Contact dermatitis associated with preservatives: Retrospective analysis of North American Contact Dermatitis Group data, 1994 through 2016

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Background: Preservatives are often necessary components of commercial products. Large-scale North American studies on preservative allergy are limited.

Objective: To evaluate demographics, positive patch test reactions (PPTRs), clinical relevance, and trends for preservatives tested by the North American Contact Dermatitis Group.

Methods: We conducted a retrospective cross-sectional analysis of North American Contact Dermatitis Group patch testing results of preservatives from 1994 through 2016.

Results: A total of 50,799 patients were tested; 11,338 (22.3%) had a PPTR to at least 1 preservative. The most frequent reactions were to methylisothiazolinone 0.2% aqueous (aq) (12.2%), formaldehyde 2% aq (7.8%), formaldehyde 1% aq (7.8%), quaternium-15 2% petrolatum (pet) (7.7%), and methyldibromo glutaronitrile/phenoxyethanol 2% pet (5.1%). Paraben mix 12% pet (1%), iodopropynyl butylcarbamate

0.1% pet (0.4%), benzyl alcohol 1% pet (0.3%), and phenoxyethanol 1% pet (0.2%) had the lowest PPTRs. Linear regression analysis of preservatives tested showed that only methylchloroisothiazolinone/methylisothiazolinone 0.01% aq (parameter estimate, 0.42; 95% CI, 0.17-0.66; $P < .005$) had a significant increase in PPTRs over time.

Limitations: Collected variables are dependent on clinical judgment. Results may be prone to referral selection bias.

Conclusions: This large North American study provides insight on preservative PPTRs and trends from 1994 through 2016. (J Am Acad Dermatol 2021;84:965-76.)

Key words: allergic contact dermatitis; benzyl alcohol; contact dermatitis; formaldehyde; formaldehyde releaser; iodopropynyl butylcarbamate; methylchloroisothiazolinone/methylisothiazolinone; methyldibromo glutaronitrile/phenoxyethanol; methylisothiazolinone; NACDG; paraben; patch test; phenoxyethanol; preservative; preservative allergy.

Preservatives are chemicals added to cosmetic, household, and industrial products to prevent or eliminate microbial growth and delay chemical degradation.[1,2] Preservatives are indispensable components of commercial products because of their ability to prolong shelf life and prevent infections. They have also been recognized as important skin sensitizers worldwide.[3-7]

Large-scale epidemiologic studies on preservative allergy in North America are few. In this study, we sought to characterize demographics, patch test reactions, relevance, and trends associated with preservatives in the North American Contact Dermatitis Group (NACDG) data set.

CAPSULE SUMMARY

- Preservatives are indispensable in commercial products and are important skin sensitizers.

- The most common patch test reactions to preservatives from 1994 through 2016 were to methylisothiazolinone, formaldehyde, quaternium-15, and methyldibromo glutaronitrile/phenoxyethanol. The preservatives with the lowest frequencies of reactions from 1994 through 2016 were phenoxyethanol, benzyl alcohol, iodopropynyl butylcarbamate 0.1%, and paraben mix.

++ (strong), + (mild), +/− (weak/doubtful), irritant, and negative in accordance with NACDG criteria.[8] In addition, the final interpretation for each allergen was determined and documented as allergic, unknown, irritant, or negative. For each reaction designated allergic, investigators determined the clinical relevance as definite, probable, possible, or past.[8] For the purposes of this study, positive patch test reaction (PPTR) was defined as a final patch test interpretation of allergic.

Two subgroups were defined a priori: (1) those with a PPTR to at least 1 preservative (preservative positive [PP] group) and (2) those with PPTRs to only nonpreservative allergens (other positive [OP] group); both groups excluded patients who had no PPTR.

Data were entered into Access or Excel (Microsoft, Redmond, WA) and analyzed using SAS, version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were performed to summarize patient demographics and frequency and percentage of PPTR. Odds ratio (the ratio of the odds of having an outcome in the PP group to the odds of the outcome in the OP group), with its 95% confidence interval, was estimated. The significance-prevalence index number (SPIN), a weighted calculation of clinical relevance combined with prevalence, where SPIN = (proportion of population allergic) × (1 × % definite relevance + 0.66 × % probable relevance + 0.33 × % possible relevance) × 100, was calculated for each test cycle.[9]

METHODS

This retrospective study was approved by the Duke University institutional review board. The NACDG consists of contact dermatitis experts in the United States and Canada. We included NACDG data from 1994 through 2016; the methodology has been reported previously.[8] Patients were tested with the NACDG screening series (Chemotechnique, Vellinge, Sweden and AllergEAZE, SmartPractice, Calgary, Alberta, Canada); allergen composition and duration of testing for individual allergens varied. Allergens were applied with patch test chambers and Scanpor tape (SmartPractice, Phoenix, AZ). Readings were designated as +++ (very strong),

The trend of PPTRs over time was analyzed with a simple linear regression model, with the formula: Positive rate = $\beta_0 + \beta_1 \text{Time} + \varepsilon$. Regression diagnostics were performed to evaluate model assumptions. Preservatives tested for fewer than 6 cycles were excluded. The parameter estimate represented the average increase or decrease of the percentage of PPTR with 1 test cycle increase. The significance of tests was assessed at alpha equal to .05.

