

Positive Patch-Test Reactions to Propylene Glycol: A Retrospective Cross-Sectional Analysis from the North American Contact Dermatitis Group, 1996 to 2006

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

Background: Propylene glycol (PG) may cause allergic or irritant contact dermatitis. It primarily functions as a vehicle, solvent, or emulsifier in cosmetics and topical medications.

Objectives: To characterize the prevalence of positive patch-test reactions to PG and the epidemiology of affected patients.

Methods: Retrospective analysis of cross-sectional data compiled by the North American Contact Dermatitis Group (NACDG) from 1996 to 2006.

Results: Of 23,359 patients, 810 (3.5%) had allergic patch-test reactions to 30% PG; 12.8% of the reactions were of definite clinical relevance (positive reaction to a personal product containing PG), 88.3% were considered to be currently relevant (definite, probable, or possible relevance), and 4.2% of reactions were occupation related, most commonly to mechanical and motor vehicle occupations. Common sources of PG were personal care products (creams, lotions, and cosmetics, 53.8%), topical corticosteroids (18.3%), and other topical medicaments (10.1%). In patients positive only to PG ($n = 135$), the face was most commonly affected (25.9%), followed by a scattered or generalized pattern (23.7%). The most common concomitant reactions included reactions to *Myroxilon pereirae*, fragrance mix, formaldehyde, bacitracin, methylidibromoglutaronitrile/phenoxyethanol, carba mix, and tixocortol pivalate.

Conclusions: In this select population of patients referred for patch testing, allergic reactions to PG were often currently clinically relevant but were rarely related to occupation. The most common sources were personal care products and topical corticosteroids.

PROPYLENE GLYCOL (PG) is a ubiquitous ingredient. It is used in many products as a solvent, vehicle, emulsifier, or humectant. It is also used as a thickening agent in many foods although some experts contend that the concentration of PG in foods is too low to cause skin reactions.¹ The amount of propylene glycol produced and used in the production of other products is staggering; the annual global production of propylene glycol was estimated to be 1.4 million metric tons in 2007, and global demand is growing at a rate of 3 to 7% per year.² Since the early 1950s, when the original patch-test studies of contact allergy to PG were conducted,³ several case series and single case reports of allergy to PG have been published.⁴⁻⁸ Although rates of sensitization to PG have

been reported periodically by the North American Contact Dermatitis Group (NACDG) and other contact dermatitis groups,⁹⁻¹² detailed evaluation of patients' characteristics, allergen sources, and related occupations has not been conducted to our knowledge. The purpose of this study was to evaluate the characteristics of patients who have allergic reactions to PG, as well as the clinical relevance, source of exposure, and occupational relationship of allergic patch-test reactions to PG.

Materials and Methods

NACDG Database

The NACDG has tested with PG since 1992, initially using a 10% aqueous solution (from 1992 to 1996) and then a 30% aqueous solution. Between 1996 and 2006, 23,359 patients were patch-tested with the NACDG standard series of 50 to 65 allergens, as previously described.⁸⁻¹¹ Patch-testing methods, reaction quantification, and final diagnoses were determined according to standard NACDG methods.^{8,9} The final determination of an allergic patch-

From the North American Contact Dermatitis Group.

Funded by an American Contact Dermatitis Society Clinical Research Grant.

Reprints not available.

DOI 10.2310/6620.2008.08039

© 2009 American Contact Dermatitis Society. All Rights Reserved.

DECKER_X



test reaction (yes or no) was a separate code from the codes for the first and second patch-test readings. This final code was based on clinical judgment and interpretation of several factors after all patch-test readings were completed. Macular erythema was generally coded as a doubtful (nonallergic) reaction. If the clinical history or other positive reactions to the same allergen in a different vehicle or a cross-reacting substance were identified, the investigator had the discretion to make the final determination that the macular erythema represented an allergic reaction.

