

Review Article

Skin-sensitizing and irritant properties of propylene glycol

Data analysis of a multicentre surveillance network (IVDK*) and review of the literature

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In the several publications reviewed in this article, propylene glycol (PG; 1,2-propylene glycol) is described as a very weak contact sensitizer, if at all. However, particular exposures to PG-containing products might be associated with an elevated risk of sensitization. To identify such exposures, we analysed patch test data of 45 138 patients who have been tested with 20% PG in water between 1992 and 2002. Out of these, 1044 patients (2.3%) tested positively, 1083 showed a doubtful, follicular or erythematous reaction (2.4%) and 271 explicit irritant reactions (0.6%). This profile of patch test reactions is indicative of a slightly irritant preparation, and thus, many of the 'weak positive' reactions must probably be interpreted as false positive. No private or occupational exposures associated with an increased risk of PG sensitization were identified, except for lower leg dermatitis. Therefore, according to our patch test data, PG seems to exhibit very low sensitization potential, and the risk for sensitization to PG on uncompromised skin seems to be very low.

Key words: 1,2-dihydroxypropane; 1,2-propanediol; 1,2-propylene glycol; CAS: 57-55-6; irritancy; monopropylene glycol; sensitizing properties. © Blackwell Munksgaard, 2005.

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Propylene glycol (PG) is used industrially as intermediate for the synthesis of other chemicals. Moreover, it is used as solvent, as plasticizer, in household products, as food additive or as ingredient of many cosmetics and pharmaceutical preparations. Skin exposure of consumers to PG

most commonly occurs through contact with cosmetics or topical medicaments.

A review of the literature reveals that several case reports of allergic reactions to PG have been published, almost always related to medical preparations for topical use (Table 1). In some cases,

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Table 1. Case reports on suspected contact sensitization to propylene glycol (PG) and outcome of patch tests performed

Tested person	Concentration (vehicle)	Result	Exposure/remarks	Reference
38-year-old woman	10% (aqueous)	Positive at D2 and D3	Possibly PG-containing acyclovir cream/also positive reaction to another PG test preparation (concentration not stated), but no reaction to a third test preparation of 10% PG (aqueous)	Bourezane et al. (64)
43-year-old man	20% (pet.)	Negative at D2, 3 + at D4	PG-containing ECG electrode	Connolly and Buckley (89)
51-year-old woman	10% (aqueous)	1 + at D2, 3 + at D3	PG-containing acyclovir cream/no reaction to acyclovir and the other components of the cream	Corazza et al. (65)
62-year-old man	(*)	Positive at D4	Skin reaction 24 hr after application of an ultrasonic gel/also positive reactions to methyl and propyl paraben	Eguino et al. (90)
1 patient	5% (aqueous)	Negative at D2, positive at D4	PG-containing ketoconazole cream; no reactions to 0.1%, 1%, 5% and 10% ketoconazole (pet.), no reactions to other ingredients of the cream	Eun and Kim (66)
80-year-old woman	5% (pet.)	2 + at D2 and D4	40% PG preparation for treatment of actinic keratoses; later skin reaction after topical use of a fluorouracil cream containing 11.5% PG/also positive reactions to 1%, 2%, 10%, 20% and 40% PG in aqueous cream BP and 20% and 40% PG (aqueous)	Farrar et al. (92)
36-year-old woman	5% (aqueous)	Positive (no other details given)	Vulvitis after exposure to PG-containing lubricant for medical examination and after intravenous injection of a diazepam preparation containing 40% PG	Fisher (67)
78-year-old woman	1% (pet.)	Positive at D3	PG-containing calcipotriol ointment	Fisher (68)
29-, 55- and 27-year-old women	5% and 10% (aqueous)	Positive at D2	Several PG-containing preparations, lubricant containing 3.75% PG / in 2 cases strongly positive reactions to 5% and 10% PG and only erythematous reaction to 2% PG; test concentration not specified for 1 case; in all 3 cases but not in 10 control subjects positive reaction to the lubricant	Fisher and Brancaccio (69)
48-year-old woman	10% (aqueous)	Negative at D2; 2 + at D4	Several PG-containing corticosteroid preparations/dermatitis resolved on changing to PG-free preparations	Fowler (70)
52-year-old woman	10%, 50% and 100% (aqueous)	Negative, + and 2 + at D3	Ear drop preparation containing 50% PG/pruritic macula rash and flare up of the ear dermatitis 20 hr after oral provocation with 5 ml PG	Frosch et al. (14)
66-year-old man	2%, 5%, 10% and 20% (aqueous)	Always 3 + at D2 and D4	PG-containing ECG electrode gel/eruptions appeared 3 hr to 4 hr after application of the gel and peaked after 48 hr; patient with multiple sensitization reactions	Gonzalo et al. (71)
52-year-old man	1% (aqueous)	1 + at D2 and D4	PG-containing acyclovir cream/also positive reaction to the cream but no reaction to other components of the cream	Kim and Kim (72)
30-year-old woman	20% (pet.)	2 + at D2, 1 + at D4	Probably PG in a brassiere-padding insert	Lamb et al. (93)

