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Contact Dermatitis Associated with Preservatives: Retrospective Analysis of North American Contact Dermatitis Group Data 1994-2016

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Abstract

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 (PPTR), clinical relevance and trends for preservatives tested by the North American Contact Dermatitis Group (NACDG).

Methods—We conducted retrospective cross-sectional analysis of NACDG patch testing results of preservatives from 1994–2016.

Results—50,799 patients were tested; 11,338 (22.3%) had a PPTR to ≥1 preservative. The most frequent reactions were to methylisothiazolinone (MI) 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 (MDBGN/PE) 2% pet (5.1%). 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%) had the lowest PPTRs. Linear regression analysis of preservatives tested revealed that only MCI/MI 0.01% aq (parameter estimate (PE) 0.42; CI 0.17–0.66; $p<0.005$) had a significant increase in PPTRs over time.

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

Conclusion—This large North American study provides insight on preservative PPTRs and trends from 1994–2016.

Keywords

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

Introduction

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 due to 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.

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 1994–2016; methodology has been reported previously.[8] Patients were tested with the NACDG screening series (Chemotechnique, Sweden; Allergeaze, Smartpractice, Canada); allergen composition and duration of testing for individual allergens varied. Allergens were applied with patch test chambers (Smartpractice, USA) and Scanpor tape (Norgesplaster, Norway). Readings were designated as +++ (very strong), ++ (strong), +(mild), +/− (weak/doubtful), irritant and negative in accordance with NACDG criteria.[8] In addition, final interpretation for each allergen was determined and documented as allergic, unknown, irritant or negative. For each reaction designated allergic, investigators determined clinical relevance as definite, probable, possible or past.[8] For the purposes of this study, positive patch test reaction (PPTR) is defined as a final patch test interpretation of allergic.

Two subgroups were defined a priori: 1) those with a PPTR to ≥1 preservative (PP) and 2) those with PPTRs to only non-preservative allergens (other positive — OP); both groups excluded patients who had no PPTR.

Data were entered into Access or Excel (Microsoft, USA) and analyzed using SAS 9.4 (SAS Institute Incorporated, USA). 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. 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] Trend of PPTRs over time was analyzed with a simple linear regression model, with the formula: $Positive\ rate = \beta_0 + \beta_1 Time + \varepsilon$. 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 one test cycle increase. Significance of tests was assessed at alpha = 0.05.

Results

50,799 patients (mean age 48 years [SD 16.9]) were included. 33,901 patients (66.7% of total tested) had at least one PPTR. 11,338 subjects had ≥1 PPTR to preservatives; this represented 22.3% of the total tested population and 33.4% of subjects with ≥1 PPTR. Demographic characteristics are summarized in Table 1.

Patients with preservative PPTRs were more likely to be male, Caucasian, > 40 years and have hand dermatitis as compared to those with non-preservative PPTR (Table 1). Preservative-positive patients were less likely to be Black, Hispanic, and have occupational

dermatitis, facial involvement, hay fever and asthma. There were no statistical differences between the two groups with respect to Asian race, history of eczema, or leg dermatitis.

Preservatives and test cycles are summarized in Table 2. Pooled preservative patch test results are summarized in Table 3. There were 24,114 PPTRs to preservatives among 11,339 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/methylisothiazolinone (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 Figure 1A and B. SPIN trends are plotted in Figure 1C and D. Interestingly, SPIN trends mirror allergen percentage trends.

The linear regression model of trends recorded parameter estimates (PE) (Table 4); these represent the average increase or decrease in reactions with each test cycle increase. This model identified only one preservative, MCI/MI 0.01% aq ($p<0.005$) with a significant increase in PPTRs. Formaldehyde 1% aq and several formaldehyde releasers (FR) (quaternium-15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol) demonstrated a decreasing trend, with quaternium-15 2% pet showing the largest decrease ($p<0.001$). MDBGN/phenoxyethanol 2% pet ($p<0.001$) and paraben mix 12% pet ($p=0.038$) 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 as they were only tested for two cycles.