In addition to positive patch-test reactions to PG 30% aqueous, collected data included demographics (age, gender, and race), dermatitis site (up to three sites), occupation, allergens (clinical relevance, source, and relationship to occupation for each positive allergen), relevant irritants (source and relationship to occupation), and final diagnoses (up to three). Relevance and source codes were linked to specific allergens whereas site codes and final diagnosis codes were linked to patients but not to specific allergens. Occupation-relevant reactions were determined by clinical history and occupational exposure. Current relevance was defined as “definite” (a positive use-test or patch-test reaction to the putative item containing the allergen), “probable” (the substance identified by patch testing was verified as present in the known skin contactants of the patient), or “possible” (the patient was exposed to circumstances in which skin contact with materials known to contain the putative allergen were likely). Three-digit source codes were implemented in 2001. Occupational codes were determined by a coding expert, on the basis of a standardized questionnaire.¹³ Relevant allergen sources from non-NACDG standard allergens were also recorded although the name of the responsible allergen was not collected as part of the database. Additional testing (such as prick testing for immediate type I reactions), if performed, was not collected as part of this database, nor were specific subtypes of allergic contact dermatitis (such as systemic contact dermatitis).

Study Population and Data Analysis

The Minneapolis Veterans Affairs Medical Center Human Studies Subcommittee provided institutional review board approval for this cross-sectional analysis of de-identified data from patients patch-tested by the NACDG between 1996 and 2006. Patients with a final interpretation of an allergic reaction to PG were included in this analysis. Two subgroups of interest were identified: (1) “definite

reactors,” those individuals with allergic reactions to PG that were of definite clinical relevance (positive patch-test or use-test reaction to a product containing PG used in the area of dermatitis in addition to a positive patch-test reaction to PG), and (2) “single reactors,” those individuals who had no other currently relevant allergic patch-test reactions other than reactions to PG. Single reactors were analyzed separately to evaluate the site of dermatitis without confounding from other positive allergens.

At the time of collection, data were entered at a central location with *Access 2003* software (Microsoft Corporation, Redmond, WA). Manual verification was performed for quality assurance. Descriptive analyses included frequencies, counts, and proportions.

Results

Demographics

A total of 23,359 patients were patch-tested by the NACDG between 1996 and 2006; 810 patients (3.5%) had an allergic patch-test reaction to PG 30% aqueous. Of these allergic reactions, 716 (88.4%) were currently relevant (Table 1). Reactions that were considered to be definitely relevant made up 12.8% of all reactions to PG (those with such reactions were considered definite reactors); 135 patients (16.6%) had a currently relevant allergic reaction to PG and had no other currently relevant allergic reactions (single reactors). Additionally, 88.9% of all reactions were considered to be weak (+), strong (++), or extreme (+++) at the second reading (see Table 1).

The demographics of all 810 PG-allergic patients are listed in Table 2; female sex and Caucasian race were the most common characteristics in this group as well as in the subgroups of definite reactors and single reactors. In single reactors, the face was the most common site of dermatitis (25.9%), followed by a scattered or generalized pattern (23.7%) (Table 3).

Occupation-Related Reactions to PG

Of all 810 patients with positive patch-test reactions to PG, 4.2% had reactions that were considered occupation related, and all of these were currently relevant (Table 4). The industry whose workers had the most occupation-related reactions was the mechanical and motor vehicle industry (38.2%) (Table 5). Five occupation-associated

Table 1. Relevance of Positive Allergic Reactions to Propylene Glycol and Second-Reading Reaction Strength

Relevance	No. of Reactions (n = 810)	%
Current*	716	88.4
Definite	104	12.8
Probable	243	30.0
Possible	369	45.5
Past	13	1.6
Unknown	81	10.0
Second reading [†]		
Weak (+)	475	58.6
Strong (++)	195	24.1
Extreme (+++)	50	6.2
Macular erythema (doubtful) [‡]	82	10.1
Other	8	1.0

*Current relevance was defined as (1) definite (the result of a use test with the suspected item was positive, or the reaction of a patch test with the item or product was positive), (2) probable (the antigen could be verified as present in known skin contactants, and the clinical presentation was consistent), and (3) possible (the patient was exposed to circumstances in which skin contact with materials known to contain the allergen is likely to occur).

