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LONG-TERM TREND IN PATCH TEST REACTIONS: A 32-YEAR STATISTICAL OVERVIEW (1970–2002), PART II

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Allergic contact dermatitis remains an important problem worldwide. The objective of this study was to analyze patch test positivity trends of the North American Contact Dermatitis Group. Publications from 1970 to 2002 were reviewed and re-analyzed. Statistical significance was determined with a Cochran-Armitage trend test. We observed a significant increase in positive reactions with carbamates, balsam of Peru, thimerosal, formaldehyde, imidazolidinyl urea, and methyl dibromoglutaronitrile. The rates of positive reactions to Dimethylol dimethyl (DMDM) hydantoin, diazolidinyl urea, and methylchloroisothiazolone/methylisothiazolone remained unchanged. We showed a significant decrease in positive reactions for all other allergens. These data provide challenges in public health—for industry, government, and medicine—to decrease the frequency of allergic contact dermatitis. However, the complexities of evaluating a 32-year analysis are numerous, so the data should be interpreted with caution and within the context of this work.

Keywords: Patch test; NACDG; Allergens; Rubber; Fragrances; Preservatives; Anaesthetics

INTRODUCTION

Allergic contact dermatitis remains an important problem worldwide, despite regulations intended to minimize sensitization.

From July 1970 to June 2002, the North American Contact Dermatitis Group (NACDG) patch tested over 35,000 patients in 11 cities in private offices and clinics. This select group of patients suspected to have allergic contact dermatitis was evaluated and patch tested with an allergen screening series.

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The first data review appeared in 1973 (1); subsequent publications provide data to 2002 (2–11). Those results constitute a database with which seems inappropriate to assess whether there is a changing trend of contact allergy with time. This study extends the analyses of Nguyen and colleagues (12). Literature review utilized PubMed, EMBASE, *Science Citation Index*, and standard dermato-allergy texts.

Material and Methods

NACDG patch testing technique. Over the 32 years from 1970 to 2002, patients suspected of having allergic contact dermatitis were evaluated by 10 to 13 NACDG dermatologists and patch tested to a tray of specified allergens. Patients were generally not patch tested if they applied topical corticosteroids to patch test sites, took immunosuppressive drugs including oral corticosteroids, or had medical conditions that could compromise the evaluation of skin sensitization.

The patients were patch tested using a standardized technique with the use of Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Oslo, Norway). Some early tests were performed with the use of A1-test patches (Hollister-Stier Div. Miles Labs, West Haven, CT) affixed with Scanpor paper tape.

The allergens were purchased at various times from Trolab (Denmark; Hellerup) and Johnson & Johnson (Skillman, NJ); Hermal-Chemie Ltd., (Reinbek, Germany); Center Laboratories, Hermal Dermatology Group (Delmar, NY); and Chemotechnique Diagnostics AB (Malmö, Sweden).

The patches remained in place for 48 hours and test sites were typically evaluated twice, initially at 48 to 72 hours and again at 72 to 168 hours after placement.

Patch test reactions were interpreted with the International Contact Dermatitis Research Group (ICDRG) scale: negative reaction (0); macular erythema (?); erythema, infiltration, and possibly papules (1+); erythematous papules and/or vesicles (2+); spreading blisters and/or crust with ulceration (3+); and irritant reaction (IR). A positive patch test allergic patch test result was generally interpreted to be 1+, 2+, or 3+ reaction (13).

The history, skin examination, and patch test results were integrated to arrive at diagnostic groups described previously: allergic contact dermatitis, irritant contact dermatitis, atopic dermatitis, occupational dermatose, nummular dermatitis, stasis dermatitis, or psoriasis (5).

Comparison of data. Results of the NACDG publications between July 1970 and June 2002 were reviewed. Substances with sufficient data available from 1970 to 2002, except those already treated by Nguyen and colleagues (12), were analyzed.

Allergens. When allergens were tested at different concentrations over the years, we mixed the data, but so specified. When a substance was tested in aqueous and non-aqueous forms, we considered these separately.

Patients. In 1970–1972, 1972–1974, and 1974–1975, the number of tested patients was stated as 1,200, 3,000 and 1,900, respectively. In 1975–1976 and

1979–1980, ranges were given rather than exact sample sizes. For these years, we used the midpoint of the range as the number of tested patients. All the other years specified the exact the number of patients actually tested.

Statistics. Statistical significance was determined with a Cochran-Armitage trend test (SAS Version 8.2), which checks for trends in binomial proportions across levels of a single factor. The trend test may give strong evidence of positive or increasing linear trends, or of negative or decreasing trends. Details are provided by Agresti (14). Each substance was tested individually. To adjust for the large number of comparisons, p -values were considered significant if they were less than or equal to 0.002.

RESULTS

One hundred twelve substances were tested by the NACDG over the 32 years. Forty-one substances had sufficient data to be analyzed (except those of Nguyen and colleagues (12)). Sensitivity rates of allergens and results of the Cochran-Armitage trend test appear in Table 1. Table 2 describes mix composition.