RESULTS

A total of 50,799 patients (mean age, 48 y; standard deviation, 16.9) were included. Of these, 33,901 patients (66.7% of total tested) had at least 1 PPTR. In addition, 11,338 patients had at least 1 PPTR to preservatives; this represented 22.3% of the total tested population and 33.4% of patients with at least 1 PPTR. The demographic characteristics are summarized in Table I.

Patients with preservative PPTRs were more likely to be male, Caucasian, and older than 40 years and have hand dermatitis compared to those with nonpreservative PPTR (Table I). Patients with preservative PPTRs were less likely to be black or Hispanic and to have occupational dermatitis, facial involvement, hay fever, and asthma. There were no statistical differences between the 2 groups with respect to Asian race, history of eczema, or leg dermatitis.

Preservatives and test cycles are summarized in Table II. Pooled preservative patch test results are summarized in Table III. There were 24,114 PPTRs to preservatives among 11,338 patients. Preservatives with the highest positive reaction frequencies were methylisothiazolinone (MI) 0.2% aqueous (aq) (12.2%), formaldehyde 2% aq (7.8%) and 1% aq

(7.8%), quaternium-15 2% petrolatum (pet) (7.7%), and methyldibromo glutaronitrile (MDBGN)/ phenoxyethanol 2% pet (5.1%). The lowest frequencies of PPTRs included paraben mix 12% pet (1%), iodopropynyl butylcarbamate (IPBC) 0.1% pet (0.4%), benzyl alcohol 1% pet (0.3%), and phenoxyethanol 1% pet (0.2%). Several preservatives, benzalkonium chloride 0.1% aq, methylchloroisothiazolinone (MCI)/MI 0.01% pet, MI 0.2% aq, formaldehyde 2% aq, and phenoxyethanol 1% pet, were tested for limited cycles.

Preservative trends over time are documented in Fig 1, *A* and *B*. SPIN trends are plotted in Fig 1, *C* and *D*. Interestingly, SPIN trends mirror allergen percentage trends.

The linear regression model of trends recorded parameter estimates (Table IV); these represent the average increase or decrease in reactions with each test cycle increase. This model identified only 1 preservative, MCI/MI 0.01% aq ($P < .005$) with a significant increase in PPTRs. Formaldehyde 1% aq and several formaldehyde releasers (FRs) (quaternium-15, diazolidinyl urea, imidazolidinyl urea, dimethylol dimethyl [DMDM] hydantoin, and 2-bromo-2-nitropropane-1,3-diol) showed a decreasing trend, with quaternium-15 2% pet showing the largest decrease ($P < .001$). MDBGN/ phenoxyethanol 2% pet ($P < .001$) and paraben mix 12% pet ($P = .038$) also showed a significant trend for decrease in PPTRs. MI 0.2% aq (first cycle, 10.9%; last cycle, 13.4%) and formaldehyde 2% aq (first cycle, 7%; last cycle, 8.4%) both showed considerable increases but were not included in the linear regression model because they were tested for only 2 cycles.

DISCUSSION

This study examined preservative allergy trends in North America. Patients with preservative PPTRs were more likely to be older than 40 years and male and to have hand involvement. Fasth et al[10] reported demographics for 8463 patients with contact sensitivity to formaldehyde and FRs (2007-2016), compared them to 8350 patients without reactions, and found that patients with PPTRs to formaldehyde 1% aq (83.5%) and diazolidinyl urea 2% pet (90.2%) were more likely to be older than 40 years.[10] Similar to our study, patients with PPTRs to formaldehyde 1% aq (63%), formaldehyde 2% aq (50%), quaternium-15 1% pet (68.1%), diazolidinyl urea 2% pet (61%), and DMDM hydantoin 2% aq (61.9%) were more likely to have hand dermatitis. However, they identified only 1 preservative, formaldehyde 2% aq (22.4% male patients allergic vs 31.5% male patients not allergic) with a difference in