Discussion

This study examined preservative allergy trends in North America. Patients with preservative PPTRs were more likely to be age >40 years, male, and have hand involvement. Fasth reported demographics for 8463 patients with contact sensitivity to formaldehyde and FR (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 >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 one preservative, formaldehyde 2% aq (22.4% males allergic vs 31.5% males not allergic) with a difference in sex prevalence. Buckley reported increasing fragrance allergy with age and theorized that this was due to repeat environmental exposure and age-related susceptibility;[11] 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 non-preservative PPTRs, given the

ubiquitous exposure of hands to products. Patients with PPTRs to preservatives, as compared to non-preservatives, were more likely to be male. This could simply be because females had greater numbers of positives to non-preservatives allergens, or could be related to differences in occupational exposures, hobbies, or other factors.

Common Preservative Allergens

Methylisothiazolinone—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 2015–16 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); Australia 14.5% (2011–2017, n=2787).[13–15] Due to 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 ppm in rinse-off products.[17] Similarly, Canada's Cosmetic Ingredient Hotlist (CIH) prohibits MI in leave-on products and mandates a maximum of 15ppm in rinse-off products.[18] In comparison, in 2010 the United States based Cosmetic Ingredient Review (CIR) panel *recommends* 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] 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.

Prior to 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 TRUE Test 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.

Methylcholoroisothiazolinone/methylisothiazolinone—Reaction frequencies were 3.8% for MCI/MI 0.01% aq and 3.2% for MCI/MI 0.01% pet, with a significant upward trend for MCI/MI 0.01% aq (2009–10 to 2015–16). MCI/MI had it's highest frequency 2015–2016 (7.3%).[8]

Similar to MI, increasing reactions to MCI/MI are an international phenomenon. On 9/30/2019, 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" with a recommendation of <15ppm for rinse-off products and <7.5ppm leave-on products.[24] The CIH prohibits MCI/MI in leave-on products, with a maximum of 15ppm in rinse-off products;[18] when MCI/MI and MI are formulated together, the total concentration of the combined chemicals may not exceed 15ppm in rinse-off products. As with MI, patients with MCI/MI allergy should avoid products containing MCI/MI.

Formaldehyde and Formaldehyde Releasers—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%). Linear regression analysis revealed 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]

Positive patch test reactions to formaldehyde and FRs are more frequent in North America than in Europe, where reports of PPTRs include formaldehyde 2% at 2.4–3.3% and FR at <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* (US) maximum concentrations of formaldehyde and FRs in cosmetic products are almost identical, with exceptions of slightly higher US allowances for imidazolidinyl urea (0.6% EU, 1% US) and DMDM hydantoin (0.6% EU, ≤0.8% US).[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%) vs Netherlands products (24.6%), and by 2017, FRs were only present in 9.9% of products catalogued by CAMP.[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 positive patch test reactions 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]

Methyldibromo glutaronitrile—MBDGN/phenoxyethanol 2% pet, with MDBGN the likely allergen, had an overall higher PPTR prevalence (5.1%) as compared to several other preservatives, but prevalence has significantly decreased over time. For comparison, Mayo Clinic (2011–2015) MDBGN 0.5% pet was 4.3%,[13] and in Europe, Giménez-Arnau (2009–2012) MDBGN/phenoxyethanol 1.5% pet was 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 US allows up to MDBGN 0.025% in leave-on products and 0.06% in rinse-off products[43]. A 2017 CAMP 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 1994–1996 to 0.6% in 2015–2016. A consistent trend is also observed in the European population, with recent estimated paraben PPTR ranges of 0.5%-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 safety of benzylparaben.[46] Parabens are regularly utilized as preservatives in US-based personal products; in 2017 parabens were present in 20.8% of ACDS CAMP 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 (1996–2009, Europe) documented benzyl alcohol 1% pet as 0.28% (n=79,770) and phenoxyethanol 1% pet as 0.24% (n=6932);[6] these numbers coincide with our results. Phenoxyethanol was the most commonly identified preservative (23.9%) in the 2017 ACDS CAMP database. Benzyl alcohol came in at #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 MBDGN vs phenoxyethanol in methyldibromo glutaronitrile/ phenoxyethanol reactions. The data demonstrate that these are rare allergens.

Iodopropynyl butylcarbamate

Discussion of iodopropynyl butylcarbamate 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%-0.2).[13,25]

As 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

Interpretation 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 population at large.