Fifty-six percent of the substances tested (23/41) had a relatively constant rate of positive reactions over the study years; 44% (18/41) had a statistically significant change of response. Table 3 summarizes the statistically significant responses.

Rubber and Rubber Additives

Black rubber mix had a significant decrease ($p = 0.0013$) in positive reactions over these years, from 2.2% in 1972 to 1% in 2002.

Carbamates (carba mix) increased in frequency of positive reactions in patch tested patients, from 2.9% in 1972 to 7.3% in 1998 ($p < 0.0001$), but then precipitously dropped to 4.5% in 2002.

Other rubber additives, mercapto mix and mercaptobenzothiazole (MBT), statistically significantly decreased in positive reactions over these years ($p < 0.0001$).

The evolution of positive reactions to rubber and rubber additives is shown in Figure 1.

Fragrances

Balsam of Peru (*Myroxylon pereirae*) had a striking significant increase of positive reactions ($p < 0.0001$). The percent positive doubled in the 32 years, from 5% to 11.5%. Fragrance mix significantly decreased between 1992 and 2002 ($p = 0.0006$).

The evolution of positive reactions to fragrances is shown in Figure 2.

Preservatives and Stabilizer

Thimerosal was the preservative with the highest sensitization rate. It significantly increased in positive reactions from 1984 to 1994 (6.2% to 10.6%,

Table 1 Sensitivity rates of allergens and Cochran-Armitage trend test

Test substance	1970–72		1972–74		1974–75		1975–76		1979–80		1984–85	
	n*	%	n	%	n*	%	n*	%	n*	%	n	%
2 Bromo-2-nitropropane 0.5%	n/a	n/a	n/a	n/a	n/a	n/a	190	13.2	n/a	n/a	652	2.6
Amidoamine 0.1% aqueous	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ammoniated mercuric chloride 1%	1,200	5.0	3,000	4.6	1,900	4.1	1,450	3.6	1,949	2.7	660	3.0
Bacitracin 20%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Balsam of Peru 25%	1,200	5.0	3,000	7.8	1,900	7.8	1,450	7.7	1,949	7.1	1,122	3.3
Benzocaine 5%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1,135	3.5
Benzophenone-3 3%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
BHA 2%	n/a	n/a	n/a	n/a	n/a	n/a	409	1.0	n/a	n/a	n/a	n/a
BHT 2%	n/a	n/a	n/a	n/a	n/a	n/a	224	0.9	n/a	n/a	n/a	n/a
Black rubber mix 0.6%	n/a	n/a	3,000	2.2	1,900	2.7	1,450	1.5	1,949	2.4	1,140	1.4
Budesonide 0.1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Caine mix 3.5%	1,200	10.0	3,000	8.4	1,900	10.5	1,450	10.7	1,949	10.5	1,117	2.0
Carba mix 3%	n/a	n/a	3,000	2.9	1,900	6.4	1,450	3.8	1,949	3.6	1,135	3.4
Chloroxylonol (PCMX) 1%	n/a	n/a	n/a	n/a	n/a	n/a	1,450	1.3	1,949	0.7	652	1.7
Cobalt chloride 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Colophony 20%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1,132	1.9
Diazolidinyl urea 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	155	1.3
Diazolidinyl urea 1% aqueous	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	647	1.9
DMDM hydantoin 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	651	0.8
DMDM hydantoin 1% aqueous	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	650	1.5
Epoxy resin 1%	n/a	n/a	3,132	2.8	1,900	2.9	1,451	3.0	1,949	3.0	1,129	1.9
EUMF 5%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ethylenediamine DHCl 1%	1,200	7.0	3,000	6.0	1,900	5.9	1,450	5.9	1,949	5.2	1,120	5.9
Formaldehyde (1% or 2%) aqueous	1,200	4.0	3,000	3.4	1,900	5.0	1,450	3.8	1,949	6.7	1,144	n/a
Fragrance mix 8%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Glutaraldehyde 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Glycerylthioglycolate 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Imidazolidinyl urea 2%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	487	1.6
Imidazolidinyl urea 2% aqueous	n/a	n/a	n/a	n/a	n/a	n/a	1,450	0.9	n/a	n/a	1,134	1.5
Lanolin 30%	1,200	3.0	3,000	2.7	1,900	3.6	1,450	2.9	1,949	2.0	1,135	1.2
Mercapto mix 1%	1,200	2.0	3,000	3.0	1,900	3.3	1,450	2.4	1,949	3.0	1,132	2.7
Mercaptobenzothiazole 1%	n/a	n/a	n/a	n/a	1,900	4.1	1,450	3.1	1,949	3.6	1,141	2.9
MDGN (2.5% or 1%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Methylmethacrylate 2%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
MCI/MI 100 ppm	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	577	0.2
MCI/MI 100 ppm aqueous	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	639	0.5
Mixed dialkyl thiourea 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Parabens mix 15%	1,200	3.0	3,000	3.5	1,900	3.7	1,450	2.7	1,949	2.1	661	1.1
Para-tert-butylphenol formaldehyde resin 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1,129	0.8
Thimerosal 0.1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1,137	6.2
Tixocortol-21-pivalate 1%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n = exact number of tested patients; n* = approximate number of tested patients; % = percentage of positive reactions; n/a = not applicable; BHA = butylhydroxyanisol; BHT = butylhydroxytoluene; DMDM = Dimethylol dimethyl; DHCl = Dihydrochloride; the two-sided *p*-value tests against either an increasing or decreasing alternative; EUMF = ethyleneurea/melamine formaldehyde resin; MDGN = methyl dibromoglutaronitrile; MCI/MI = methylchloroisothiazolone/methylisothiazolone. Test concentration: Formaldehyde test concentration was 2% from 1970 to 1980 and 1% from 1984 to 2002. MDGN test concentration was 1% from 1992 to 1996 and 2.5% from 1996 to 2002.