[†]Weak = nonvesicular reaction consisting of erythema, infiltration, and (possibly) papules; strong = edematous or vesicular reaction; extreme = spreading, bullous, and ulcerative reaction; other = missing or irritant with a final interpretation of "allergic reaction."

[‡]Only macular erythema with a final interpretation of "allergic reaction" was included in this study.

reactions were ascribed to automotive products, and five were ascribed to personal care products (Table 6).

Sources of Exposure to PG

Data from 2000 to 2006 ($n = 465$) included source codes for allergen exposure. Personal care products (e.g.,

moisturizers and cosmetics) were the most common source of exposure to PG (53.8%), followed by topical steroids (18.3%) and other topical medicaments (6.2%) (see Table 6).

Concomitant Allergic Reactions

Concomitant allergic reactions in PG-allergic patients were similar to those allergens that are most commonly seen in the general study population; these included *Myroxylon pereirae* (balsam of Peru), fragrance mix, formaldehyde, nickel, bacitracin, neomycin, quaternium-15, and cobalt (Table 7). Allergy to tixocortol pivalate, a marker for group A corticosteroid allergy and an infrequent allergen in the general study population, was frequently associated with allergy to PG.

Discussion

Demographics

This study yielded several findings. First, although the overall prevalence of allergic reactions to PG was relatively low (3.5%), almost all reactions (88.4%) were currently relevant (12.8% definite, 30% probable, and 45.5% possible). Second, in the single-reactor subgroup, 25.9% of patients were affected by dermatitis of the face and 23.7% had dermatitis in a scattered or generalized pattern. Although leg dermatitis has been reported as a significant risk factor for sensitization to PG,² the leg was the fifth most common site of dermatitis in our single reactors (14.8%) (see Table 3). It is thought that many PG-allergic patients are exposed through cosmetics (especially moisturizers) or topical medicaments (especially corticoster-

Table 2. Demographics of Study Patients Allergic to Propylene Glycol

Characteristic		PG-Allergic Patients (n = 810)	Single Reactors* (n = 135)	Definite Reactors [†] (n = 104)
Sex	Male	380 (46.9%)	65 (48.1%)	50 (48.1%)
Age (yr)	≥ 40	546 (67.4%)	76 (56.3%)	71 (68.3%)
	Range	4–88	4–88	11–82
	Average	47.9	44.1	48.2
Race	Caucasian	681 (84.1%)	109 (80.7%)	95 (91.4%)
Atopy	Allergic rhinitis	197 (24.3%)	32 (23.7%)	31 (29.8%)
	Atopic dermatitis	166 (20.5%)	39 (28.9%)	28 (26.9%)
	Asthma	119 (14.7%)	13 (9.6%)	10 (9.6%)
	Any of the above	296 (36.5%)	57 (42.2%)	32 (30.8%)

PG = propylene glycol.

*Patients with a currently relevant reaction to propylene glycol (definite, probable, or possible) and no other currently relevant reactions.

[†]Patients with a definite clinically relevant positive reaction to propylene glycol.

Table 3. Dermatitis Sites in 135 Single Reactors

<i>Site of Involvement</i>	<i>Single Reactors</i> ^{*†}	
	<i>n</i>	<i>%</i>
Face	35	25.9
Scattered or generalized	32	23.7
Trunk	22	16.3
Arm	22	16.3
Leg	20	14.8
Hand	17	12.6
Other	61	44.6

*Patients with a currently relevant reaction to propylene glycol (definite, probable, or possible) and no other currently relevant reactions.

†Total sites add up to > 135 and > 100% because up to three sites were possible per patient.

Table 4. Occupation-Related Reactions to Propylene Glycol

<i>Occupation-Related Reactions</i>	<i>Relevance</i> [*]		<i>Total (n = 810)</i>	
	<i>Probable</i>	<i>Possible</i>	<i>No.</i>	<i>%</i>
Yes	12	6	18	2.2
Unsure	2	14	16	2.0
Total	14	20	34	4.2

*No occupation-related reactions of definite, past, or unknown relevance were reported.

oids), which are left on the skin.² This theory is consistent with our data in regard to both site (see Table 3) and source (52.9% for personal care products and 24.5% for topical medicaments).