25-year-old woman	2% and 10% (aqueous)	1 + at D2; 2 + at D4	PG-containing acyclovir cream/also positive reaction to the cream but no reaction to other components of 10% PG (aqueous)	Piletta et al. (73)
1 patient	10% (aqueous)	3 +	PG-containing minoxidil preparation/time of reading not stated; also positive reaction to minoxidil	Ruas et al. (74)
41-year-old man	3% (pet.), 1% (aqueous)	2 +	PG-containing ketoconazole cream/time of reading not stated; also positive reactions to ketoconazole, miconazole and sulconazole	Santucci et al. (75)
61-year-old man	0.5% (aqueous)	2 + at D2	Possibly PG in a topical rifamycin preparation/no results of further reading given; no reaction to 5% PG (pet.)	el-Sayed et al. (91)
47-year-old woman	5% (pet.)	3 + at D3	PG-containing minoxidil preparation/also positive reaction to 50% PG (aqueous)	Schman et al. (98)
60-year-old man	20% (aqueous)	? + at D1; 1 + at D2 and D3	ECG electrode gel containing 15% PG/only doubtful reactions to 10% PG (aqueous) and no reaction to 5% and 1% PG (aqueous); despite corticoid prophylaxis during further use of PG-containing ECG reactions on application sites and flare up on previous application sites developed, positive ROAT with 20% PG (aqueous)	Uter and Schwantz (76)

Aqueous = water, pet. = petrolatum.

*Product concentration of PG tested (vehicle and concentration not stated).

patch test results were equivocal without further substantiation by use tests or repeated open application tests (ROATs). Therefore, true contact sensitization is not always definitely proven or can even be doubted. In a few other studies, verification tests had been performed to prove relevant contact sensitization, accordingly (1). Several patch test studies in different test populations ($n = 400$ – 5804 patients) with PG in concentrations between 2% and 30% revealed a frequency of positive reactions in a range of 0.1% to 3.8% of patients tested (Table 2). This great variability may indicate considerable differences in the diagnostic methods and the study populations (i.e. patient selection) between centres. Therefore, it is difficult to draw definite conclusions with regard to (a) the sensitizing properties of PG, (b) the possible role of trigger factors of sensitization and (c) the overall impact of sensitization to PG.

Therefore, an analysis of a large pool of clinical data was performed, addressing the possible association between PG patch test reactions and patient characteristics (demographic and clinical features and different exposures). This analysis is based on the frequency of reactions in routine patch testing with 20% PG in water, recorded in the participating clinics of the Information Network of Departments of Dermatology (IVDK; <http://www.ivdk.org>) between 1992 and 2002.

Propylene Glycol Properties and Human Exposure

Use and potential exposure

PG, a viscous, colourless fluid with almost no odour and a very low toxicity, is mixable with water and alcohol and it is soluble in a variety of organic solvents. The chemical melts at -60°C , its boiling point is at 188°C and it is prepared by the reaction of propylene oxide with water. PG-production capacity has been reported to have been about 600 000 tons in the US (1998) and about 325 000 tons in Western Europe (1989). Of this volume, 40–45% is estimated to be used as intermediate in the synthesis of other chemicals, especially unsaturated polyester resins. The remainder of the production volume is used in a multitude of industrial products, for example:

- (1) as solvent in lacquers and varnishes (about 4% of the production)
- (2) for certain resins and also as plasticizer, for example, in vinyl resins (about 4–10%)
- (3) as component in antifreeze products, lubricants, cutting-fluids, inks (about 10–13%)

Table 2. Patch test studies with propylene glycol (PG) in dermatological patients