^aCochran-Armitage trend test.

^bBoldface type indicates statistical significance.

1985–89		1992–94		1994–96		1996–98		1998–00		2001–02		Statistic ^a	Two-sided
n	%	n	%	n	%	n	%	n	%	n	%	(Z)	Pr > Z ^b
n/a	n/a	3,477	2.2	3,074	2.3	4,094	3.2	5,800	3.1	4,511	3.4	−1.31	0.1898
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5,773	3.4	4,511	2.4	2.97	0.0029
n/a	n/a	3,468	3.2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.07	< 0.0001
n/a	n/a	3,482	7.8	3,079	9.1	4,103	8.7	5,812	9.2	4,514	7.7	0.05	0.9637
3,960	5.1	3,496	7.5	3,112	10.4	3,439	11.8	5,832	12.3	4,524	11.5	−13.20	< 0.0001
3,985	2.1	3,524	2.2	3,112	2.6	3,444	2.0	5,833	1.7	4,522	1.7	3.58	0.0003
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5,800	0.6	4,513	0.6	0.03	0.9731
n/a	n/a	3,472	0.2	3,076	0.5	n/a	n/a	n/a	n/a	n/a	n/a	−0.34	0.733
n/a	n/a	3,470	0.1	3,076	0.2	n/a	n/a	n/a	n/a	n/a	n/a	0.34	0.7311
3,991	2.1	3,492	2.1	3,113	2.3	n/a	n/a	n/a	n/a	4,521	1.0	3.23	0.0013
n/a	n/a	n/a	n/a	1,678	1.1	4,098	1.2	5,806	1.4	4,515	1.1	−0.09	0.9316
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	3.41	0.0007
3,994	3.1	3,524	4.8	3,115	5.7	3,437	7.3	5,829	4.8	4,521	4.5	−4.54	< 0.0001
n/a	n/a	3,506	1.4	3,074	1.2	4,093	1.0	5,800	0.8	4,512	0.6	3.08	0.0021
n/a	n/a	3,499	6.8	3,087	8.0	4,095	9.0	5,811	7.6	4,512	7.5	−0.48	0.6338
3,948	2.2	3,520	1.9	3,113	2.6	3,443	2.0	5,833	2.5	4,522	2.7	−2.16	0.0311
3,947	2.0	3,481	3.0	3,085	3.7	4,096	3.7	5,802	3.0	4,511	3.2	−2.74	0.0062
3,723	2.4	3,471	3.1	3,060	3.7	4,094	2.9	5,778	2.6	4,511	3.3	−1.38	0.1687
n/a	n/a	3,485	1.6	3,082	2.3	4,093	2.6	5,801	2.0	4,511	2.8	−2.78	0.0055
n/a	n/a	3,479	1.8	3,064	2.1	4,093	1.9	5,767	1.6	4,511	2.2	−0.58	0.5618
3,990	2.1	3,500	1.8	3,114	2.2	3,439	1.9	5,832	2.7	4,522	2.4	−1.70	0.0884
n/a	n/a	n/a	n/a	3,071	5.0	4,095	7.2	5,799	5.0	4,511	2.2	7.69	< 0.0001
3,983	3.8	3,525	2.5	3,113	2.9	3,439	2.6	5,831	2.5	4,523	2.8	13.52	< 0.0001
3,920	n/a	3,478	7.8	3,082	9.2	4,095	9.3	5,802	9.2	4,515	8.5	−13.24	< 0.0001
n/a	n/a	3,478	11.4	3,082	14.0	4,095	11.7	5,802	10.9	4,511	10.2	3.44	0.0006
n/a	n/a	3,502	3.3	3,075	2.2	4,094	2.6	5,802	1.9	4,489	1.3	6.06	< 0.0001
n/a	n/a	3,463	2.1	3,075	5.0	4,094	1.9	5,800	2.0	4,510	1.9	4.20	< 0.0001
3,763	2.1	3,482	2.6	3,080	3.1	4,094	3.2	5,821	2.0	4,511	3.1	−1.57	0.1168
3,837	1.7	3,523	1.9	3,101	2.6	4,101	2.5	5,784	2.5	4,523	1.8	−3.10	0.0019
3,986	1.5	3,528	2.9	3,114	3.3	3,442	3.3	5,834	2.4	4,521	2.3	0.72	0.4723
3,983	2.5	3,497	2.6	3,115	2.2	3,439	1.8	5,834	1.3	4,522	0.6	8.82	< 0.0001
3,974	2.5	3,525	1.8	3,115	2.1	3,440	1.8	5,834	2.0	4,521	0.8	9.42	< 0.0001
n/a	n/a	3,481	1.5	3,074	2.0	4,053	2.7	5,778	6.0	4,511	5.5	−12.73	< 0.0001
n/a	n/a	3,472	1.1	3,080	1.2	4,099	1.6	5,812	1.4	4,514	1.5	−1.61	0.1079
n/a	n/a	3,504	2.4	3,078	3.0	n/a	n/a	5,812	1.4	n/a	n/a	1.87	0.0622
n/a	n/a	3,471	2.9	3,075	3.0	4,083	2.9	5,792	2.7	4,509	2.3	0.45	0.6532
n/a	n/a	3,480	1.1	3,075	0.7	4,098	1.3	5,807	1.1	4,512	0.7	0.90	0.3689
n/a	n/a	3,476	2.3	3,086	1.8	4,096	1.7	5,803	1.0	4,512	0.6	11.84	< 0.0001
3,996	1.6	3,499	1.7	3,114	2.7	3,442	1.8	5,832	1.6	4,524	1.9	−1.13	0.2567
3,959	7.1	3,472	10.6	3,075	10.4	4,087	10.9	5,795	10.8	n/a	n/a	−6.65	< 0.0011
n/a	n/a	3,462	2.5	3,091	2.3	4,100	2.3	5,807	2.7	4,515	2.9	−1.58	0.1141