Table I. Demographics*

| | | | PPTR to preservatives | | |
Characteristics	Total tested population, n (%) (N = 50,799)	Any PPTR, n (%) (n = 33,901)	Yes, n (%) (n = 11,338)	No, n (%) (n = 22,563)	OR (95% CI)
Male	17,119 (33.7)	10,746 (31.7)	4210 (37.1)	6536 (29.0)	1.45 (1.38-1.52)
Race					
Caucasian	43,653 (86.4)	29,187 (86.6)	9977 (88.6)	19,210 (85.6)	1.30 (1.22-1.40)
Black	3042 (6.0)	1969 (5.8)	513 (4.6)	1456 (6.5)	0.69 (0.62-0.76)
Asian	2186 (4.3)	1501 (4.5)	475 (4.2)	1026 (4.6)	0.92 (0.82-1.03)
Hispanic	924 (1.8)	564 (1.7)	165 (1.5)	399 (1.8)	0.82 (0.68-0.99)
Occupational[†]	N/A	3570 (10.5)	721 (6.4)	2286 (10.1)	0.60 (0.55-0.66)
Atopic triad					
Hay fever	14,131 (27.9)	9356 (27.7)	2994 (26.5)	6362 (28.3)	0.91 (0.87-0.96)
Eczema	11,054 (21.8)	7375 (21.8)	2405 (21.3)	4970 (22.1)	0.96 (0.90-1.01)
Asthma	7269 (14.3)	4761 (14.1)	1509 (13.4)	3252 (14.4)	0.91 (0.85-0.97)
Hand dermatitis	12,319 (24.3)	8524 (25.2)	3280 (28.9)	5244 (23.3)	1.34 (1.28-1.41)
Leg dermatitis	2103 (4.1)	1375 (4.1)	472 (4.2)	903 (4.0)	1.04 (0.93-1.17)
Face dermatitis	7965 (15.7)	5419 (16.0)	1662 (14.7)	3757 (16.7)	0.86 (0.81-0.92)
Age >40 y	33,931 (66.8)	23,081 (68.1)	8432 (74.4)	14,649 (64.9)	1.57 (1.49-1.65)
Positivity rate (≥1 PPTR)	33,901 (66.7)	N/A	N/A	N/A	N/A

CI, Confidence interval; *N/A*, not applicable; *OR*, odds ratio; *PPTR*, positive patch test reaction.
*Only patients with nonmissing values for these variables were included.
[†]Calculated only for patients with PPTRs.

sex prevalence. Buckley et al[11] reported increasing fragrance allergy with age and theorized that this was due to repeat environmental exposure and age-related susceptibility; perhaps a similar phenomenon exists for preservatives. It is not surprising that hand dermatitis was more common in preservative-positive patients as compared to those with nonpreservative PPTRs, given the ubiquitous exposure of the hands to products. Patients with PPTRs to preservatives as compared to nonpreservatives were more likely to be male. This could simply be because female patients had greater numbers of positive results to nonpreservatives allergens, or it could be related to differences in occupational exposures, hobbies, or other factors.

Common preservative allergens

MI. Of the tested preservatives, MI 0.2% aq had the highest overall PPTRs (12.2%). Cycle frequencies increased from 10.9% (2013-2014) to 13.4% (2015-2016).[8,12] The 2015-2016 SPIN of 685, the highest recorded, confirms that MI usually has clinical relevance.[8] These data are consistent with international studies of MI 0.2% aq: Mayo Clinic, 13.6% (2011-2015, n = 964); International Contact Dermatitis Research Group, 7.3% (2014, n = 3865); and Australia, 14.5% (2011-2017, n = 2787).[13-15] Because of this epidemic of contact allergy, MI was named the 2013 Allergen of the Year by the American Contact Dermatitis Society (ACDS).[16]

In 2016, the European Commission banned MI in leave-on products and allowed a maximum of 15 parts per million (ppm) in rinse-off products.[17] Similarly, Canada's Cosmetic Ingredient Hotlist prohibits MI in leave-on products and mandates a maximum of 15 ppm in rinse-off products.[18] In comparison, in 2010, the US−based Cosmetic Ingredient Review (CIR) panel recommended a maximum of 100 ppm.[19] The 2014 CIR update recommended a maximum of 100 ppm in rinse-off products and described MI as "safe in leave-on products when formulated to be non-sensitizing based on the results of a quantitative risk assessment (QRA) or similar methodology."[20(p8)] Groups in Australia and the United Kingdom have noted recent downtrends in PPTRs to MI.[15,21] It is possible that this is related to regulations; this has not been identified in North America.

Before 2013, the NACDG tested MI only via MCI/MI 0.01% aq. This hapten includes 76.7% MCI and 23.3% MI; at this formulation, MI is tested at 0.002% aq. Higher test concentrations are required to detect sensitization[22]; MI 0.2% aq is recommended. Because the Thin-Layer Rapid Use Epicutaneous Patch (TRUE) Test (Smartpractice) includes MCI/MI but not MI, users should add MI 0.2% aq to confirm contact allergy.[23] Patients with MI allergy should avoid any product that contains MI, regardless of reported MI product concentration.

