

Patch Testing to Methyldibromoglutaronitrile/Phenoxyethanol: North American Contact Dermatitis Group Experience, 1994–2018

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Background: Methyldibromoglutaronitrile/phenoxyethanol (MDBGN/PE) is a broad-spectrum preservative mixture used in consumer and industrial products.

Objectives: The aims of the study were (1) to characterize the prevalence and clinical relevance of patch test reactions to MDBGN/PE and the epidemiology of positive patients and (2) to determine the frequency of concomitant reactions of MDBGN/PE and its components.

Methods: This study used a retrospective analysis of cross-sectional data compiled by the North American Contact Dermatitis Group from 1994 to 2018.

Results: Of 55,477 tested patients, 2674 (4.8%) had positive patch test reactions to MDBGN/PE (1.0%–2.5% petrolatum [pet]); most were + (63.3%) or ++ (22.3%). Clinical relevance was considered definite in 3.0% and probable in 19.3% of reactions. Common dermatitis sites included the hands (26.4%), scattered/generalized distribution (24.7%), and the face (18.3%). Patients with a positive reaction to MDBGN/PE and/or MDBGN and/or PE were significantly more likely to be male and older than 40 years and/or had hand dermatitis ($P \leq 0.0033$). Positivity to MDBGN/PE 2.0% pet decreased significantly over time (from 6.0% in 1998–2000 to 2.5% in 2017–2018, $P < 0.0001$). Personal care products were the most common exposure source (53.2%).

Conclusions: Over time, positivity to MDBGN/PE 2.0% pet decreased significantly from 6.0% (in 1998–2000) to 2.5% (in 2017–2018). The high proportion of weak (63.3%) reactions underscore the need for careful interpretation of patch test sites. Important demographic associations included male sex and age older than 40 years.

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A.R.A. received a grant from Pfizer Independent Grant for Learning & Change and has consulted for Henkel. J.S.T. owns noncontrolling shares of stock in AstraZeneca, Cigna, Merck, Johnson & Johnson, and Opko Health. He has consulted for Kao Brands and Monsanto (Bayer), is a member of the Cosmetic Ingredient Review Steering Committee, and has a nondependent child employed by Pfizer. E.M.W. has received an investigator-initiated grant from and served as a consultant for Wen by Chaz Dean. She has also served as a consultant for Noven Pharmaceuticals. D.S. receives royalties from UpToDate (Wolters Kluwer Health). The other authors have no funding or conflicts of interest to declare.

This study was supported by resources and use of facilities at the Minneapolis Veterans Affairs Medical Center. The contents do not represent the views of the US Department of Veterans Affairs or the US Government.

DOI: 10.1097/DER.0000000000000732

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Methyl dibromoglutaronitrile/phenoxyethanol (MDBGN/PE), a 1:4 ratio preservative mixture of MDBGN (1,2-dibromo-2,4-dicyanobutane) to PE commonly known by the trade name Euxyl K400, has been used in personal care and industrial products as a biocide against bacteria, fungi, and yeast.¹ Methyl dibromoglutaronitrile/phenoxyethanol was introduced in European consumer products in 1985 and in the United States 5 years later.² Manufacturers began using it as a preservative after initial animal testing suggested its low sensitizing potential.^{2,3} This study was later challenged as MDBGN was found to cause significant contact allergy leading the European Commission to ban use from leave-on products in 2003, followed by rinse-off products in 2008.^{2,4,5} There have been no regulations regarding use of MDBGN in personal care products in the United States. The Cosmetic Ingredient Review Expert Panel found that MDBGN/PE is safe for use in concentrations of 0.125% (0.025% MDBGN) in leave-on products and 0.3% (0.06% MDBGN) in rinse-off products.⁶ Personal communication with the manufacturer (a Schülke & Mayr customer service representative, personal communication, September 17, 2020) confirmed that Euxyl K400 has not been produced since 2010.

Allergic contact dermatitis to MDBGN/PE has been well known for decades, and the sensitizing ingredient is nearly always MDBGN.^{1,2,6} The first cases of contact allergy to MDBGN/PE were reported from Germany in 1989: one from an antiwrinkle lotion and the other a massage lotion.⁷ Of cases that followed, most identified personal care products as the culprit source.² The prevalence of contact allergy to MDBGN alone, or in combination with PE as MDBGN/PE, in routinely patch-tested patients has been complicated by the fact that different concentrations of MDBGN and MDBGN/PE were used in patch test preparations. A comprehensive review summarized data before 2009²; the 2 largest studies from that period showed positive patch test proportions of 1.7% (n = 25,584)⁸ and 3.5% (n = 48,485).⁹ More recent data are summarized in Table 1.

Although proportions of patients with positive patch tests to MDBGN/PE, MDBGN, and PE were reported periodically by the North American Contact Dermatitis Group (NACDG), detailed data from a large North American cohort are lacking. This study describes patients with positive patch test reactions to MDBGN/PE and compares concomitant reactions to MDBGN and PE. Reaction characteristics, allergen sources, and clinical relevance are also summarized.

MATERIALS AND METHODS

The NACDG Database

This analysis of deidentified data was approved by the Minneapolis VA Medical Center's Subcommittee on Human Studies. Between 1994 and 2018, the NACDG screening series consisted of 50 to 70 allergens (Chemotechnique Diagnostics AB [Malmö, Sweden] and allergEAZE; SmartPractice [Calgary, Alberta, Canada]). Data collected included the following: demographics (age, sex, race, occupation), history of atopy (asthma, hay fever, atopic dermatitis), and anatomic sites of dermatitis (up to 3 sites). Methods of patch testing, grading of reactions, and recording of data were performed according to the NACDG protocol.¹⁹

Briefly, for each allergen, there were several recorded codes. At the 48-hour and final readings (4–7 days after application), reactions were graded as weak + (nonvesicular, erythema), strong ++ (edematous or vesicular), extreme +++ (spreading, bullous, ulcerative), doubtful +/- (macular erythema only), irritant, or negative. In addition, an overall interpretation was assessed as “allergic” or “not allergic”; doubtful (+/-) reactions could be interpreted as allergic or not allergic, depending on crescendo/decrecendo pattern, allergen characteristics (eg, neomycin as a late reactor or fragrance mix I as an irritant), and/or other patch test reactions/clinical presentation.