Table 2 Mix composition

Mix	Composition
Black rubber mix	N-isopropyl-N-phenyl-4-phenylenediamine N-cyclohexyl-N-phenyl-4-phenylenediamine N,N-diphenyl-4-phenylenediamine
Caine mix	Benzocaine Tetracaine hydrochloride Dibucaine hydrochloride
Carba mix	N,N-diphenylguanidine Zinc diethyldithiocarbamate Zinc dibutyldithiocarbamate
Fragrance mix	Amylcinnamaldehyde Cinnamic aldehyde Cinnamic alcohol Eugenol Isoeugenol Geraniol Hydroxycitronellal Oak moss absolute
Mercapto mix	N-cyclohexylbenzothiazyl sulfonamide Dibenzothiazyl disulphide Mercaptobenzothiazole Morphoinylmercaptobenzothiazole
Parabens mix	Methyl-4-hydroxybenzoate Ethyl-4-hydroxybenzoate, Propyl-4-hydroxybenzoate Butyl-4-hydroxybenzoate

$p < 0.0001$). The rate of positive reactions remained stable from 1994 to 2000, at approximately 10.5%.

The formaldehyde sensitivity rate averaged 4% from 1970 to 1976 and significantly increased throughout the years 1976 to 1996 ($p < 0.0001$), remaining stable at approximately 9% since 1996.

DMDM hydantoin and diazolidinyl urea (aqueous and non-aqueous forms) remained unchanged since 1992. Imidazolidinyl urea (aqueous form only) showed a significant increase in positive reactions from 1975 to 2002 (0.9% to over 2%, $p = 0.0019$).

The rate of sensitization to methyldibromoglutaronitrile (MDGN) increased strikingly from 1992 to 2002 (from 1.5% to 5.5%, $p < 0.0001$).

The rate of sensitization to methylchloroisothiazolone/methylisothiazolone (MCI/MI) was stable at approximately 2.5%.

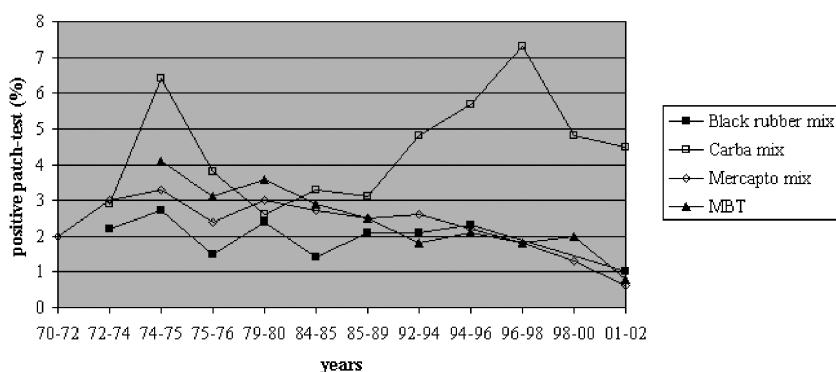
Parabens and ethylenediamine Dihydrochloride (DHCl) decreased strikingly in sensitization rates over these years (from 3% to less than 1% and from 7% to less than 3%, respectively; $p < 0.0001$ each).

The decrease in positive reactions to chloroxylenol (PCMX) was nearly statistically significant ($p = 0.0021$).