Conclusion

The most common preservative allergens were methylisothiazolinone, formaldehyde, quaternium-15 and methyldibromo glutaronitrile/phenoxyethanol. Parabens, benzyl alcohol, iodopropynyl butylcarbamate 0.1% and phenoxyethanol had consistently low reactions. There was a significant increasing trend for methylchloroisothiazolinone/ methylisothiazolinone; methylisothiazolinone and formaldehyde 2% also increased. Formaldehyde and FR had significant downward trends, as did methyldibromo glutaronitrile/phenoxyethanol and parabens.

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References

1. Deza G, Gimenez-Arnau AM. Allergic contact dermatitis in preservatives: current standing and future options. Curr Opin Allergy Clin Immunol. 2017;17(4):263–268. [PubMed: 28548971]
2. Sasseville D. Hypersensitivity to preservatives. Dermatol Ther. 2004;17(3):251–263. [PubMed: 15186371]
3. Yim E, Baquerizo Nole KL, Tosti A. Contact dermatitis caused by preservatives. Dermatitis. 2014;25(5):215–231. [PubMed: 25207684]
4. Cheng S, Leow YH, Goh CL, Goon A. Contact sensitivity to preservatives in Singapore: frequency of sensitization to 11 common preservatives 2006–2011. Dermatitis. 2014;25(2):77–82. [PubMed: 24603520]
5. Svedman C, Andersen KE, Brandao FM, et al. Follow-up of the monitored levels of preservative sensitivity in Europe: overview of the years 2001–2008. Contact Dermatitis. 2012;67(5):312–314. [PubMed: 23039007]
6. Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. Br J Dermatol. 2011;164(6):1316–1325. [PubMed: 21332463]
7. Yu SH, Sood A, Taylor JS. Patch Testing for Methylisothiazolinone and Methylchloroisothiazolinone-Methylisothiazolinone Contact Allergy. JAMA Dermatol. 2016;152(1):67–72. [PubMed: 26536492]
8. DeKoven JG, Warshaw EM, Zug KA, et al. North American Contact Dermatitis Group Patch Test Results: 2015–2016. Dermatitis. 2018;29(6):297–309. [PubMed: 30422882]
9. Maouad M, Fleischer AB Jr., Sherertz EF, Feldman SR. Significance-prevalence index number: a reinterpretation and enhancement of data from the North American contact dermatitis group. J Am Acad Dermatol. 1999;41(4):573–576. [PubMed: 10495378]
10. Fasth IM, Ulrich NH, Johansen JD. Ten-year trends in contact allergy to formaldehyde and formaldehyde-releasers. Contact Dermatitis. 2018;79(5):263–269. [PubMed: 30079600]
11. Buckley DA, Rycroft RJ, White IR, McFadden JP. The frequency of fragrance allergy in patch-tested patients increases with their age. Br J Dermatol. 2003;149(5):986–989. [PubMed: 14632803]