Concomitant Reactions

During select years, parallel testing of MDBGN/PE (1.0%, 2.0%, and/or 2.5% petrolatum [pet]) was performed with MDBGN (0.4% pet) and/or PE (1.0% pet; Table 2). Concomitant reactions were analyzed in only those patients tested to both allergens (MDBGN/PE and MDBGN or MDBGN/PE and PE, respectively).

Study Population

All patients patch tested with MDBGN/PE, MDBGN, and PE were included in this analysis. Data from 1 NACDG site, in part, have been previously reported.²⁰ Study groups were defined as follows: patients positive for MDBGN/PE only (MDBGN/PE+ only), patients positive for MDBGN only (MDBGN+ only), patients positive for PE only (PE+ only), or patients positive for any of these 3 allergens at any tested concentration (“positive”). Patients tested to at least 1 of these 3 allergens with all negative results comprised the “negative” group. Demographics were compared between positive and negative patients. Positive reactions to MDBGN/PE, MDBGN only, or PE only were further analyzed based on clinical relevance, strength of last reading, and sources of allergen exposure.

Data Analysis

Data were manually entered at a centralized location using Access software (Access 2010; Microsoft) and Microsoft Excel (Excel 2019; Microsoft). Demographic data were presented according to MOAHLFA (male, occupational, atopic, hand, leg, foot, age >40 years) guidelines.²¹ Reaction strength, clinical relevance, and source of exposure were presented using descriptive analyses. Statistical analyses comparing positive and negative patients as well as different periods were conducted using GraphPad Prism software (version 8.2.1; GraphPad Software) with 2-sided χ^2 test. *P* values of less than 0.05 were considered statistically significant. Proportional Venn diagrams were created using the Pacific Northwest National Laboratory Venn Diagram Plotter software (<https://omics.pnl.gov/software/venn-diagram-plotter>).

RESULTS

Reaction Prevalence

Between 1994 and 2018, 55,477 patients were patch tested to MDBGN/PE in concentrations ranging from 1.0% to 2.5% pet. The proportion of

TABLE 1. Patch Testing of MDBGN/PE and/or MDBGN

First Author (Year Published)	Period of Data Collection, Location	Allergen(s) Tested	Total No. Patients Tested	No. Patients Positive (%)
Uter ¹⁰ (2009)	2005–2006, 10 European countries	MDBGN/PE (1.0% pet)	1242	41 (3.3)
		MDBGN (0.3% pet)	14,499	379 (2.6)
Schnuch ¹¹ (2011)	1998–2009 (select years only); Germany, Switzerland, and Austria	MDBGN/PE (1.0% pet)	60,936	2593 (3.9)
		MDBGN (0.3% pet)	53,545	2695 (4.5)
		MDBGN (0.2% pet)	13,369	371 (2.4)
Wentworth ¹² (2014)	2006–2010, United States	MDBGN/PE (1.5% pet)	3077	203* (6.6)
Cheng ¹³ (2014)	2006–2011, Singapore	MDBGN/PE (1.5% pet)	345	7 (2.0)
		MDBGN (0.5% pet)	3170	38 (1.2)
Toholka ¹⁴ (2015)	2001–2010, Australia	MDBGN/PE (0.5% pet)	5133	142 (2.8)
		MDBGN (0.3% pet)	4644	75 (1.6)
Giménez-Arnau ¹⁵ (2017)	2009–2012, 12 European countries	MDBGN/PE (1.5% pet)	4590	90* (2.0)
		MDBGN (0.5% pet)	16,673	299* (2.5)
		MDBGN (0.3% pet)	30,984	610* (2.7)
		MDBGN (0.2% pet)	13,581	419* (2.8)
Uter ¹⁶ (2017)	2013–2014, 12 European countries	MDBGN (0.5% pet)	8246	198* (2.4)
		MDBGN (0.3% pet)	13,831	276* (2.0)
		MDBGN (0.2% pet)	5498	137* (2.5)
Veverka ¹⁷ (2018)	2011–2015, United States	MDBGN (0.5% pet)	987	42 (4.3)
Kreft ¹⁸ (2020)	2009–2018; Germany, Switzerland, and Austria	MDBGN (0.3% pet)	16,278	776 (4.8)
		MDBGN (0.2% pet)	51,904	1430 (2.8)

MDBGN, methyl dibromoglutaronitrile; MDBGN/PE, methyl dibromoglutaronitrile/phenoxylethanol; pet, petrolatum.

*Number determined from data provided in the article.

positive reactions to MDBGN/PE (any concentration) in the overall patch test population was 4.8% (2674/55,477). Prevalence rates of positive patch test reactions to PE (1.0% pet) and MDBGN (0.4% pet) were 0.16% and 3.2%, respectively (Table 2). Over 20 years, positivity to MDBGN/PE (2.0% pet) decreased significantly from 6.0% (in 1998–2000) to 2.5% (in 2017–2018, $P < 0.0001$).

Concomitant Reactions

During the 1996–1998 cycle, 4050 patients were patch tested to 2 different MDBGN/PE concentrations (1.0% and 2.5% pet). Of the 323 positive reactions, 213 (65.9%) were positive for 2.5% pet only, 15 (4.6%) were positive for 1.0% pet only, and 95 (29.4%) were positive for both (Fig. 1).