The evolution of positive reactions to preservatives and ethylenediamine DHCl is shown in Figure 3.

Table 3 Chemicals with a statistically significant response

Test substance	Statistic ^a (Z)	Two-sided Pr > Z ^b
Ammoniated mercuric chloride 1%	4.0662	< 0.0001
Balsam of Peru 25%	-13.1994	< 0.0001
Benzocaine 5%	3.5826	0.0003
Black rubber mix 0.6%	3.2265	0.0013
Caine mix 3.5%	3.4093	0.0007
Carba mix 3	-4.5393	< 0.0001
Ethyleneurea/melamine formaldehyde resin 5%	7.6872	< 0.0001
Ethylenediamine DHCI 1%	13.5227	< 0.0001
Formaldehyde aqueous (1% or 2%)	-17.099	< 0.0001
Fragrance mix 8%	3.4413	0.0006
Glutaraldehyde 1%	6.0601	< 0.0001
Glycerylthioglycolate 1%	4.2037	< 0.0001
Imidazolidinyl urea 2% aqueous	-3.1028	0.0019
Mercapto mix 1%	8.8248	< 0.0001
Mercaptobenzothiazole 1%	9.4236	< 0.0001
MDGN (2.5 or 1%)	12.7277	< 0.0001
Parabens mix 15%	11.8392	< 0.0001
Thimerosal 0.1%	-6.6497	< 0.0011

**Figure 1** Evolution showing an increase in the rate of positive reactions to black rubber mix, mercapto mix, and mercaptobenzothiazole (MBT), but an increase for carbamates (carba mix).

Anesthetics

The sensitization rate to benzocaine and caine mix significantly decreased (from 3.5% to 1.7%, $p = 0.0003$, and from 10% to 2%, $p = 0.0007$, respectively).

The evolution of positive reactions to anesthetics is shown in Figure 4.

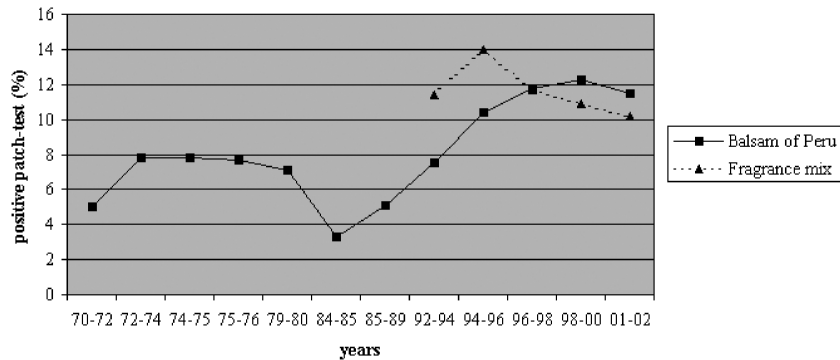


Figure 2 Evolution showing an increase in the rate of positive reactions to balsam of Peru, but a decrease for fragrance mix.

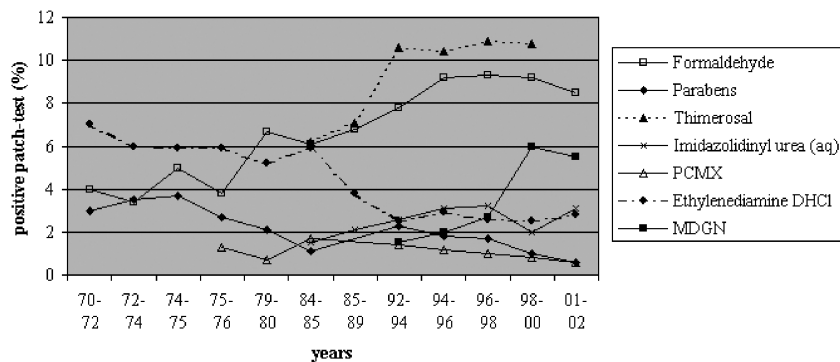


Figure 3 Evolution showing an increase in the rate of positive reactions for thimerosal, formaldehyde, imidazolidinyl urea (aqueous), and methyldibromoglutaronitrile (MDGN). The decrease for chloroxylenol (PCMX) was nearly significant. Ethylenediamine, a stabilizer, had a significant decrease in positive reactions.

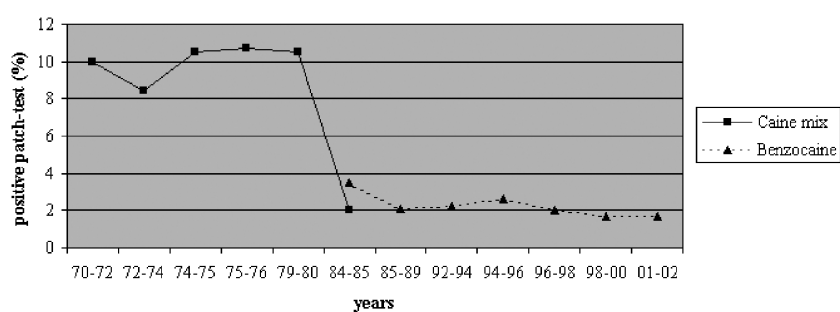


Figure 4 Evolution showing a constant decrease in the rate of positive reactions for caine mix and benzocaine.