Occupation

In the context of PG allergy, relationship to occupation was rather uncommon and occurred in only 4.2% of all PG-positive patients and only 2.2% had reactions that were coded as definitely related to occupation. This relatively low number of occupation-related allergic reactions to PG is consistent with the fact that most sources identified in our study were personal care products or topical medicaments, which are less likely to be linked with occupation. It is also often difficult to identify “nonhazardous” ingredients (such as PG) in a workplace setting, as these ingredients are not commonly declared on Material Safety Data Sheets. Mechanical and motor vehicle work was most often associated with occupation-related reactions, likely owing to the use of automotive oil and grease.

Sources

Approximately half of the allergic reactions to PG were either definitely or probably clinically relevant and were associated with a personal care product. This is not surprising. The National Institutes of Health and the National Library of Medicine oversee the Specialized Information Services, which maintains the Household Products Database. This database lists 505 household products containing PG; a search of these 505 products found that 406 (80.4%) are personal care products.¹⁴ A review of 1,771 personal care products listed in the

Table 5. Occupations of Patients with Occupation-Related Reactions to Propylene Glycol

<i>Occupation</i>	<i>Occupation-Related Reactions</i>		
	<i>Yes</i>	<i>Unsure</i>	<i>Total</i>
Mechanical and motor vehicle workers*	7	6	13
Printing press operators	2	1	3
Electrical engineers, electricians	2	1	3
Nurses	0	3	3
Hospital administrators	0	2	2
Students	2	0	2
Homemakers	1	0	1
Dentists	0	1	1
Physicians	0	1	1
Barbers	1	0	1
Personal service workers	1	0	1
Unknown	2	1	3
Total	18	16	34

*Includes aircraft purchasing managers (1), welders/cutters (1), assemblers (2), janitors (1), machinists and machine operators (3), mechanics (1), accountants (2), mechanical inspectors (1), and auto and home supply retail workers (1).

Table 6. Sources Associated with Propylene Glycol, 2001 to 2006

Source Category	Source Subcategory	Reactions (n = 465)		Relevance		
		No.	% of n	Definite	Probable	Possible
Personal care products	NOS	138 (4)*	29.7	18	42	78 (4)*
	Lotions or creams	76 (1)*	16.3	18	21	37 (1)*
	Cosmetics or makeup	27	5.8	1	5	21
	Deodorants	5	1.1	3	2	0
	Hand sanitizers	1	< 1	0	0	1
	Nail care products	1	< 1	0	0	1
	Hair styling products	1	< 1	1	0	0
	Oral hygiene products	1	< 1	0	1	0
	Shampoos	4	< 1	0	1	3
	Personal hygiene cleanser	2	< 1	0	0	2
Medicaments	Topical steroids	85	18.3	14	32	39
	Topical drugs NOS	29	6.2	5	13	11
	Topical antibiotics	1	< 1	1	0	0
	Topical antifungals	4	< 1	1	2	1
	Topical analgesics	2	< 1	2	0	0
	Topical anti-acne products	1	< 1	0	1	0
	Adhesive bandages and tapes	3	< 1	2	0	1
	Oral drugs (including ETOH)	3	< 1	0	2	1
	Medical devices NOS	2	< 1	1	1	0
	Street drugs	2	<1	0	1	1
Miscellaneous	Automotive products	6 (5)*	1.3	0	3 (2)*	3 (3)*
	Food	5	1.1	0	2	3
	Nonskin cleansers	2	< 1	0	0	2
	Chemical products NOS	1 (1)*	< 1	0	1 (1)*	0
	Unknown	31 (1)*	6.7	0	0	31 (1)*
	Not applicable	32	6.9	0	6	26
Total		465	100	67	136	262

ETOH = alcohol; NOS = not otherwise specified.

*Number of occupation-related reactions from 2000 to 2006.