Of the 10,673 patients patch tested to both MDBGN (0.4% pet) and MDBGN/PE (2.0% pet), 64 (9.2%) were positive for MDBGN only, 360 (51.6%) were positive for MDBGN/PE only, and 273 (39.2%) were positive for both (Fig. 2).

Of the 2007 patients patch tested to both MDBGN/PE (1.0% pet) and PE (1.0% pet), 1 was positive for PE only, 49 were positive for MDBGN/PE only, and none were positive for both. Of the 4887 patients patch tested to both MDBGN/PE (2.0% pet) and PE (1.0% pet), 5 were positive for PE only (1.7%), 280 (96.6%) were positive for MDBGN/PE only, and 5 (1.7%) were positive for both (combined data, Fig. 3).

Demographics

MOAHLFA index data²¹ are presented in Table 3. Compared with negative patients, positive patients were significantly more likely to

be male (43.0% vs 32.7%, $P \leq 0.0001$) and/or older than 40 years (80.6% vs 66.0%, $P \leq 0.0001$). Positive patients were statistically less likely to have a history of asthma (12.5% vs 14.8%, $P = 0.0012$) and/or childhood atopic dermatitis (15.6% vs 23.1%, $P \leq 0.0001$).

Dermatitis Anatomic Sites

Among the patients who tested positive for MDBGN/PE (any concentration), the most common primary site of dermatitis was the hands (26.4%), followed by scattered/generalized distribution (24.7%) and the face (18.3%). Likewise, these were the most common primary sites of dermatitis among patients who were positive for MDBGN only or PE only (Table 4). As compared with negative patients, positive patients were more likely to present with dermatitis involving the hand (19.7% vs 17.9%, $P = 0.0033$) and/or the leg (8.1% vs 6.7%, $P = 0.0003$) but less likely to have facial dermatitis (10.3% vs 14.2%, $P \leq 0.0001$), although absolute differences were small.

Reaction Grade and Relevance

In the final reading grade for MDBGN/PE (any concentration), most were + (63.3%, 1752/2769), with fewer ++ (22.3%, 618/2769) and +++ (4.0%, 110/2769; Table 5). For reactions to MDBGN, most were + (60.9%) or ++ (21.9%). Similarly, PE reactions were primarily + (50.0%) or ++ (33.3%). Of the positive reactions to MDBGN/PE (any concentration), 1800 (65.1%) were currently relevant; most were considered to have possible (42.8%) or probable (19.3%) relevance with relatively few definite (3.0%) relevance. By NACDG grading standards, a determination of “definite relevance” requires a positive patch test both to the allergen

TABLE 2. Distribution of Patients by NACDG Data Collection Period

NACDG Data Cycle	Total No. Patients	Allergen(s) Tested	No. Patients Tested	No. Positive Reactions (%)
1994–1996	2035	MDBGN/PE (1.0% pet)	2007	49 (2.4)
		Phenoxyethanol (1.0% pet)	2011	1 (0.05)
1996–1998	4146	MDBGN/PE (1.0% pet)	4050	110 (2.8)
		MDBGN/PE (2.5% pet)	4050	308 (7.6)
1998–2000	5839	MDBGN/PE (2.0% pet)	5778	348 (6.0)
		MDBGN (0.4% pet)	5797	205 (3.5)
2001–2002	4913	MDBGN/PE (2.0% pet)	4897	285 (5.8)
		Phenoxyethanol (1.0% pet)	4887	11 (0.23)
		MDBGN (0.4% pet)	4897	134 (2.7)
2003–2004	5148	MDBGN/PE (2.0% pet)	5142	310 (6.0)
2005–2006	4454	MDBGN/PE (2.0% pet)	4437	259 (5.8)
2007–2008	5085	MDBGN/PE (2.0% pet)	5083	279 (5.5)
2009–2010	4308	MDBGN/PE (2.0% pet)	4303	162 (3.8)
2011–2012	4246	MDBGN/PE (2.0% pet)	4240	157 (3.7)
2013–2014	5024	MDBGN/PE (2.0% pet)	5020	186 (3.7)
2015–2016	5597	MDBGN/PE (2.0% pet)	5592	195 (3.5)
2017–2018	4947	MDBGN/PE (2.0% pet)	4928	121 (2.5)
TOTAL		MDBGN/PE (any concentration): 2674/55,477 (4.8)		
		Phenoxyethanol (1.0% pet): 11/6898 (0.16)		
		MDBGN (0.4% pet): 337/10,694 (3.2)		

MDBGN, methyl dibromoglutaronitrile; MDBGN/PE, methyl dibromoglutaronitrile/phenoxyethanol; NACDG, North American Contact Dermatitis Group; pet, petrolatum.

and to a product containing the allergen; this testing is performed only sometimes by NACDG members.

Trends in clinical relevance of MDBGN/PE-positive reactions (any concentration) are summarized in Table 6. Period A corresponds to the period before any regulatory intervention of MDBGN/PE occurred, whereas period B includes the period after the European Union (EU) ban of MDBGN in cosmetics went into effect. Period C identifies the time when Schülke & Mayr stopped manufacturing Euxyl K400 (a Schülke & Mayr customer service representative, personal communication, September 17, 2020). Compared with period B, period C had significantly fewer currently relevant reactions (77.3% vs 59.8%, $P \leq 0.0001$). Significance-Prevalence Index Number calculations²² for periods A, B, and C were 181.5, 182.1, and 89.5, respectively.

Exposure Sources

Overall, MDBGN/PE was most commonly associated with cosmetics/beauty/skin/health care products (1039 of 1954 [53.2%]); most were not specifically categorized (Table 7). Of specific identified categories, the most common were moisturizers/lotions/creams (25.3%), personal hygiene soap/cleansers (2.0%), and hair care products (1.7%). Of the MDBGN/PE reactions with definite and probable clinical relevance (requiring identification of ingredients in sources, $n = 464$), cosmetics/beauty/skin/health care products were the most common (443/464, 95.5%). Occupationally related sources did not differ by period (data not shown).