No. of tested persons	Concentration (vehicle)	No. of allergic/total no. of reactions	Remarks	Reference
84	100%	5 (6%)/12 (14.3%)	5 allergic type reactions reproduced in 2 of 5 patients and verified in 3 other of these 5 patients by positive use test; 7 irritant reactions were not reproducible in retesting	Andersen and Storrs (8)
1556	100%	59 (3.8%)/194 (12.5%)	Allergic type reactions verified by morphology of the reaction and by reaction kinetics; 17, 11 and 9 of 42 tested patients with initial reaction to 100% PG reacted in retesting to 32%, 10% and 3.2% PG (aqueous) respectively with an allergic type reaction and 3, 1 and 0 patients with a toxic type reaction; 4 allergic cases proven by use test in 15 patients with allergic type reactions	Hannuksela et al. (11)
98	100%	0/11 (11.2%)	8 × 1 +, 2 × 2 + and 1 × 3 + reaction; no reaction was considered allergic because all patients were without history of PG dermatitis; in retesting no reactions in 5 patients	Nater et al. (9)
866	100%	n.s./138 (15.7%)	Mainly irritant reactions (no further verification); reactions reproducible in 17/23 persons; 5 of 23 persons with initial reaction to 100% PG reacted also to 10% PG (aqueous)	Warsaw and Herrmann (77)
248	100% and 20% (aqueous)	21 (8.5%), 15 (6.1%)/80 (32.3%), 45 (18.2%)	11 × and 7 × 1 + -reaction to 100% and 20% PG respectively; only 2 reactions quoted as relevant; 2 reactions (1 relevant) and 2 doubtful reactions to 2% PG; oral provocation test positive in 2 of 5 patients tested; use test negative in all 3 patients tested	Andersen and Storrs (8)
1236	50%, 30% and 10% (aqueous)	21 (1.7%), 18 (1.5%), 8 (0.6%)/209 (16.9%), 201 (16.3%), 108 (8.7%)	Presumably allergic reactions, with relevance in 2 cases only; doubtful erythematous reactions regarded as irritant reactions	Aberer et al. (16)
1701	30% (aqueous)	13 (0.8%)/187 (11%)	9 doubtful and 165 irritant reactions; in 3, 3 and 6 of 17 patients (with initial doubtful or irritant reaction) also reactions in retesting with 1%, 2% and 10% PG (aqueous) respectively; in 1/2 and 2/2 patients with allergic reactions to 30% PG, also reaction in retesting to 2% and 10% PG respectively	Fan et al. (12)
86	30% (aqueous)	n.s./19 (22.1%)	Type of reaction not verified; 2/19 and 5/19 with positive reaction to at least 10% or 1% PG (aqueous) respectively; positive ROAT with 5% PG in cream base in 4/12, 1/2 and 5/5 of these patients	Hannuksela and Salo (10)
823	30% (aqueous)	n.s./31 (3.8%)	Type of reaction not verified; in 2/18 and 1/18 patients with initial reaction to 30% PG-positive response in retesting to 10% or 1% PG (aqueous) respectively	Kinnunen and Hannuksela (13)
4095	30% (aqueous)	n.s. (3.8%)/n.s.	Test results from July 1996 to June 1998; relevance assumed in 68.5% of positive reactions	Marks et al. (95)
5804	30% (aqueous)	n.s. (3.7%)/n.s. (4.4%)	Type of reaction unknown in further 1.2%; test results from July 1998 to December 2000; definite/probable/possible or past relevance assumed in 8.3%, 28.2%, 47.7% and 2.8% of positive reactions	Marks et al. (96)
4899	30% (aqueous)	n.s. (4.2%)/n.s. (4.9%)	Type of reaction unknown in further 0.9%; test results from 2001 to 2002; definite/probable/possible or past relevance assumed in 18.1%, 20.1%, 51.0% and 0.5% of positive reactions	Pratt et al. (97)