MCI/MI. Reaction frequencies were 3.8% for MCI/MI 0.01% aq and 3.2% for MCI/MI 0.01% pet,

Table II. Preservatives tested 1994 to 2016*

Preservative type	1994-1996	1996-1998	1998-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016
Formaldehyde and formaldehyde releasers	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq	Formaldehyde 1% aq Formaldehyde 2% aq	Formaldehyde 1% aq Formaldehyde 2% aq
	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1, 3-diol 0.5% pet	2-Bromo-2-nitropropane-1,3-diol 0.5% pet
	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet Diazolidinyl urea 1% aq	Diazolidinyl urea 1% pet	Diazolidinyl urea 1% pet	Diazolidinyl urea 1% pet	Diazolidinyl urea 1% pet
	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet	DMDM hydantoin 1% pet
	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq	DMDM hydantoin 1% aq				
	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet Imidazolidinyl urea 2% aq	Imidazolidinyl urea 2% pet	Imidazolidinyl urea 2% pet	Imidazolidinyl urea 2% pet	Imidazolidinyl urea 2% pet
	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet	Quaternium-15 2% pet
Isothiazolinones	MCI/MI 0.01% aq MCI/MI 0.01% pet	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq	MCI/MI 0.01% aq
										Methylisothiazolinone 0.2% aq	Methylisothiazolinone 0.2% aq

Continued

Table II. Cont'd

Preservative type	1994-1996	1996-1998	1998-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016
Others				Benzalkonium chloride 0.1% aq							
							Benzyl alcohol 1% pet	Benzyl alcohol 1% pet	Benzyl alcohol 1% pet		
		IPBC 0.1% pet		IPBC 0.1% pet	IPBC 0.1% pet	IPBC 0.1% pet					
						IPBC 0.5% pet	IPBC 0.5% pet	IPBC 0.5% pet	IPBC 0.5% pet	IPBC 0.5% pet	IPBC 0.5% pet
		MDBGN/ phenoxyethanol 2.5% pet[†]	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet	MDBGN/ phenoxyethanol 2% pet
	MDBGN/ phenoxyethanol 1% pet	MDBGN/ phenoxyethanol 1% pet	MDBGN 0.4% pet[‡]	MDBGN 0.4% pet[‡]							
	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet	Paraben mix 12% pet
	Phenoxyethanol 1% pet			Phenoxyethanol 1% pet							

aq, Aqueous; *DMDM*, dimethylol dimethyl; *IPBC*, iodopropynyl butylcarbamate; *MCI*, methylchloroisothiazolinone; *MDBGN*, methyldibromo glutaronitrile; *MI*, methylisothiazolinone; *pet*, petrolatum.

*North American Contact Dermatitis Group allergens are tested in 2-year cycles. The table includes preservatives tested from 1994 through 2016.

[†]Included in analysis for MDBGN/phenoxyethanol 2%.

[‡]Included in analysis for MDBGN/phenoxyethanol 1%.

Table III. Percentage, strength, and clinical relevance of positive patch test reactions to preservatives, 1994 through 2016[*]