Others

After an incidence peak in 1996–1998 with 7.2% of positive responses, positive reactions to ethyleneurea/melamine formaldehyde resin (EUMF) significantly decreased to 2.2% in 2002 ($p < 0.0001$).

The rate of positive reactions to glutaraldehyde significantly decreased, from 3.3% in 1992 to 1.3% in 2002 ($p < 0.0001$).

The rate of positive reactions to glyceryl thioglycolate peaked in 1994–1996 at 5%, then decreased significantly ($p < 0.0001$) to approximately 2% by 1992.

Ammoniated mercuric chloride dramatically decreased in positive reactions from 1970 to 1980 (from 5% to 3%, $p < 0.0001$). The sensitization rate remained stable at approximately 3% from 1980 to 1994.

DISCUSSION

For most substances, the rate of positive reactions remained relatively constant since 1970, with some provocative exceptions.

Rubber and Rubber Additives

Black rubber mix ingredients are most often used in industrial and heavy use rubber products such as tires and cables. The rate of sensitization to black rubber mix significantly decreased ($p = 0.0013$). We are unable to explain this. More extensive cooperation between industrial chemical engineers and dermato-allergists interested in decreasing dermatitis might facilitate a reasonable hypothesis.

Reactions to carbamates (carba mix) significantly increased in frequency from 1972 to 1998 ($p < 0.0001$), as found by Sertoli and colleagues in their Italian study from 1988 to 1993 (15). After the sensitization epidemic due to thiuram (a rubber additive found in latex) in the mid-1980s, gloves manufacturers reduced the levels and use of thiuram. Carbamates have been used as a substitute, which may partially explain the increased positivity. Gibbon and colleagues (2001) (16) found a statistically significant increased incidence in thiuram-positive patch test results in their 1989–1993 group of healthcare workers compared with their 1983–1988 group, as did Nguyen and colleagues from 1970 to 1994 (12). Knudsen and colleagues found a decrease in thiuram sensitization between 1995 and 2004 as a result of European legislation (17). In the patients reviewed here, the evolution of positive reactions to carbamate followed the same trend as that with thiuram: increased positivity from 1972 to 1998 and decreased positivity from 1998 to 2002. Concomitant sensitization has been suggested between these 2 chemical classes (16, 18).

Mercaptobenzothiazole (MBT) and mercapto mix (which contains 0.5% MBT) significantly decreased in positive reactions ($p < 0.0001$). This is surprising because these agents are frequently used in rubber gloves, but the decrease may be explained as the levels may have been lowered in the manufacturing process, as suggested by Knudsen and Menné (18). Geier and colleagues found no increase with MBT from 1995 to 2001 (19). Here, too, further collaboration between industrial chemical engineers and dermato-allergists is indicated.

Fragrance

In 2000, fragrance allergy was reviewed in a cohort of 25,455 patch tested patients by Buckley and colleagues (United Kingdom) (20). The rate of positive reactions to fragrance mix remained relatively constant from 1980 to 1996, ranging from 6.1% to 10.9% (mean 8.5%) in female patients and from 5.1% to 12.9% (mean 6.7%) in male patients. In contrast, Johansen and Menné in Denmark found an increase in positivity to fragrance mix from 1980 to 1992 in their cohort of 8,215 patients (21). We cannot compare these data with ours because the NACDG tested the fragrances separately up to 1992. However, balsam of Peru, used as a fragrance allergy marker, showed a significant increase in sensitization ($p < 0.0001$) between 1992 and 2000. It was unexpected that our results would show an increase, because balsam of Peru is widely used in perfumery; however, since 1991, the International Fragrance Association limited its use to a level of 0.4% per products. In contrast to our results, Buckley and colleagues described a decrease of 5% per year in balsam of Peru positivity (20).

Balsam varies from lot to lot, and possibly from tree to tree; hence, defining relevance of changing positivity over years remains problematic.

The significant decrease in the prevalence of fragrance mix allergy between 1992 and 2002 ($p = 0.0006$) may be partially explained by the decrease in cinnamic aldehyde positive reactions noted by Nguyen et al. and Buckley et al. and the decrease in cinnamic alcohol described by Buckley et al. (12, 20).

Preservatives and Stabilizer

Thimerosal was the preservative causing the most reactions. Its sensitization rate increased strikingly from 1984 to 1994 ($p < 0.0001$), with the rate ranging from 6.2% in 1984 to 10.6% in 1992–1994. The number of positive reactions to thimerosal seemed stable from 1994 to 2000 at approximately 10.5%. Zoller and colleagues, who collected data on all patients tested in a referral center in Israel from 1995 to 2004, found a sensitization rate to thimerosal stable but lower at approximately 4% (22). Similarly, Wilkinson and colleagues, who monitored levels of preservative sensitivity in Europe between 1991 and 2000, found a stable low rate of positive reactions at approximately 1% (23). Thimerosal has been a widely used preservatives in biologics and vaccines since the 1930s, especially in the United States, which may explain the high rate. Recently, because of an increasing concern about a possible relation between thimerosal (an organomercurial) and neurotoxicity, thimerosal has been eliminated from most vaccines. Since 2000, most vaccines are thimerosal-free and the NACGD stopped testing this substance. Moreover, a positive patch test reaction with thimerosal was infrequently clinically relevant.