400	20% (aqueous)	6 (1.5%)/n.s.	Reactions verified by history of contact with PG-containing preparations, appearance of the reactions and positive retests; no data given for irritant reactions	Angelini and Meneghini (78)
330	10% (aqueous)	n.s./13 (3.9%)	Type of reaction not verified	Blondeel et al. (79)
500	10% (aqueous)	n.s./32 (6.4%)	Type of reaction not verified	Calas et al. (80)
4005	10% (aqueous)	n.s./44 (1.1%)	Type of reaction not verified	Fransway (81)
775	10% (aqueous)	12 (1.6%)/34 (4.4%)	Only positive reactions at D3 were quoted as allergic reactions	Iden and Schroeter (82)
3478	10% (aqueous)	n.s. (1.1%)/n.s.	Test results from July 1992 to June 1994; relevance assumed in 62.2% of positive reactions	Marks et al. (94)
3077	10% (aqueous)	n.s. (1.1%)/n.s.	Test results from 1994 to 1996	Marks et al. (95)
1450	10%/5% (aqueous)	n.s./15 (1%)	Type of reaction not verified; in retesting with 1% or 2% PG (aqueous)-positive reactions in 7/15 patients tested	Romaguera et al. (83)
3364	5% (aqueous)	27 (0.8%)/n.s.	Reactions verified by retesting, oral provocation test and/or use test; no data on irritant reactions given	Angelini et al. (84)
63	5% (aqueous)	n.s./1 (1.6%)	Type of reaction not verified	George et al. (85)
851	5% (aqueous)	21 (2.5%)/54 (6.4%)	Only atopic patients tested	Lammintausta et al. (86)
1236	5% (pet.)	0/9 (0.7%)	Only erythematous (doubtful) reactions	Aberer et al. (16)
4948	5% (pet.)	4 (0.1%)/4 (0.1%)	Only 2+ and 3+ reactions were quoted as allergic reactions; additionally, 3 doubtful reactions	Scheuer et al. (87)
880	2% (aqueous)	2 (0.2%)/n.s.	Kind of verification not quoted; no data on irritant reactions	Hannuksela et al. (88)

Aqueous = water, pet. = petrolatum, n.s. = not stated.

and in many products for private use:

- (1) as component in many cosmetics and pharmaceutical preparations and as food additive (for example, as solvent for food colours or flavours) due to its low toxicity (about 12–17%)
- (2) in household cleansers, liquid laundry or detergents (about 9–15%)
- (3) in pet foods (about 5%) or
- (4) as humectant in tobacco (about 4%) (2).

Hence, the skin of consumers is primarily exposed to PG through contact with cosmetics and topical medicaments (12–17% of the total production), especially if the prototypical prolonged skin contact with such leave-on products is considered. These products may contain up to 25–50% PG and in some cases more than 50% PG (2, 3). Furthermore, medical devices such as ECG electrodes or ultrasonic contact gels have some relevance with regard to PG exposure.

Irritant potential and appropriate patch test concentration

Although PG has very little irritant potential on open application (4), it may cause irritant reactions when tested epicutaneously under occlusion. In a study with healthy volunteers, 14 of 35 persons tested with 100% PG showed irritant reactions (5). PG preparations in concentrations above 20% in water were irritant upon occluded patch testing, exhibiting a clear concentration gradient (6). A study with the use of laser Doppler flow technique has demonstrated that even 20% PG in water may be slightly irritant under occlusion in humans. In this study, healthy volunteers had been tested with 60 µl test preparations in large Finn Chambers® for 48 hr. While a notable increase in skin blood flow at 48 hr and 72 hr was observed after exposure to 20% PG in water, visible changes of the skin did not occur. A concentration of 5% PG in petrolatum (pet.) was found to be non-irritant (7).

Patch test reactions to undiluted PG or high PG concentrations, whether irritant or allergic, are often not reproducible upon retesting (8, 9). Moreover, only few reactions to 100% PG or 30% PG in water could later be verified as being allergic upon retesting with graded dilutions of PG in water (10–13). However, in a few patch-test-positive patients, subsequent ROATs with 5% PG preparations have yielded positive results (10, 13).

The appropriate concentration for patch testing with PG has been discussed in several

publications (7, 14, 15). For diagnostic reasons (striving for sufficient sensitivity), PG 20% in water has been suggested by Frosch et al. (14) in a case report and later also by Aberer et al. (16) based on the results of a multicentre study. In special cases, even a higher test concentration may be necessary to detect a true sensitization to PG (14). On the other hand, the irritant potential of test concentrations above 5% in water must always be considered, i.e. the possibility of false-positive patch test reactions. Regarding the low reaction index (RI) and the high positivity ratio (PR), PG has been considered a 'problematic allergen' when tested 20% in water, similar to benzoyl peroxide (1% pet.) or benzalkonium chloride (0.1% pet.) (17) [The RI is defined as the quotient: $(a - d - i)/(a + d + i)$, with a being number of allergic reactions, d number of doubtful reactions and i number of irritant reactions (18). The PR is defined as the percentage of 1+ reaction among the total of positive reactions (17)]. Therefore, positive results should be verified by retesting with 10% and 4% PG in water and particularly by a use-related test (16) such as ROAT or provocative use test.