Preservative	N	Final interpretation: allergic, n (%)[†]	Second read code, n (%)[†]				Relevance, n (%)[‡]			
			+++	++	+	+/−	Definite	Probable	Possible	Past
MI 0.2% (2000 ppm) aq	10,613	1294 (12.2)	364 (26.5)	411 (29.9)	443 (32.2)	147 (10.7)	88 (6.9)	626 (48.8)	470 (36.6)	28 (2.2)
Formaldehyde 2% aq	10,613	826 (7.8)	101 (8.4)	329 (27.4)	480 (39.9)	187 (15.6)	6 (0.7)	184 (22.3)	481 (58.3)	17 (2.1)
Formaldehyde 1% aq	50,050	3880 (7.8)	251 (5.7)	1278 (29.0)	2184 (49.5)	655 (14.8)	77 (2.0)	847 (22.1)	2112 (55.1)	95 (2.5)
Quaternium-15 2% pet	50,042	3827 (7.7)	665 (16.4)	1319 (32.6)	1620 (40.0)	437 (10.8)	148 (3.9)	1139 (30.0)	2056 (54.2)	139 (3.7)
MDBGN/phenoxyethanol 2% pet	48,550	2491 (5.1)	102 (2.8)	556 (15.2)	1710 (46.7)	1121 (30.6)	69 (2.8)	493 (20.1)	1102 (45.0)	93 (3.8)
Benzalkonium chloride 0.1% aq[§]	4892	212 (4.3)	3 (0.7)	54 (12.0)	173 (38.4)	138 (30.7)	2 (1.0)	11 (5.2)	44 (21.0)	18 (8.6)
IPBC 0.5% pet	28,676	1086 (3.8)	51 (2.6)	190 (9.6)	751 (37.9)	808 (40.8)	28 (2.6)	358 (33.6)	515 (48.4)	15 (1.4)
MCI/MI 0.01% (100 ppm) aq	50,588	1907 (3.8)	170 (8.4)	743 (36.8)	910 (45.1)	182 (9.0)	152 (8.1)	800 (42.4)	739 (39.2)	68 (3.6)
MCI/MI 0.01% (100 ppm) pet[‖]	2012	65 (3.2)	0 (0)	26 (34.2)	37 (48.7)	13 (17.1)	10 (15.4)	32 (49.2)	15 (23.1)	5 (7.7)
MDBGN/phenoxyethanol 1% pet	16,762	499 (3.0)	11 (1.7)	103 (15.5)	306 (46.0)	235 (35.3)	28 (5.7)	74 (15.0)	220 (44.7)	7 (1.4)
Diazolidinyl urea 1% pet	50,638	1393 (2.8)	118 (7.9)	363 (24.4)	753 (50.6)	250 (16.8)	84 (6.1)	394 (28.7)	774 (56.3)	34 (2.5)
Diazolidinyl urea 1% aq	31,424	833 (2.7)	45 (5.0)	202 (22.3)	483 (53.2)	173 (19.1)	40 (4.9)	264 (32.1)	425 (51.7)	12 (1.5)
2-Bromo-2-nitropane-1,3-diol 0.5% pet	50,623	1249 (2.5)	83 (5.2)	273 (17.1)	832 (52.0)	387 (24.2)	21 (1.7)	161 (13.2)	696 (56.9)	38 (3.1)
Imidazolidinyl urea 2% pet	50,616	1199 (2.4)	121 (9.4)	301 (23.3)	639 (49.4)	233 (18.0)	49 (4.1)	334 (28.1)	703 (59.2)	31 (2.6)
DMDM hydantoin 1% pet	50,634	997 (2.0)	45 (4.2)	210 (19.4)	57 (53.0)	249 (23.0)	52 (5.3)	292 (29.5)	572 (57.8)	22 (2.2)
Imidazolidinyl urea 2% aq	31,542	576 (1.8)	41 (6.1)	108 (16.1)	357 (53.1)	161 (23.9)	33 (5.8)	167 (29.6)	291 (51.5)	14 (2.5)
DMDM hydantoin 1% aq	31,417	520 (1.7)	17 (2.8)	121 (20.2)	308 (51.4)	150 (25.0)	26 (5.0)	144 (28.0)	280 (54.4)	14 (2.7)
Paraben mix 12% pet	50,645	527 (1.0)	38 (5.3)	153 (21.5)	303 (42.5)	203 (28.5)	49 (9.5)	211 (40.7)	207 (40)	14 (2.7)
IPBC 0.1% pet	20,238	81 (0.4)	4 (3.0)	15 (11.1)	56 (41.5)	49 (36.3)	5 (6.3)	17 (21.5)	40 (50.6)	1 (1.3)
Benzyl alcohol 1% pet	13,628	44 (0.3)	1 (1.5)	8 (12.1)	39 (59.1)	16 (24.2)	7 (16.3)	17 (39.5)	10 (23.3)	1 (2.3)
Phenoxyethanol 1% pet	6900	12 (0.2)	1 (3.7)	3 (11.1)	9 (33.3)	11 (40.7)	1 (8.3)	0 (0.0)	6 (50.0)	1 (8.3)

aq, Aqueous; *DMDM*, dimethylol dimethyl; *IPBC*, iodopropynyl butylcarbamate; *MCI*, methylchloroisothiazolinone; *MDBGN*, methyldibromo glutaronitrile; *MI*, methylisothiazolinone; *pet*, petrolatum; *ppm*, parts per million.

*First and second readings were designated as +++ (very strong), ++ (strong), + (mild), +/- (weak/doubtful), irritant, and negative in accordance with North American Contact Dermatitis Group criteria. The final interpretation for each allergen was coded as allergic, unknown, irritant, or negative. For each reaction designated allergic, clinical relevance was described as definite, probable, possible, and past. Discrepancies in the final interpretation and second read code will differ due to interpretation of results.

[†]Excludes unknown/uncertain.

[‡]Excludes those with *not tested* or *not applicable*. Percentages were calculated for patients who had positive patch test reactions. The relevance category *unknowns* was included in the denominator for the percentage calculation. However, *unknowns* is not shown.

[§]Allergen tested only during the 2001-2002 cycle.