DISCUSSION

Overall, 4.8% of routinely patch-tested patients were positive for MDBGN/PE (1.0%–2.5% pet); this percentage decreased significantly

over the 20-year study period (2.0% pet) from 6.0% to 2.5% ($P < 0.0001$). Positive patients were significantly more likely to be male and/or older than 40 years. Although more than half of the reactions to MDBGN/PE (any concentration) were currently relevant, this proportion significantly decreased over time. Personal skin care products were the most common source of MDBGN/PE exposure, especially moisturizers/lotions/creams.

Positive Reactions to Different MDBGN/PE Patch Test Concentrations

The overall proportion of positive reactions to MDBGN/PE (1.0%–2.5% pet) ranged from 2.4% to 7.6%, corresponding with increasing test concentration. Peak proportion was observed with MDBGN/PE 2.5%, whereas parallel testing with a 1.0% concentration during the same cycle yielded a nearly 3-fold lower frequency. Previous studies noted that when 2 concentrations of MDBGN/PE or MDBGN were tested, higher patch test concentrations resulted in a greater number of reactions.^{23–25} Between 1991 and 1994, Tosti and Vincenzi²³ found that of 44 patients positive for MDBGN/PE 2.5% pet, two-thirds or fewer were positive for lower concentrations (20%–0.2%, 41%–0.5%, 52%–1.0%, 61%–1.5%, 64%–2.0%). In our study, the proportions of positive patch test reactions to 2.5% and 1.0% concentrations were lower (29%) than those in the study by Tosti and Vincenzi²³ (52%). In 1998, Jackson and Fowler²⁴ analyzed 163 patients patch tested to MDBGN/PE 1.0% and 2.5% pet and found that 45 patients had test site skin changes; 23 were considered irritant reactions, 19 were considered allergic, and 3 were considered uncertain. The

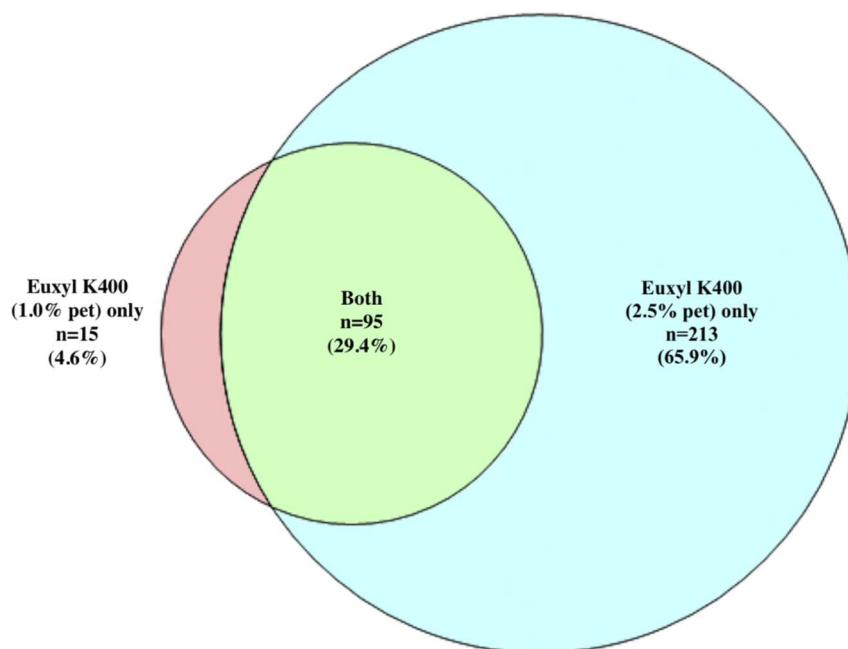


Figure 1. The distribution of positive reactions among 4050 patients patch tested to both MDBGN/PE 2.5% and 1.0% concentrations between 1996 and 1998.

authors noted that although, overall, more patients had reactions to 2.5% pet, there were a greater number of false positives.²⁴ In 2002, Gruvberger et al²⁵ patch tested 2661 patients to MDBGN at 4 concentrations; positive reaction proportions ranged from 4.4% to 1.1%, correlating with decreasing test concentrations (4.4%–1.0%, 3.0%–0.5%, 1.9%–0.3%, 1.1%–0.1%). Our experience is that testing MDBGN/PE at a concentration of 2.0% is a compromise

between potential false-positive results with 2.5% and false-negative results with 1.0%.

Positive Reactions to MDBGN/PE (2.0% Pet) Over Time

Over 20 years, the proportion of positive reactions to MDBGN/PE decreased from 6.0% (1998–2000) to 2.5% (2017–2018, $P < 0.0001$).