12. DeKoven JG, Warshaw EM, Belsito DV, et al. North American Contact Dermatitis Group Patch Test Results 2013–2014. Dermatitis. 2017;28(1):33–46. [PubMed: 27775967]
13. Veverka KK, Hall MR, Yiannias JA, et al. Trends in Patch Testing With the Mayo Clinic Standard Series, 2011–2015. Dermatitis. 2018;29(6):310–315. [PubMed: 30422883]
14. Isaksson M, Ale I, Andersen KE, et al. Multicenter Patch Testing With Methylisothiazolinone and Methylchloroisothiazolinone/Methylisothiazolinone Within the International Contact Dermatitis Research Group. Dermatitis. 2017;28(3):210–214. [PubMed: 28338542]
15. Flury U, Palmer A, Nixon R. The methylisothiazolinone contact allergy epidemic in Australia. Contact Dermatitis. 2018;79(3):189–191. [PubMed: 29761504]
16. Castanedo-Tardana MP, Zug KA. Methylisothiazolinone. Dermatitis. 2013;24(1):2–6. [PubMed: 23340392]
17. Gimenez-Arnau AM. Opinion of the Scientific Committee on Consumer safety (SCCS) - Opinion on the safety of the use of Methylisothiazolinone (MI) (P94), in cosmetic products (sensitisation only). Regul Toxicol Pharmacol. 2016;76:211–212. [PubMed: 26790577]
18. Cosmetic Ingredient Hotlist: Prohibited and Restricted Ingredients. https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html#tbl2. Accessed February 20, 2020.
19. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of methylisothiazolinone. Int J Toxicol. 2010;29(4 Suppl):187s–213s. [PubMed: 20634507]
20. Cosmetic Ingredient Review. Amended Safety Assessment of Methylisothiazolinone as Used in Cosmetics. https://www.cir-safety.org/sites/default/files/mthiaz092014FR_final.pdf. Published 2014. Accessed April 19, 2019.
21. Urwin R, Craig S, Latheef F, Wilkinson M. Methylisothiazolinone: the epidemic is declining - but not gone. Contact Dermatitis. 2017;76(5):301–302. [PubMed: 28386974]
22. Engfeldt M, Brared-Christensson J, Isaksson M, et al. Swedish Experiences From Patch Testing Methylisothiazolinone Separately. Acta Derm Venereol. 2015;95(6):717–719. [PubMed: 25474255]
23. T.R.U.E. TEST® Ready-to-Use Patch Test Panels. https://www.smartpractice.com/shop/wa/category?id=508222&m=SPA. Accessed January 9, 2020, 2020.
24. Review CI. Amended Safety Assessment of Methylisothiazolinone and Methylchloroisothiazolinone as Used in Cosmetics. https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/TR787.pdf. Accessed January 9, 2020.
25. Gimenez-Arnau AM, Deza G, Bauer A, et al. Contact allergy to preservatives: ESSCA* results with the baseline series, 2009–2012. J Eur Acad Dermatol Venereol. 2017;31(4):664–671. [PubMed: 27896884]
26. Ponten A, Aalto-Korte K, Agner T, et al. Patch testing with 2.0% (0.60 mg/cm 2) formaldehyde instead of 1.0% (0.30 mg/cm 2) detects significantly more contact allergy. Contact Dermatitis. 2013;68(1):50–53. [PubMed: 23035891]
27. Hauksson I, Ponten A, Gruvberger B, Isaksson M, Bruze M. Routine diagnostic patch-testing with formaldehyde 2.0% (0.6 mg/cm2) may be an advantage compared to 1.0%. Acta Derm Venereol. 2010;90(5):480–484. [PubMed: 20814622]
28. Ponten A, Bruze M. Formaldehyde. Dermatitis. 2015;26(1):3–6. [PubMed: 25581665]
29. Svedman C, Isaksson M, Bjork J, Mowitz M, Bruze M. 'Calibration' of our patch test reading technique is necessary. Contact Dermatitis. 2012;66(4):180–187. [PubMed: 22404193]
30. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R1223-20160812. Accessed January 16, 2020, 2020.
31. Boyer IJ, Heldreth B, Bergfeld WF, et al. Amended safety assessment of formaldehyde and methylene glycol as used in cosmetics. Int J Toxicol. 2013;32(6 Suppl):5s–32s.
32. Becker LC. Quaternium-15. Int J Toxicol. 2017;36(5_suppl2):52s. [PubMed: 29025332]
33. Annual review of cosmetic ingredient safety assessments: 2005/2006. Int J Toxicol. 2008;27 Suppl 1:77–142. [PubMed: 18569164]