[‖]Allergen tested only during the 1994-1996 cycle.
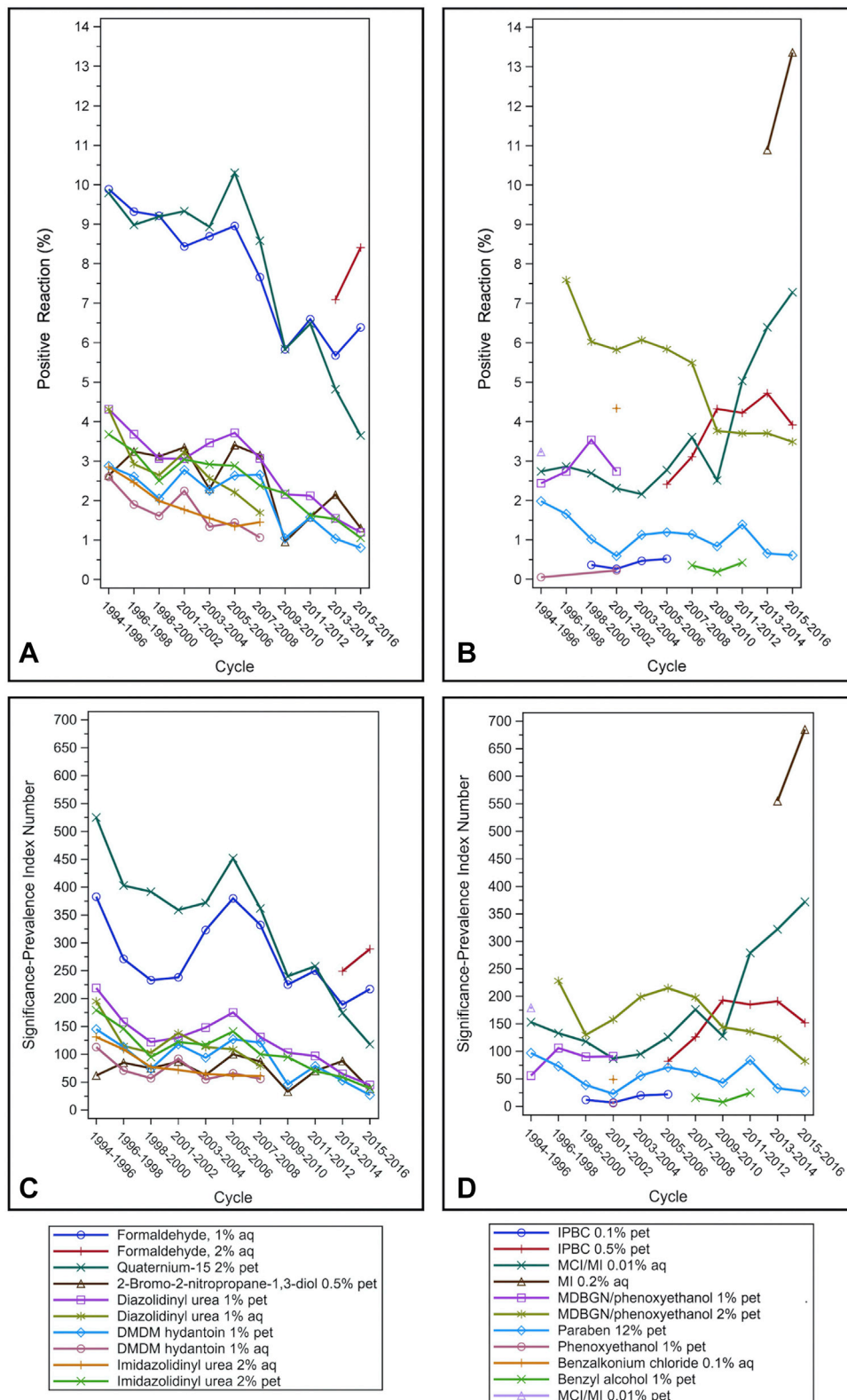
Fig 1. Trends of PPTRs for preservatives, 1994 through 2016. **A**, PPTRs for formaldehyde and formaldehyde-releasing preservatives. **B**, PPTRs for isothiazolinones, parabens, and other preservatives. **C**, Significant-prevalence index number for formaldehyde and formaldehyde-releasing preservatives. **D**, Significant-prevalence index number for isothiazolinones, parabens, and other preservatives. *aq*, Aqueous; *DMDM*, dimethylol dimethyl; *IPBC*, iodopropynyl butylcarbamate; *MCI*, methylchloroisothiazolinone; *MDBGN*, methyldibromo glutaronitrile; *MI*, methylisothiazolinone; *pet*, petrolatum; *PPTR*, positive patch test reaction.