Table 7. Top 13 Concomitant Allergens for Patients Who Reacted to Propylene Glycol

Allergen	No. of Allergic Patients	% (n = 810)
<i>Myroxilon pereirae</i> 25% pet	201	24.8
Fragrance mix 8% pet	138	17.0
Formaldehyde 1% aq	137	16.9
Nickel sulfate 2.5% pet	130	18.7
Bacitracin 20% pet	114	14.1
Neomycin sulfate 20% pet	110	13.6
MDGN/PE 1%, 2%, and 2.5% pet	109	13.5
Quaternium-15 2% pet	109	13.5
2-Bromo 2-nitropropane 0.5% pet	101	12.5
Carba mix 3% pet	101	12.5
Cobalt chloride 1% pet	92	11.3
Tixocortol pivalate 1% pet	81	10
Potassium dichromate 0.25% pet	71	8.8

aq = aqueous; MDGN/PE = methyldibromoglutaronitrile/phenoxyethanol; pet = petrolatum.

Contact Allergy Replacement Database (CARD) found that 531 (30%) contained PG or one of its cross-reactors.¹⁵

Topical medicaments were an important source of PG allergy in our study, especially topical corticosteroids, which caused 18.3% of all reactions. The high number of reactions ascribed to a topical corticosteroid source is noteworthy, given that corticosteroids are often first-line therapy for eczematous dermatitis and may thus confound or delay a correct diagnosis of allergic contact dermatitis.⁶ Concomitant allergy to tixocortol pivalate was more common than expected in our study population (10%), suggesting the likelihood of cosensitization from topical corticosteroid preparations. A recent evaluation of corticosteroid vehicles found that PG was the most common allergen identified in topical corticosteroids (106/166 products, 64%).¹⁶

Concomitant Reactions

In an analysis of 45,138 patients tested with 20% PG, Lessman and colleagues reported higher rates of concomitant reactions to fragrance mix and *Myroxilon pereirae* in PG-sensitive patients as compared to patients with other allergies; 31% of PG-positive patients reacted to fragrance mix as compared to 12.1% of PG-negative patients whereas 27.8% of PG-positive patients reacted to *Myroxilon pereirae* as compared to 9.3% of PG-negative patients.⁴ Our findings were similar: 24.8% of our study patients had concomitant reactions to *Myroxilon pereirae*, making it the most common concomitant allergen, and 17.0% of our study patients had a concomitant allergen to fragrance mix, making it the second most common. It is important that *Myroxilon pereirae* and fragrance mix are among the five most commonly reported allergens in many large patch-test databases.^{10,11,17} Thus, this finding may simply be due to chance, or it could represent cosensitization to fragrance ingredients in personal care products (which are almost always scented).

A higher rate of concomitant reactions to cocamidopropyl betaine in PG-allergic patients has also been reported.¹⁸ This was not seen in our 810 PG-allergic patients; only 4.3% had a concomitant reaction to cocamidopropyl betaine.

Limitations

This study had several limitations. First, the data was cross-sectional; thus, causal relations cannot be determined. Second, the characteristics of the referral population of the NACDG are not representative of either the general population or the general patch-test population; therefore,

generalizability is limited. Third, some experts believe (owing to the irritant nature of PG and a reported low frequency of reproducible reactions)¹⁹ that positive patch-test reactions to PG should be followed by serial dilutions, repeated open application tests, oral challenge tests, or all three of these tests to help determine clinical significance and confirm allergy.^{20–28} If additional tests were performed, results were not collected as part of this database. Fourth, reactions to PG can be irritant, allergic, nonimmunologic contact urticaria, or sensory irritation; however, the NACDG database focuses on allergic reactions.²⁷ Fifth, because of the referral nature of the NACDG patient population, a determination of relevance (as it pertains to the clearance of dermatitis after avoidance of the allergen) is often not possible owing to limited follow-up.

Conclusions

Dermatitis on the face and scattered or generalized dermatitis were the most common patterns of dermatitis in patients with allergy to only PG (single reactors). Further, occupation-related reactions were uncommon. Personal care products were the most common source of allergy, followed by topical medicaments, especially topical corticosteroids. Fragrance mix and *Myroxilon pereirae* were the two most common concomitant allergens associated with PG allergy.