34. Annual Review of Cosmetic Ingredient Safety Assessments--2001/2002. Int J Toxicol. 2003;22 Suppl 1:1–35.
35. Annual review of cosmetic ingredient safety assessments-2004/2005. Int J Toxicol. 2006;25 Suppl 2:1–89.
36. de Groot AC, Veenstra M. Formaldehyde-releasers in cosmetics in the USA and in Europe. Contact Dermatitis. 2010;62(4):221–224. [PubMed: 20236159]
37. Beene KM, Scheman A, Severson D, Reeder MJ. Prevalence of Preservatives Across All Product Types in the Contact Allergen Management Program. Dermatitis. 2017;28(1):81–87. [PubMed: 28098722]
38. Ham JE, Siegel PD, Maibach H. Undeclared formaldehyde levels in patient consumer products: formaldehyde test kit utility. Cutan Ocul Toxicol. 2019;38(2):112–117. [PubMed: 29719992]
39. Hauksson I, Ponten A, Isaksson M, Hamada H, Engfeldt M, Bruze M. Formaldehyde in cosmetics in patch tested dermatitis patients with and without contact allergy to formaldehyde. Contact Dermatitis. 2016;74(3):145–151. [PubMed: 26696132]
40. Isaksson M, Ale I, Andersen KE, et al. Patch Testing With Formaldehyde 2.0% (0.60 mg/cm2) Detects More Contact Allergy to Formaldehyde Than 1.0. Dermatitis. 2019;30(6):342–346. [PubMed: 31730552]
41. Schwensen JF, White IR, Thyssen JP, Menne T, Johansen JD. Failures in risk assessment and risk management for cosmetic preservatives in Europe and the impact on public health. Contact Dermatitis. 2015;73(3):133–141. [PubMed: 26184096]
42. Johansen JD, Veien N, Laurberg G, et al. Decreasing trends in methyldibromo glutaronitrile contact allergy--following regulatory intervention. Contact Dermatitis. 2008;59(1):48–51. [PubMed: 18537990]
43. Cosmetic Ingredient Review (Methyldibromo Glutaronitrile and Polyvinyl Acetate) https://www.cir-safety.org/sites/default/files/RR_buff_w_tabs.pdf. Accessed January 19, 2020, 2020.
44. Castelain F, Castelain M. Parabens: a real hazard or a scare story? Eur J Dermatol. 2012;22(6):723–727. [PubMed: 23131320]
45. Fransway AF, Fransway PJ, Belsito DV, et al. Parabens: Contact (Non)Allergen of the Year. Dermatitis. 2018.
46. Review CI. Amended Safety Assessment of Parabens as Used in Cosmetics https://www.cir-safety.org/sites/default/files/Parabens_0.pdf. Accessed January 16, 2020.
47. Warshaw EM, Raju S, DeKoven JG, et al. Positive patch test reactions to carba mix and iodopropynyl butylcarbamate: data from the North American Contact Dermatitis Group, 1998–2008. Dermatitis. 2013;24(5):241–245. [PubMed: 24030371]