Table IV. Linear regression analysis of positive patch test reactions, 1994 to 2016*

Preservative	Parameter estimate, %, (95% CI)	*P* value
MCI/MI 0.01% (100 ppm) aq	0.42 (0.17, 0.66)	.005
IPBC 0.5% pet	0.35 (−0.07, 0.76)	.080
Paraben mix 12% pet	−0.08 (−0.16, −0.01)	.038
2-Bromo-2-nitropropane-1,3-diol 0.5% pet	−0.18 (−0.33, −0.03)	.024
DMDM hydantoin 1% pet	−0.19 (−0.29 to −0.09)	.002
DMDM hydantoin 1% aq	−0.21 (−0.37 to −0.05)	.021
Imidazolidinyl urea 2% pet	−0.23 (−0.29 to −0.16)	<.001
Imidazolidinyl urea 2% aq	−0.24 (−0.34 to −0.15)	.001
Diazolidinyl urea 1% pet	−0.26 (−0.36 to −0.17)	<.001
Diazolidinyl urea 1% aq	−0.33 (−0.55 to −0.12)	.011
Formaldehyde 1% aq	−0.42 (−0.56 to −0.28)	<.001
MDBGN/phenoxyethanol 2% pet	−0.43 (−0.56 to −0.30)	<.001
Quaternium-15 2% pet	−0.57 (−0.84 to −0.31)	<.001

aq, Aqueous; *CI*, confidence interval; *DMDM*, dimethylol dimethyl; *IPBC*, iodopropynyl butylcarbamate; *MCI*, methylchloroisothiazolinone; *MDBGN*, methyldibromo glutaronitrile; *MI*, methylisothiazolinone; *pet*, petrolatum; *ppm*, parts per million.
*The trend of positive patch test reactions over time was analyzed with a simple linear regression model: Positive rate = $\beta_0 + \beta_1$Time + ε.

with a significant upward trend for MCI/MI 0.01% aq (2009-2010 to 2015-2016). MCI/MI had its highest frequency in 2015-2016 (7.3%).[8]

Similar to MI, increasing reactions to MCI/MI are an international phenomenon. On September 30, 2019, the US CIR panel described MCI/MI as "safe in cosmetics when formulated to be non-sensitizing, based on the results of a QRA or similar methodology,"[24(p8)] with a recommendation of less than 15 ppm for rinse-off products and less than 7.5 ppm for leave-on products. The Cosmetic Ingredient Hotlist prohibits MCI/MI in leave-on products, with a maximum of 15 ppm in rinse-off products[18]; when MCI/MI and MI are formulated together, the total concentration of the combined chemicals may not exceed 15 ppm in rinse-off products. As with MI, patients with MCI/MI allergy should avoid products containing MCI/MI.

Formaldehyde and FRs. Formaldehyde (1% aq and 2% aq) and quaternium-15 2% pet had the highest frequencies of formaldehyde-related PPTRs (7.8%, 7.8%, and 7.7%, respectively). Linear regression analysis showed that formaldehyde 1% aq and FR had statistically significant decreasing trends. Therefore, the high PPTRs to formaldehyde and quaternium-15 over the study period do not reflect current trends for these preservatives. Europe has experienced a similar downward trend.[10]

PPTRs to formaldehyde and FRs are more frequent in North America than in Europe, where reports of PPTRs include formaldehyde 2% at 2.4% to 3.3% and FR at less than 1%.[25-27] The reason for these discrepancies is unknown; potential contributors may be differences in patch test technique[28] and investigator interpretation of results.[29] It has also

been argued that variances may be due to regulatory differences, even though the required (European Union) and recommended (United States) maximum concentrations of formaldehyde and FRs in cosmetic products are almost identical, with the exceptions of slightly higher US allowances for imidazolidinyl urea (0.6% European Union; 1% United States) and DMDM hydantoin (0.6% European Union; ≤0.8% United States).[30-35] One might also theorize that continental differences in PPTRs are due to divergent rates of preservative utilization in products. However, a 2010 study identified a similar number of FRs in US-based cosmetic products (23.8%) versus Netherlands products (24.6%), and by 2017, FRs were present in only 9.9% of products catalogued by Contact Allergen Management Program.[36,37] This conversation is not complete without a final caution that undeclared formaldehyde has been identified in North American and European consumer products; for this reason, our ability to comprehensively understand consumer formaldehyde and FR exposure remains incomplete.[38,39]

The ideal patch test allergen identifies the highest number of relevant PPTRs with the lowest possible irritant reactions. Formaldehyde 2% aq identifies more PPTRs than formaldehyde 1% aq, with similar irritant frequencies.[26,27,40] Importantly, 2% aq should be aliquoted with a micropipette, when possible, to avoid irritant reactions.[28]