References

1. Fisher AA. Systemic contact dermatitis caused by ingestion of certain foods in propylene glycol-sensitive patients. *Am J Contact Dermat* 1996;7:259.
2. Ashland Inc. Ashland and Cargill to combine talents for bio-based chemical joint venture. Available at: http://www.ashland.com/press_room/news_detail.asp?s=1524 (accessed September 24, 2008).
3. Warshaw TG, Herrmann F. Studies of skin reactions to propylene glycol. *J Invest Dermatol* 1953;19:423–9.
4. Lessman H, Schnuch A, Geier J, Uter W. Skin-sensitization and irritant properties of propylene glycol. *Contact Dermatitis* 2005;53: 247–59.
5. Corazza M, Virgili A, Mantovani L, La-Malfa W. Propylene glycol allergy from acyclovir cream with cross-reactivity to hydroxypropyl cellulose in transdermal estradiol cream? *Contact Dermatitis* 1993; 29:283–4.
6. Gonzalo MA, de Argila D, Garcia JM, Alvarado MI. Allergic contact dermatitis to propylene glycol. *Allergy* 1999;54:82–3.
7. Fowler JF. Contact allergy to propylene glycol in topical corticosteroids. *Am J Contact Dermat* 1993;4:37–8.
8. Francalanci S, Giorgini S, Ricci L, Sertoli A. Patch testing by additional series of allergens: results of further experiences. *Am J Contact Dermat* 2001;12:203–7.

9. Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000;136:272–3.
10. Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1998–2000. *Am J Contact Dermat* 2003;14:59–62.
11. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch test results, 2001–2002 study period [published erratum appears in *Dermatitis* 2005;16:106]. *Dermatitis* 2004;15:176–83.
12. Warshaw EM, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2003–2004 study period. *Dermatitis*. 2008;19:129–36.
13. U.S. Census Bureau: Industry and occupation 2000. Available at: http://www.census.gov/hhes/www/ioindex/cens_300_354.html (accessed May 6, 2008).
14. U.S. Department of Health and Human Services. Household Products Database. <http://hpd.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=47&query=propylene+glycol> (accessed May 6, 2008).
15. American Contact Dermatitis Society. Contact Allergen Replacement Database. <http://www.cardsite.org/> (accessed May 6, 2008).
16. Coloe J, Zirwas MJ. Allergens in corticosteroid vehicles. *Dermatitis* 2008;19:38–42.
17. Lazarov A. European standard series patch test results from contact dermatitis clinic in Israel during the 7-year period from 1998 to 2004. *Contact Dermatitis* 2006;55:73–6.
18. Shaffer KK, Jaimes JP, Hordinsky MK, et al. Allergenicity and reactivity of coconut-oil derivatives: A double-blind randomized controlled pilot study. *Dermatitis* 2006;17:71–6.
19. Trancik RJ, Maibach HI. Propylene glycol: irritation or sensitization? *Contact Dermatitis* 1982;8:185–9.
20. Fan W, Kinnunen T, Niinimäki A, Hannuksela M. Skin reactions to glycols used in dermatologic and cosmetic vehicles. *Am J Contact Dermat* 1991;2:181–3.
21. Wahlberg JE, Nilsson G. Skin irritancy from propylene glycol. *Acta Derm Venereol (Stockh)* 1984;64:286–90.
22. Willis CM, Stephens JM, Wilkinson JD. Experimentally induced irritant contact dermatitis: determination of optimum irritant concentrations. *Contact Dermatitis* 1988;18:20–4.
23. Zesch A. Skin irritation by topical drugs. *Derm Beruf Umwelt* 1983; 31:74–8.
24. Andersen KE, Storrs FJ. Skin irritation caused by propylene glycols. *Hautarzt* 1982;33:12–4.
25. Frosch PJ, Pekar U, Enzmann H. Contact allergy to propylene glycol. Do we use the appropriate test concentration? *Dermatol Clin* 1990;8:111–3.
26. Lahti A, Poutianen A-M, Hannuksela M. Alcohol vehicles in tests for non-immunological immediate contact reactions. *Contact Dermatitis* 1993;29:22–5.
27. Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986;14:221–7.
28. Funk JO, Maibach HI. Propylene glycol dermatitis: re-evaluation of an old problem. *Contact Dermatitis* 1994;31:236–41.