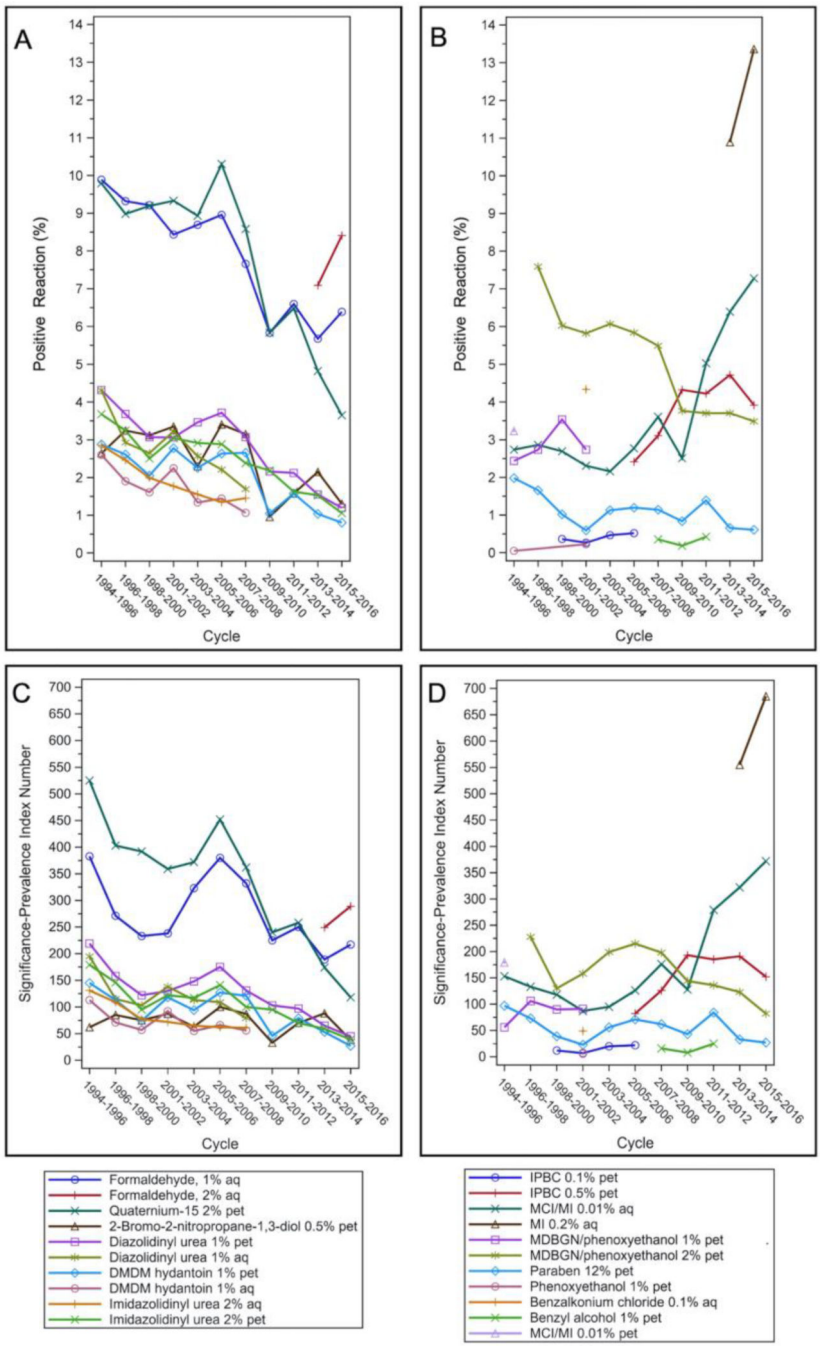

Figure 1 —. Trends of PPTR for Preservatives 1994 — 2016.

(A) Positive patch test reactions for formaldehyde and formaldehyde releasing preservatives.

(B) Positive patch test reactions for isothiazolinones, parabens and other preservatives.

(C) Significance-prevalence index number (SPIN) for formaldehyde and formaldehyde releasing preservatives.

(D) SPIN for isothiazolinones, parabens and other preservatives.

SPIN = Prevalence*(1*Definite+0.66*Probable+0.33*Possible).

Abbreviations: Aq, aqueous; Pet, petrolatum; MI, methylisothiazolinone; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; IPBC, iodopropynyl butylcarbamate; DMDM, dimethylol dimethyl.

Table 1

Demographics*

Characteristic	Total Tested Population n=50799 Number (%)	Any Positive Patch Test Reaction n=33901 Number (%)	Positive Patch Test Reaction to Preservatives		
			Yes n=11338 Number (%)	No n=22563 Number (%)	OR (95% CI)
Male	17119 (33.7)	10746 (31.7)	4210 (37.1)	6536 (29.0)	1.45 (1.38, 1.52)
Race					
Caucasian	43653 (86.4)	29187 (86.6)	9977 (88.6)	19210 (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	14131 (27.9)	9356 (27.7)	2994 (26.5)	6362 (28.3)	0.91 (0.87, 0.96)
Eczema	11054 (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	12319 (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 years	33931 (66.8)	23081 (68.1)	8432 (74.4)	14649 (64.9)	1.57 (1.49, 1.65)
Positivity rate (≥1PPTR)	33901 (66.7)	n/a	n/a	n/a	n/a

*Only patients with non-missing values for these variables were included

#Calculated only for patients with positive patch test reactions.

1–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016
naldehyde 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 2% aq
romo-2- opropane-1,3-diol 0.5%	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
olidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet	Diazolidinyl Urea 1% pet
olidinyl Urea 1% aq	Diazolidinyl Urea 1% aq	Diazolidinyl Urea 1% aq	Diazolidinyl Urea 1% aq				
DM 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
DM Hydantoin 1% aq	DMDM Hydantoin 1% aq	DMDM Hydantoin 1% aq	DMDM Hydantoin 1% aq				
dazolidinyl Urea 2%	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet	Imidazolidinyl Urea 2% pet
dazolidinyl Urea 2% aq	Imidazolidinyl Urea 2% aq	Imidazolidinyl Urea 2% aq	Imidazolidinyl Urea 2% aq				
aternium-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
hylchloroisothiazolone/ hylisothiazolone 0.01%	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq	Methylchloroisothiazolone/ methylisothiazolone 0.01 % aq	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq	Methylchloroisothiazolone/ methylisothiazolone 0.01% aq
						Methylisothiazolinone 0.2% aq	Methylisothiazolinone 0.2% aq
zalkonium Chloride % aq							
			Benzyl alcohol 1% pet	Benzyl alcohol 1% pet	Benzyl alcohol 1% pet		
opropynyl lcarbamate 0.1% pet	Iodopropynyl butylcarbamate 0.1% pet	Iodopropynyl butylcarbamate 0.1% pet					
		Iodopropynyl butyl carbamate 0.5% pet	Iodopropynyl butylcarbamate 0.5% pet	Iodopropynyl butylcarbamate 0.5% pet	Iodopropynyl butylcarbamate 0.5% pet	Iodopropynyl butylcarbamate 0.5% pet	Iodopropynyl butylcarbamate 0.5% pet
hyldibromo aronitrile / noxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet	Methyldibromo glutaronitrile / phenoxyethanol 2% pet