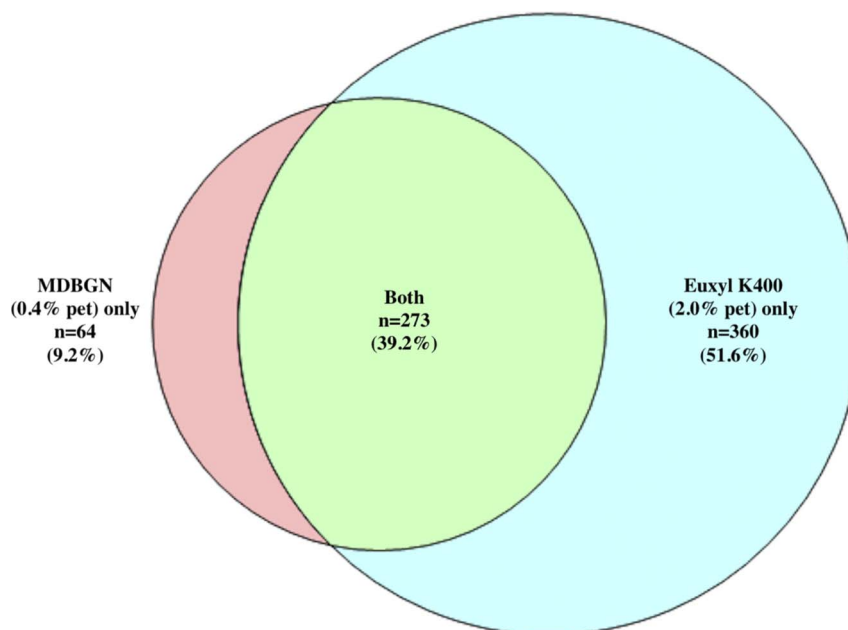


Figure 2. The distribution of positive reactions among 10,673 patients patch tested to both MDBGN (0.4% petrolatum [pet]) and MDBGN/PE (2.0% pet) between 1998–2000 and 2001–2002.

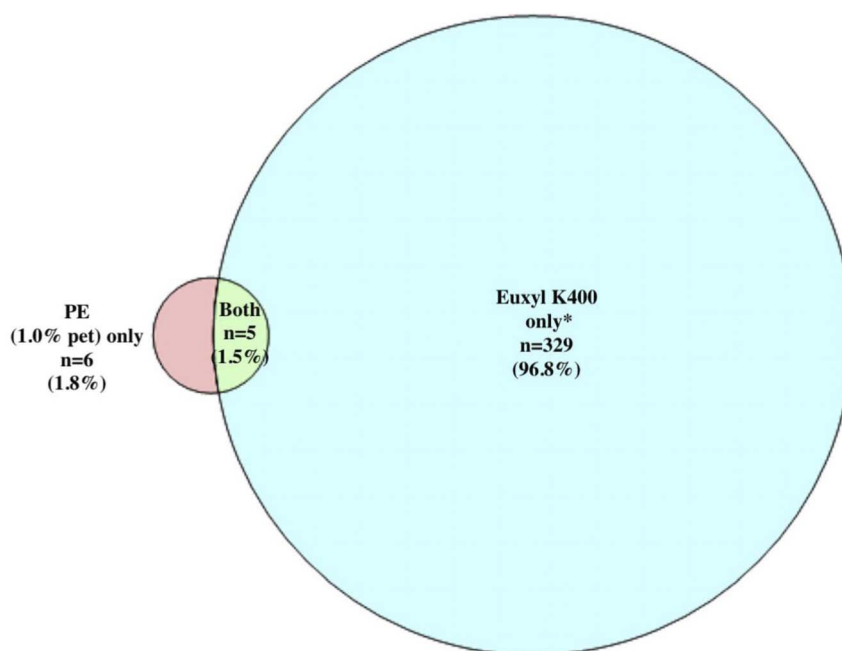


Figure 3. The distribution of positive reactions among 6894 patients patch tested to both PE (1.0% petrolatum [pet]) and MDBGN/PE (1.0% pet) between 1994 and 1996 or both PE (1.0% pet) and MDBGN/PE (2.0% pet) between 2001 and 2002.

TABLE 3. MOAHLFA Index²¹ Characteristics of Patients Positive for MDBGN/PE, PE Alone, or MDBGN Alone

	MDBGN/PE+ Only (Any Concentration), n = 2674	MDBGN+ Only (0.4% Pet), n = 64	PE+ Only (1.0% Pet), n = 6	Total Positive (PE and/or MDBGN/ PE and/or MDBGN), n = 2744	Total Negative (PE and/or MDBGN/ PE and/or MDBGN), n = 52,733	Total Positive vs Total Negative Patients, RR (95% CI), <i>P</i>
Male	1157 (43.3)	24 (37.5)	0 (0.0)	1181 (43.0)	17,234 (32.7)*	1.32 (1.26–1.37), <0.0001
Occupation related [†]	382 (14.3)	1 (1.6)	1 (16.7)	392 (14.3) [‡]	7209 (13.7) [§]	1.04 (0.95–1.15), 0.3815
Personal history of atopic markers						
Asthma	336 (12.6)	5 (7.8)	1 (16.7)	342 (12.5)	7757 (14.8)	0.85 (0.77–0.94), 0.0012
Atopic dermatitis	419 (15.7)	5 (7.8)	2 (33.3)	426 (15.6)	12,164 (23.1)	0.67 (0.62–0.74), <0.0001
Hay fever	638 (23.9)	15 (23.4)	2 (33.3)	655 (24.0) [§]	15,170 (28.8) [§]	0.98 (0.91–1.05), 0.5036
Hand [#]	824 (30.8)	12 (18.8)	3 (50)	839 (19.7)	14,742 (17.9)	1.10 (1.03–1.17), 0.0033
Leg [#]	333 (12.5)	10 (15.6)	1 (16.7)	344 (8.1)	5480 (6.7)	1.21 (1.09–1.35), 0.0003
Face, NOS [#]	426 (15.9)	10 (15.6)	1 (16.7)	437 (10.3)	11,651 (14.2)	0.72 (0.66–0.79), <0.0001
Age, >40 y	2161 (80.8)	49 (76.6)	3 (50)	2213 (80.6)	34,750 (66.0)**	1.22 (1.20–1.25), <0.0001

Data are presented as n (%), unless otherwise indicated.

*Twenty-four patients missing sex in database.

[†]Overall skin condition related to occupation.

[‡]Three (+) and 155 (–) patients missing occupational relevance.

[§]Eleven (+) and 142 (–) patients missing hay fever in database.

^{||}Ten (+) and 147 (–) patients missing asthma in database.

^{||}Twelve (+) and 186 (–) patients missing eczema in database.

[#]Listed as any of up to 3 anatomic sites per patient.