MDBGN. MDBGN/phenoxyethanol 2% pet, with MDBGN the likely allergen, had an overall higher PPTR prevalence (5.1%) compared to several other preservatives, but prevalence has significantly decreased over time. For comparison, in the Mayo Clinic study (2011-2015), the MDBGN 0.5%

pet prevalence was 4.3%,[13] and in Europe, Giménez-Arnau et al (2009-2012) found the MDBGN/phenoxyethanol 1.5% pet prevalence to be 2.04%.[25] MDBGN was originally marketed as a less-sensitizing alternative to formaldehyde and MCI/MI. However, numerous reports highlighted its sensitizing potential, resulting in more stringent regulations and a decreased frequency of PPTRs in Europe beginning in the early 2000s.[41,42] The United States allows up to 0.025% MDBGN in leave-on products and 0.06% in rinse-off products.[43] A 2017 Contact Allergen Management Program database analysis identified MDBGN in only 0.02% of products.[37] The decreasing trend for PPTRs may be due to the fact that MDBGN is now only rarely used as a preservative in personal care products.

Uncommon preservative allergens

Parabens. Parabens are inexpensive, odorless, colorless, and biodegradable.[44] Because of their low prevalence of allergy despite pervasive consumer concerns, parabens were selected as the 2019 ACDS (Non)Allergen of the Year.[45]

In this study, the overall reaction frequency to paraben mix 12% pet was 1%. Like the formaldehyde preservatives, paraben PPTRs have steadily declined from 2% in 1994 to 1996 to 0.6% in 2015 to 2016. A consistent trend is also observed in the European population, with recent estimated paraben PPTR ranges of 0.5% to 1%.[5,25]

Parabens are tightly regulated in Europe, with a ban on isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben since 2014 and a limit on the combined concentration of propylparaben and butylparaben (0.19%) since 2015.[1] In comparison, the US CIR panel states that 20 of 21 reviewed parabens are recommended as safe for use in cosmetic products when used at a combined concentration of up to 0.8%; data were insufficient to determine the safety of benzylparaben.[46] Parabens are regularly used as preservatives in US-based personal products; in 2017, parabens were present in 20.8% of ACDS Contact Allergen Management Program personal products.[37]

Benzyl alcohol and phenoxyethanol. Two other preservatives had consistently low reactions: benzyl alcohol 1% pet (0.3%) and phenoxyethanol 1% pet (0.2%). Few large series report the reaction frequencies to these preservatives. However, Schnuch et al[6] (1996-2009, Europe) documented benzyl alcohol 1% pet as 0.28% (n = 79,770) and phenoxyethanol 1% pet as 0.24% (n = 6932); these numbers coincide with our results. Phenoxyethanol was the most commonly identified preservative (23.9%) in the 2017 ACDS

Contact Allergen Management Program database. Benzyl alcohol came in at number 4, present in 12.7% of products.[37]

Both benzyl alcohol 10% and phenoxyethanol 1% pet were added to the 2019/2020 NACDG screening series. Benzyl alcohol was added because of its increasing use in products. Phenoxyethanol was included because of its frequent use in cosmetic products and to better differentiate MDBGN versus phenoxyethanol in MDBGN/phenoxyethanol reactions. The data show that these are rare allergens.

IPBC

Discussion of IPBC is challenging, because although IPBC 0.1% had one of the lowest reaction frequencies at 0.4%, and although IPBC 0.5% pet does not represent one of the most common preservative allergens (3.8%), IPBC 0.5% pet did, in fact, have a marginal increase in reactions over time. Directly comparable data are not available, because other patch test groups test IPBC at lower concentrations (Mayo Clinic and Europe, 0.1% to 0.2%).[13,25]

Because IPBC is a known marginal irritant,[47] it is possible that the higher reported reactions in North America are due to false positive reactions; ongoing and additional studies are needed. Stricter regulations for the use of IPBC in cosmetics in Europe, with a maximum concentration of 0.02% in rinse-off products and 0.01% in leave-on products, could also explain differences in reaction frequencies between North America and Europe.[13,25]

Limitations

The interpretations of patch test reactions and other collected variables are dependent on clinical judgment. Results may be prone to referral population selection bias; results may not be representative of the general dermatology population or the population at large.

CONCLUSION

The most common preservative allergens were MI, formaldehyde, quaternium-15, and MDBGN/phenoxyethanol. Parabens, benzyl alcohol, IPBC 0.1%, and phenoxyethanol had consistently low reactions. There was a significant increasing trend for MCI/MI; MI and formaldehyde 2% also increased. Formaldehyde and FRs had significant downward trends, as did MDBGN/phenoxyethanol and parabens.

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