Positive reactions to formaldehyde increased from 1970 to 1998 ($p < 0.0001$) in spite of the reduction in the concentration tested (2% from 1970 to 1985; 1% from 1985 to 2002). The positivity rate ranged from 4% in 1970 to 9.3% in 1998. Zoller and colleagues showed a similar increase during their study period, but their rate was lower (from 0.3% in 1995 to 1.9% in 2004) (22). Similarly, the quaternium-15 sensitivity rate, a formaldehyde releaser that is widely used, significantly increased from 1976 to 2002, as shown by Nguyen and colleagues (12). The increased rate of

formaldehyde sensitization may be partially attributed to quaternium-15. To the contrary, in their European study, Wilkinson and colleagues found that the sensitivity to formaldehyde remained stable, mostly between 2% and 2.5% from 1991 to 2000 (23). Explanation for the higher rate in United States remains unclear—and is presumed to be related to different use patterns.

The sensitization rates of DMDM hydantoin (aqueous and non-aqueous), imidazolidinyl urea (non-aqueous), and diazolidinyl urea (aqueous and non-aqueous), which are also formaldehyde releasers, remained stable since 1992, as found by Zoller and colleagues (22). The significant increase in positive reactions to the aqueous form of imidazolidinyl urea from 1984 to 2002 ($p = 0.002$) may have contributed to the increase in positive reactions to formaldehyde; increased use patterns may have also been responsible. Jong and colleagues also observed an increased positivity rate of imidazolidinyl urea from 2000 to 2005 in the United Kingdom (UK) (24).

MCI/MI, a preservative mainly used in rinse-off cosmetics, had a stable rate of positive reactions, at approximately 2.5%. Our results resemble those of Wilkinson and colleagues (23). MDGN, a preservative also used in cosmetics in stay-on and rinse-off products, had a significant increase from 1992 to 2000, from 1.5% to 6% ($p < 0.0001$). It was introduced in Europe in the mid-1980s and in North America in the early 1990s. Wilkinson and colleagues found a dramatic increase in the incidence of positive patch test reactions to MDGN in the same period (23). Their highest rate was lower at 3.5%. The lower concentration test (0.2% vs. 1% or 2.5% in our study) may be a partial explanation. Zoller and colleagues (22) also found an increase in the sensitization rate of Euxyl K400 (mixture of MDGN and phenoxyethanol), but non-statistically significant and with rates similar to those of Wilkinson and colleagues (23). After controversy over the MDGN test concentration, 0.5% seems to be appropriate (25). From the year 2005 on, MDGN at 0.5% is recommended for the European series. The dramatic increase in positive reactions to MDGN should alert cosmetics manufacturers, and the maximal concentration should be redefined. The European Commission recommends that MDGN not be present in any cosmetic products because no safe use level in rinse-off products has been established (26). In their UK study, Jong and colleagues observed a significantly decreased MDGN sensitization rate from 2.4% in 2000 to 1.1% in 2004–2005 (24). No explanation for this decrease was found.

The rate of positive reactions to parabens, widely used in cosmetics, pharmaceutical products, and food, decreased strikingly over the years ($p < 0.0001$) and ranged from 0.5% to 1% since 1998. Wilkinson and colleagues also found a stable rate of sensitization in the 0.5–1% range, but beginning earlier (1991) (23). As the use of parabens remains widespread, an explanation for this decrease is welcome.

Ethylenediamine DHCl is used in topical antibiotic and corticosteroid creams for its chemical stabilizing properties. Many individuals with ethylenediamine sensitization were treated with the original Mycolog cream, a combination of a broad-spectrum antifungal and a corticosteroid, widely used in the United States. Ethylenediamine remained one of the 10 most common allergens from 1970 to 1989 and was removed from Mycolog[®] cream, but not from the generic versions. Ethylenediamine had a striking decrease in the rate of sensitization from 1970 to 1994 ($p < 0.0001$). The fact that ethylenediamine is an excipient still present in the generic formulation of Mycolog may explain the low persisting rate of positive reactions

since 1994 ($\sim 2.5\%$). Moreover, local and systemic reactions have been described with the use of oral aminophylline (27, 28).

Chloroxylenol (PCMX) is used as a preservative in cosmetics and as an active ingredient in antimicrobial soaps. We observed an unexplained, nearly significant decrease in positive reactions to PCMX over the years ($p = 0.0021$). Because it is not utilized in other standard patch test series, we cannot compare our data with those of another study.