1–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016
nyldibromo aronitrile 0.4% pet &							
ben 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
noxyethanol 1% pet							

Table 3 –

Percentage, Strength and Clinical Relevance of Positive Patch Test Reactions to Preservatives 1994–2016

Preservative	n	Final Interpretation Allergic n (%)[a]	Second Read Code n (%)				Relevance n (%)[b]			
			+++	++	+	+/−	Definite	Probable	Possible	Past
MI 0.2% (2000 ppm) aq.	10613	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.	10613	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.	50050	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.	50042	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.	48550	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.[c]	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.	28676	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.	50588	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.[d]	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.	16762	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.	50638	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.	31424	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.	50623	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.	50616	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.	50634	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.	31542	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.	31417	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.	50645	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.	20238	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.	13628	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)

First and second readings were designated as +++ (very strong), ++ (strong), +(mild), +/− (weak/doubtful), irritant and negative in accordance with ICDRG criteria. 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 final interpretation and second read code will differ due to interpretation of results.

[a]Excludes unknown/uncertain.

[b] Excludes those with “not tested” or “not applicable”. Percentages were calculated for patients who had PPTR. Relevance category “unknowns” was included in the denominator for percentage calculation. However, “unknowns” not shown.

[c] Allergen tested only during the 2001–2002 cycle.

[d] Allergen tested only during the 1994–1996 cycle.

Abbreviations: Aq, aqueous; Pet, petrolatum; MI, methylisothiazolinone; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; IPBC, iodopropynyl butylcarbamate; DMDM, dimethylol dimethyl.

Table 4

Linear Regression Analysis of Positive Patch Test Reactions 1994–2016

Preservative	Parameter estimate (%) with 95% CI	p-value
MCI/MI 0.01% (100 ppm) aq	0.42 [0.17, 0.66]	0.005
IPBC 0.5% pet	0.35 [−0.07, 0.76]	0.080
Paraben mix 12% pet	−0.08 [−0.16, −0.01]	0.038
2-bromo-2-nitropropane-1,3-diol 0.5% pet	−0.18 [−0.33, −0.03]	0.024
DMDM hydantoin 1% pet	−0.19 [−0.29, −0.09]	0.002
DMDM hydantoin 1% aq	−0.21 [−0.37, −0.05]	0.021
Imidazolidinyl urea 2% pet	−0.23 [−0.29, −0.16]	<0.001
Imidazolidinyl urea 2% aq	−0.24 [−0.34, −0.15]	0.001
Diazolidinyl urea 1% pet	−0.26 [−0.36, −0.17]	<0.001
Diazolidinyl urea 1% aq	−0.33 [−0.55, −0.12]	0.011
Formaldehyde 1% aq	−0.42 [−0.56, −0.28]	<0.001
MDBGN/phenoxyethanol 2% pet	−0.43 [−0.56, −0.30]	<0.001
Quaternium-15 2% pet	−0.57 [−0.84, −0.31]	<0.001

Trend of PPTRs over time was analyzed with a simple linear regression model, where $Positive\ rate = \beta_0 + \beta_1 Time + \varepsilon$.

Abbreviations: CI, Confidence Interval; Aq, aqueous; Pet, petrolatum; MI, methylisothiazolinone; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; IPBC, iodopropynyl butylcarbamate; DMDM, dimethylol dimethyl.