**Fifty-four patients missing age in database.

CI, confidence interval; MDBGN, methyl dibromoglutaronitrile; MDBGN/PE, methyl dibromoglutaronitrile/phenoxyethanol; NOS, not otherwise specified; PE, phenoxyethanol; pet, petrolatum; RR, risk ratio.

TABLE 4. Sites of Dermatitis

	MDBGN/PE (Any Concentration), n = 2674*	MDBGN Only (0.4% Pet), n = 64	PE Only (1.0% Pet), n = 6	Total No. Positive Patients, n = 2741
Primary site				
Hand	705 (26.4)	10 (15.6)	3 (50)	718 (26.2)
Scattered/generalized	659 (24.7)	17 (26.6)	2 (33.3)	678 (24.7)
Face, total	490 (18.3)	13 (20.3)	1 (16.7)	504 (18.4)
Face, NOS	317 (11.9)	9 (14.1)	1 (16.7)	327 (11.9)
Eyelids	115 (4.3)	3 (4.7)	—	118 (4.3)
Lips	43 (1.6)	1 (1.6)	—	44 (1.6)
Eyes	13 (0.5)	—	—	13 (0.5)
Nose	2 (0.1)	—	—	2 (0.1)
Trunk	161 (6.0)	2 (3.1)	—	163 (5.9)
Arm	158 (5.9)	5 (7.8)	—	163 (5.9)
Neck/scalp/ear	124 (4.6)	1 (1.6)	—	125 (4.6)
Leg	119 (4.5)	5 (7.8)	—	124 (4.5)
Other	80 (3.0)	2 (3.1)	—	82 (3.0)
Anal/genital	65 (2.4)	1 (1.6)	—	66 (2.4)
Foot	58 (2.2)	3 (4.7)	—	61 (2.2)
Only under clothing	52 (1.9)	5 (7.8)	—	57 (2.1)
Up to 3 sites of dermatitis [†]				
Hand	824 (30.8)	12 (18.8)	3 (50.0)	839 (30.6)
Scattered generalized	780 (29.2)	19 (29.7)	2 (33.3)	801 (29.2)
Arm	451 (16.9)	7 (10.9)	1 (16.7)	459 (16.7)
Face, total	666 (24.9)	15 (23.4)	1 (16.7)	682 (24.9)
Face, NOS	426 (15.9)	10 (15.6)	1 (16.7)	437 (15.9)
Eyelids	157 (5.9)	4 (6.3)	—	161 (5.9)
Lips	59 (2.2)	1 (1.6)	—	60 (2.2)
Eyes	22 (0.8)	—	—	22 (0.8)
Nose	2 (0.1)	—	—	2 (0.1)
Trunk	356 (13.3)	7 (10.9)	—	363 (13.2)
Leg	333 (12.5)	10 (15.6)	1 (16.7)	344 (12.6)
Neck/scalp/ear	320 (12.0)	6 (9.4)	—	326 (11.9)
Foot	166 (6.2)	3 (4.7)	—	169 (6.2)
Other	112 (4.2)	2 (3.1)	—	114 (4.2)
Anal/genital	94 (3.5)	2 (3.1)	—	96 (3.5)
Only under clothing	59 (2.2)	6 (9.4)	—	65 (2.4)

Data are presented as n (%), unless otherwise indicated.

*Three MDBGN/PE (+) patients missing primary site of dermatitis.

[†]Total of percentages may exceed 100% because up to 3 sites per patient could be listed.

MDBGN, methyl dibromoglutaronitrile; MDBGN/PE, methyl dibromoglutaronitrile/phenoxyethanol; NOS, not otherwise specified; PE, phenoxyethanol.

Although direct comparisons with other studies (which commonly test to 1.5% or 1.0% pet) are difficult, our proportions are higher than those reported during the corresponding years in Europe (3.3% in 2005–2006,¹⁰ 3.9% in select years 1998–2009,¹¹ and 2.0% in 2009–2012¹⁵), Singapore (2.0% in 2006–2011),¹³ and Australia (2.8% in 2001–2010).¹⁴ Other US studies also reported high proportions of positive reactions to MDBGN/PE (1.5% pet, 6.6% [2006–2010]) and MDBGN (0.5% pet, 4.3% [2011–2015]).^{12,17}

European regulatory intervention has been cited as a major factor contributing to decreasing rates of sensitization to MDBGN/PE.^{26–28} The Danish Contact Dermatitis Group compared reaction percentages to MDBGN among 19,279 routinely tested patients

before and after the EU ban and noted a statistically decreased proportion from 4.6% in 2003 to 2.6% in 2007.²⁶ Effectiveness of EU regulation on MDBGN/PE was also seen across 3 patch test centers in Northeastern Italy, where peak sensitization was observed between 2002 and 2007 and declined thereafter.²⁷ Although there is no corresponding restrictive regulation in the United States, the fact that Euxyl K400 is no longer manufactured by Schülke and Mayr (a Schülke & Mayr customer service representative, personal communication, September, 17, 2020) and the removal of MDBGN/PE and/or MDBGN from US products (Johnson & Johnson, personal communication, September 23, 2020) probably explain decreasing positivity.