Anesthetics

“Caine” anesthetics are widely used local and topical anesthetics. Ester anesthetics (procaine, benzocaine, tetracaine, etc.) have been a common cause of allergy since the 1920s. Krob and colleagues’ meta-analysis revealed that caine mix belongs to the 10 most common allergens between 1996 and 2000, with 0.7% of positive reactions (29). Caine mix was our second most frequent allergen from 1970 to 1980, with approximately 10% of positive reactions. Since 1984, the NACDG only patch tested benzocaine, used as a screening chemical for sensitization to topical anesthetics. We showed a significant decrease of positive reactions to both caine mix and benzocaine ($p = 0.0007$ and $p = 0.0003$, respectively). This decrease may be explained by the use of amide anesthetics (lidocaine, mepivacaine, bupivacaine, etc.), which are less common sensitizers (30). Although we observed a decrease in positive reactions to benzocaine, our rate of benzocaine sensitization ($\sim 2\%$) remained higher compared with Sertoli and colleagues’ and Shireen’s studies, which found approximately 1.3% and 0.4%, respectively, of benzocaine positive reactions (15, 31). In 2001, the NACDG added lidocaine, commonly used in anti-hemorrhoidal preparations, to their standard tray.

Others

Ethyleneurea/melamine formaldehyde resin (EUMF) is used to render clothing wrinkle-resistant. EUMF has been patch tested by NACDG since 1994 to screen for allergic contact dermatitis in the permanent press textile industry, as recommended by Fowler and colleagues in 1992 (32). We observed a significant decrease in positive reactions to EUMF from 1996 to 2002 ($p < 0.0001$), with 2.2% of positives in 2002. We have no explanation concerning this decrease, but our rate in 2002 is similar to that of Lazarov’s study, which showed 2.6% of positive reactions to EUMF from 1999 to 2002 (33). As reported by Scheman and colleagues and later by Metzler-Brenckle and Rietschel, dimethylol dihydroxy ethyleneurea (DMDHEU) seems to be the best choice to screen textile allergy (34, 35). This chemical has been tested by NACDG since 2001.

Glutaraldehyde, commonly used as sterilizing agent in medical facilities, is an occupational allergen in healthcare workers (35, 36). The significant decrease in positive reactions to glutaraldehyde ($p < 0.0001$) may be explained by a decreased exposure or more refined user education, i.e., “no touch” techniques in cold sterilization (35–37).

Glycerylthioglycolate (GTG), used in “acid permanent” wave solutions since the 1970s, can cause contact dermatitis in hairstylists and their clients (38). Tested since 1992, GTG positive reactions peaked in 1994–1996, at 5%, then decreased significantly ($p < 0.0001$) around 2%, as it was in 1992. Our positive rate is lower than that found in Laing and colleagues’ Irish study, which showed a rate of positive reactions of 23.5% from 1987 to 2004 (39). Because of the alarming rate of sensitization (45%), GTG was withdrawn from the German market in 1992. Uter et al., who studied the Information Network of Departments of Dermatology (IVDK) data, showed a decrease of GTG from 1995 to 2005 in their study of hairstylists as a direct consequence of the chemical withdrawal (40). In the past, GTG had already showed differences in terms of rate of sensitization, depending on the usage of this chemical in different countries (41).

Ammoniated mercuric chloride, a local antiseptic also used in whitening creams, dramatically decreased in positive reactions from 1970 to 1980 ($p < 0.0001$). Intoxications have been described with topical mercury (42, 43). This decrease may be explained by the removal of this chemical in the United States.

CONCLUSION

Our results should be interpreted with caution and not be quoted or used out of context of this work. Firstly, the patients who were tested by the NACDG constitute a select population referred to specific patch test centers; they are not representative of a general population. Secondly, the clinical significance of positive reactions to patch tests is incompletely documented. Patch test positivity represents a start—determining clinical relevance and allergen source present a societal challenge (44–46). A positive patch test result may have no past or present clinical relevance. Finally, because different allergen suppliers were utilized, this must be considered an independent variable as we have no qualitative or quantitative analytic data to confirm bioequivalence (47).

The changes reported are in rates or proportions of positive findings for specific allergens in those individuals who sought treatment for dermatitis. The term “significant change of response” used for materials refers to observed incidences of response in the sample studied—not directly to numbers of responders in the general occupational population or to the severity of their responses. We need analysis of data from other groups, such as the International Contact Dermatitis Research Group (ICDRG), the European Environmental and Contact Dermatitis Research Group (EECDRG), and the Information Network of Departments of Dermatology (IVDK). Still, comparison with data from other centers should be interpreted with caution and not be quoted or used out of context of this work because the populations tested and the investigators are different.

If we are to be effective in reducing allergic contact dermatitis in the exposed population, we need to identify what people are exposed to in their normal daily lives and whether there is any clinical relevance to the observations in these trends of patch test data.

Taken together, we are impressed with the possible meaning of some of the trends. They constitute an opportunity for industry, government, and dermatologists—as

a challenge to prevent new cases of allergic contact dermatitis. As suggested by Wesley and Maibach, the frequency of contact dermatitis hopefully will decrease through dermatotoxicologic- and epidemiologic-based interventions (48).

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