveirne M, Drieghe J, et al. The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study. Contact Dermatitis 2005;53: 201–6.
9. Freeman S. Shoe dermatitis. Contact Dermatitis 1997;36:247–51.
10. Lynde CW, Warshawski L, Mitchell JC. Patch test results with a shoewear screening tray in 119 patients, 1977-80. Contact Dermatitis 1982;8:423–5.
11. Rietschel RL, Fowler JF Jr. Textile and shoe dermatitis. In: Rietschel RL, Fowler JF Jr, editors. Fisher's contact dermatitis, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 305–19.
12. Cockayne SE, Shah M, Messenger AG, Gawkrodger DJ. Foot dermatitis in children: causative allergens and follow-up. Contact Dermatitis 1998;38:203–6.
13. Angelini G, Vena GA, Meneghini CL. Shoe contact dermatitis. Contact Dermatitis 1980;6:279–83.
14. Calnan CD, Sarkany I. Studies in contact dermatitis IX. Shoe dermatitis. Trans St Johns Hosp Derm Soc 1959;43:8–26.
15. Correia S, Brandao FM. Contact dermatitis of the feet. Derm Beruf Umwelt 1986;34:102–6.
16. Romaguera C. Shoe contact dermatitis. Int J Dermatol 1987;26: 532–5.

17. Varelzides A, Katsambas A, Georgala S, Capetanakis J. Shoe dermatitis in Greece. Dermatologica 1974;149:236–9.
18. Trattner A, Farchi Y, David M. Shoe contact dermatitis in Israel. Am J Contact Dermat 2003;14:12–4.
19. Rani Z, Hussain I, Haroon TS. Common allergens in shoe dermatitis: our experience in Lahore, Pakistan. Int J Dermatol 2003;42:605–7.
20. Onder M, Atahan AC, Bassoy B. Foot dermatitis from the shoes. Int J Dermatol 2004;43:565–7.
21. Bajaj AK, Gupta SC, Chatterjee AK, Singh KG. Shoe dermatitis in India. Contact Dermatitis 1988;19:372–5.
22. Vani G, Rao AG, Gowri V, Lakshmi TS. Allergic contact dermatitis of the hands and/or feet—common sensitizers. Contact Dermatitis 2005;52:50–2.
23. Chen HH, Sun CC, Tseng MP. Type IV hypersensitivity from rubber chemicals: a 15-year experience in Taiwan. Dermatology 2004;208:319–25.
24. Epstein E. Shoe contact dermatitis. JAMA 1969;209:1487–92.
25. Dahl MV. Allergic contact dermatitis from footwear. Shoe dermatitis in 42 patients. Minn Med 1975;58:871–4.
26. Belsito DV. Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. Am J Contact Dermat 2003;14:95–6.
27. Lazzarini R, Duarte I, Marzagao C. Contact dermatitis of the feet: a study of 53 cases. Dermatitis 2004;15:125–30.
28. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2001-2002 study period [published erratum appears in Dermatitis 2005 Jun;16(2): 106]. Dermatitis 2004;15:176–83.
29. Malten KE, Rath R, Pastors PH. p-tert-Butylphenol formaldehyde and other cause of shoe dermatitis. Derm Beruf Umwelt 1983;31: 149–53.
30. Podmore P. Shoes. In: Rycroft RJG, Menné T, Frosch PJ, editors. Textbook of contact dermatitis. 2nd ed. Berlin: Springer-Verlag; 1995. p. 516–26.
31. Hansen MB, Menné T, Johansen JD. Cr(III) reactivity and foot dermatitis in Cr(VI) positive patients. Contact Dermatitis 2006;54: 140–4.
32. Woo DK, Militello G, James WD. Neoprene. Dermatitis 2004;15: 206–9.
33. Seidenari S, Giusti F, Massone F, Mantovani L. Sensitization to disperse dyes in a patch test population over a five-year period. Am J Contact Dermat 2002;13:101–7.
34. Goon AT-J, Gilmour NJ, Basketter DA, et al. High frequency of simultaneous sensitivity to disperse orange 3 in patients with positive patch tests to para-phenylenediamine. Contact Dermatitis 2003;48:248–50.
35. Jordan WP. Clothing and shoe dermatitis. Postgrad Med 1972;52: 143–8.
36. Larsen WG, Adams RM, Maibach HI. Color text of contact dermatitis. Philadelphia: WB Saunders; 1992. p. 168–9.
37. Storrs FJ. Shoe contact dermatitis. 2004. Available at: http://www.contactderm.org/members/FootDermatitis.pdf (accessed June 8, 2006).