TABLE 5. Reaction Strength and Clinical Relevance

	MDBGN/PE 1.0% Pet, n = 159	MDBGN/PE 2.5% Pet, n = 308	MDBGN/PE 2.0% Pet, n = 2302*	Total MDBGN/PE (Any Concentration), n = 2769*	MDBGN Only 0.4% Pet, n = 64	PE Only 1.0% Pet, n = 6	Total Positive, n = 2839*
Final reading grade							
Doubtful +/-+†	23 (14.5)	24 (7.8)	220 (9.6)	267 (9.6)	10 (15.6)	0 (0.0)	277 (9.8)
Mild +	98 (61.6)	200 (64.9)	1454 (63.2)	1752 (63.3)	39 (60.9)	3 (50)	1794 (63.2)
Moderate ++	30 (18.9)	75 (24.4)	513 (22.3)	618 (22.3)	14 (21.9)	2 (33.3)	634 (22.3)
Strong +++	3 (1.9)	7 (2.3)	100 (4.3)	110 (4.0)	1 (1.6)	0 (0.0)	111 (3.9)
Other‡	5 (3.1)	2 (0.6)	14 (0.6)	21 (0.8)	0 (0.0)	1 (16.7)	22 (0.8)
Clinical relevance							
Current§	104 (65.4)	182 (59.1)	1514 (65.8)	1800 (65.1)	44 (68.8)	2 (33.3)	1846 (65.0)
Definite	13 (8.2)	23 (7.5)	47 (2.0)	83 (3.0)	2 (3.1)	0 (0.0)	85 (3.0)
Probable	33 (20.8)	48 (15.6)	453 (19.7)	534 (19.3)	5 (7.8)	0 (0.0)	539 (19.0)
Possible	58 (36.5)	111 (36.0)	1014 (44.1)	1183 (42.8)	37 (57.8)	2 (33.3)	1222 (43.1)
Past	2 (1.3)	4 (1.3)	106 (4.6)	112 (4.0)	0 (0.0)	1 (16.7)	113 (4.0)
Unknown/NA	53 (33.3)	122 (39.6)	680 (29.6)	855 (30.9)	20 (31.3)	3 (50.0)	878 (30.9)

Data are presented as n (%), unless otherwise indicated.

*One patient missing strength of reaction and 2 patients missing clinical relevance.

†Excludes doubtful reactions with final interpretation of "nonallergic/negative" (following percentage is of all doubtful reactions): MDBGN/PE (1.0% pet) = 42/65 (64.6%), MDBGN/PE (2.5% pet) = 108/132 (81.8%), MDBGN/PE (2.0% pet) = 869/1089 (79.8%), total (any concentration) = 1019/1286 (79.2%), MDBGN (0.4% pet) = 74/84 (88.1%), and PE (1.0% pet) = 10/10 (100%).

‡Miscoded as irritant or negative.

§Current relevance was considered to be a patch test reaction coded as of definite, probable, or possible relevance.

MDBGN, methyl dibromoglutaronitrile; MDBGN/PE, methyl dibromoglutaronitrile/phenoxylethanol; NA, not available; PE, phenoxylethanol.

Concomitant Reactions

A positive reaction to MDBGN/PE does not necessarily correlate with its individual ingredients.^{23,29} Between 1991 and 1994, Tosti and Vincenzi²³ found that 99 (3.0%) of 3455 patients had a positive reaction to MDBGN/PE 2.5%; however, when tested with MDBGN and PE alone, 46 (51.1%) of 99 patients had no reaction. Indeed,

when comparing patients tested to both MDBGN/PE 2.0% pet and MDBGN 0.4% pet (Fig. 2), the highest proportion (51.6%) was to MDBGN/PE 2.0% pet only, whereas fewer (39.2%) were positive for both. In our study, only 39.2% of the patients reacted to both MDBGN/PE 2.0% pet and MDBGN 0.4% pet.

Although sensitivity to MDBGN/PE is almost exclusively due to MDBGN, PE has rarely been identified.²³ In the 1991–1994 study by Tosti and Vincenzi,²³ the authors analyzed 3455 patients routinely tested with MDBGN/PE 2.5% pet and found that only 2 of 99 patients positive for MDBGN/PE were also positive for PE 5% pet. Of our 6894 patients tested to both MDBGN/PE and PE, only 5 patients (0.07%) reacted to both.

TABLE 6. Clinical Relevance of MDBGN/PE Positive Reactions Over Time

	Period A* (1994–2004), n = 1410	Period B† (2005–2010), n = 700	Period C‡ (2011–2018), n = 657
Current	866 (61.4)	541 (77.3)	393 (59.8)
Definite	58 (4.1)	21 (3.0)	4 (0.6)
Probable	221 (15.7)	179 (25.6)	134 (20.4)
Possible	587 (41.6)	341 (48.7)	255 (38.8)
Past	25 (1.8)	27 (3.9)	60 (9.1)
Unknown/NA	519 (36.8)	132 (18.8)	204 (31.1)
Occupational relevance§	16 (1.6)	15 (2.1)	18 (2.8)

Data are presented as n (%), unless otherwise indicated.

*Period A: before regulatory intervention of MDBGN/PE.

†Period B: after EU banned use of MDBGN, first from leave-on products in 2005 and later from rinse-off cosmetics in 2008.²

‡Period C: after Schülke and Mayr discontinued manufacturing MDBGN/PE (a Schülke & Mayr customer service representative, personal communication, September 17, 2020).

§Missing occupational relevance data: n = 21 period A, n = 1 period B, and n = 5 period C; occupational relevance not recorded for 1996–1998 cycle.

NA, not available.

Demographics and Sites of Dermatitis

Positive patients were significantly more likely to be male and/or older than 40 years. Sex and age associations may be due to occupational sensitization. Statistical significance was also identified for dermatitis of the hands or the legs, although absolute differences were small. Other studies noted an association between increased MDBGN sensitivity and hand dermatitis.^{23,30–32} Previous analysis in a subset of the current data (1994–2004) found that MDBGN/PE was the third most common preservative associated with allergic contact dermatitis of the hands.³³ A study from the Netherlands found MDBGN to be the fifth most frequent sensitizer in patients with hand eczema (95/1571, 6.0%) tested between 2002 and 2013.³¹ Other common sites of dermatitis in our cohort were a scattered/generalized distribution (24.7%) and the face (18.3%). The involved

TABLE 7. Methyldibromoglutaronitrile/Phenoxyethanol Source Data

3-Digit Source Codes, 2001–2018	All (N = 1954), n (%)	Definite and Probable (n = 464), n (%)
Cosmetics, beauty, skin, and health care products	1039 (53.2)	443 (95.5)
Cosmetics, beauty, skin, and health care products, NOS	649	306
Hair care products	18	5
Personal skin care products	344	120
Personal skin care products, NOS (all n = 73, definite/probable n = 13)		
Moisturizers, lotions, and creams (all n = 263, definite/probable n = 104)		
Other		
Make-up (all n = 7, definite/probable n = 3)		
Deodorant/antiperspirant (all n = 1, definite/probable n = 0)		
Soaps and cleansers (personal hygiene)	21	8
Sunscreens	4	3
Eye care products	2	0
Essential oils, massage oils, and aromatherapy	1	1
Chemicals and chemical products	28 (1.4)	3 (0.7)
Chemicals and chemical products, NOS	1	
Rodenticides	1	
Coatings (paint, lacquer, shellac, varnish, stains)/adhesives, glues, and bonding agents	6	1
Solvents, oils, lubricants, and fuels	20	2
Other	26 (1.3)	11 (2.4)
Unknown/not applicable	861 (44.1)	7 (1.5)

Bold values indicate statistical significance.

NOS, not otherwise specified.

locations are not surprising, given that personal skin care products, such as moisturizers/lotions/creams, were the most common exposure source.

Strength of Reactions and Relevance

Reactions to MDBGN/PE (any concentration) were mostly + (63.3%), with fewer ++ (22.3%) and +++ (4.0%). The positivity ratio (PR) and reaction index (RI) are metrics that provide information on the relative frequency of irritant and weak reactions; a perfect patch test formulation has a PR of 0% (range = 0%–100%) and RI of +1 (range = –1 to +1).^{34,35} Given its high PR (72%) and low RI (0.30) values, the NACDG decreased the concentration of MDBGN/PE from 2.5% to 2.0% in 1998.² Although there were fewer weak (+) reactions (63.2%), this difference was not statistically significant ($P = 0.57$, data not shown). Previous studies noted that irritant reactions to concentrations of 2.0% or greater MDBGN/PE are not infrequent.^{23,24} In an attempt to avoid irritancy, the Mayo Clinic tested MDBGN/PE 1.5% pet in 3077 patients (2006–2010); 1.4% were considered irritant.¹² Although the Mayo Clinic no longer includes MDBGN/PE in its screening series, data from their group (2011–2015) found that MDBGN 0.5% pet yielded mostly weak positives (88.1%).¹⁷ Interpretation of these patch test preparations should be undertaken carefully, given the high proportion of doubtful and weak reactions. Repeat open application test studies and concomitant patch testing with different concentrations of MDBGN suggest that higher patch test concentrations yield “false-positive” patch tests; false-positive patch tests (ie, repeat open application test negatives) increase from 41% to 60% when comparing MDBGN

0.3% with 1.0%.^{36–38} Data from the Information Network of Departments of Dermatology suggest that a maximum sensitivity of 95% is reached with a concentration of 0.2% (and is not further improved by increasing the concentration), whereas the specificity decreases from 88% (MDBGN 0.2%) to 12.5% (MDBGN 0.5%).³⁹

Here, of the positive reactions to MDBGN/PE (any concentration), 65.1% were currently relevant; most were possible (42.8%) or probable (19.3%) with rare definite (3.0%) clinical relevance. The proportion of currently relevant reactions decreased significantly from 77.3% to 59.8% ($P \leq 0.0001$) when comparing data before and after 2011. This is likely due to discontinuation of the production of Euxyl K400 used for consumer products.

Exposure Sources

Methyldibromoglutaronitrile/phenoxyethanol reactions were mainly associated with personal care products (53.2%), most commonly moisturizers/lotions/creams (25.3%); occupationally related sources did not differ by period (data not shown). Information provided to the US Food and Drug Administration through its Voluntary Cosmetic Registration Program indicated that in 1996, MDBGN was present in 35 products at concentrations up to 0.06% and, in 2011, 36 products in concentrations up to 0.04%.⁴⁰ The US National Institutes of Health's Consumer Product Information Database indicated that MDBGN is in 5 personal care products; however, manual verification found that all had been discontinued or changed formulation (November 18, 2020).⁴¹ According to the Environmental Working Group's Skin Deep Cosmetics Database, in October 2020, MDBGN

was present in 4 of 83,121 personal care products (2 sunscreens, 1 hair conditioner, and 1 face serum).⁴² The American Contact Dermatitis Society's Contact Allergen Management Program database lists only 2 products with MDBGN (a soap and a sunscreen; CAMP Database Manager, personal communication, October 18, 2020). Manual verification of these later 6 products identified both MDBGN and PE as ingredients in all, except for the face serum, which has been reformulated (October 18, 2020).

Limitations

As a cross-sectional analysis, causal relationships could not be established. The characteristics of referral patients of the NACDG are not representative of the general population nor representative of the average population of dermatology patients with or without suspected contact dermatitis. The concentration of MDBGN/PE used for patch testing in this study ranged from 1.0% to 2.5%, whereas many other centers use a 1.0% or 1.5% concentration, making direct comparisons difficult. A single source was recorded for each allergen. In the event that MDBGN/PE was present in multiple products, only the source that was most likely to be clinically correlated with the patient's symptoms was recorded.

CONCLUSIONS

This study analyzed MDBGN/PE reactions in routinely patch-tested patients in North America and shows that positivity to MDBGN/PE (2.0% pet) has decreased significantly over time. Demographic associations included male sex and/or age older than 40 years. Exposure sources were predominantly personal care products, especially moisturizers/lotions/creams. Methyl dibromoglutaronitrile/phenoxyethanol is rarely used in these products today.

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