Funk and Maibach (15) classified the skin reactions to PG into 4 possible mechanisms (irritant contact dermatitis, allergic contact dermatitis, non-immunologic contact urticaria and subjective/sensory irritation). They did not define a subirritant optimal test concentration suitable for general use and thus proposed a complex diagnostic algorithm for the evaluation of patch test reactions to PG. However, this algorithm may not always be practicable.

Further evidence for a true immunological reaction has been provided by the observation of delayed exanthematic reactions (haematogenous contact eczema) in oral provocation challenge with (diluted) PG in sensitized patients (19).

In conclusion, it seems impossible to define a test concentration of PG which will yield sufficient sensitivity, which does not, at the same time, cause a considerable proportion of false-positive reactions, i.e. insufficient specificity. Therefore, further diagnostic steps may be helpful or even necessary to validate patch test reactions to PG. These difficulties should be kept in mind when considering the reports on allergic contact dermatitis or positive patch test reactions to PG in the following sections. Reports and statistics based merely on a 1+ reaction in patients with no history of dermatitis after exposure to a PG-containing product should be interpreted with caution.

Review on Published Sensitization Data

Case reports

Allergic reactions to PG have been reported in several recent cases. In most cases, PG-containing medical preparations for topical use have been found causative for the skin reactions. In diagnostic patch testing of these cases, a broad range of PG concentrations in water or pet. was used (Table 1).

In some cases, contradictory patch test results were obtained and use tests or ROATs have not been performed. In these instances, true contact sensitization cannot be regarded as proven.

Frequency of reactions in clinical populations

Several patch test studies in different test populations (400–5804 patients) with PG in concentrations between 2% and 30% revealed a frequency of positive reactions in a range of 0.1–3.8% of the patients tested. Other test results with 5–30% PG have not been distinguished between immunological and irritative responses. In particular, due to the well-known irritant potential of pure PG, when patch tested, results of testing with 100% PG should be disregarded.

These patch test studies are summarized in Table 2; the older studies have been reviewed a decade ago (3, 15, 20).

Unfortunately, in several studies, there is insufficient information on the test concentration and type of reactions (21–24); hence, results of these studies are difficult to interpret. In a former study from the IVDK, 1865 patients had been tested with 5% PG in pet. Only 11 patients (0.6%) showed a positive reaction, while 67 (3.4%) reactions were classified as doubtful (erythema only). Therefore, a test concentration of 5% in pet. might be too low to diagnose sensitization (25). Without further evaluation as outlined above, these patch test results are difficult to interpret: a certain proportion of doubtful reactions might have been weak allergic, with the concentration too low for a full-blown positive allergic reaction. Alternatively, erythematous reactions may have been predominantly irritant with this low test concentration already.

Experimental studies in humans

A human maximization test (induction 25%, challenge 10% PG in pet.) did not induce sensitization in 24 volunteers (26). Further experimental studies with the Draize procedure failed to induce any sensitization in 204 and 89 volunteers using 12% and 60% PG, respectively (27, 28). In

a modified Draize-sensitization test, equivocal reactions have been observed during the 21-day induction period in 12 of 203 panellists. 2 weeks after the last 72-hr occlusive application of 100% PG, 19 of the 203 volunteers showed reactions at the site of 48–72-hr challenge with 100% PG (29). However, it is entirely possible that (most of) the reactions observed in these experiments were irritant, as a control group was not included, and as irritation studies already quoted indicate that pure PG has irritating properties.

Experimental studies in animals

No sensitization could be achieved in a guinea pig maximization test in 10 animals (intradermal, topical induction as well as challenge with 100% PG) (30). Negative results have also been reported in another less well-documented guinea pig maximization test, an open epicutaneous test and a chamber test (3 48-hr occlusive applications in 4 Finn Chambers[®] on each site of the scapular region) with 70% PG in water (31). Likewise, the epicutaneous challenge with 100% PG in an optimization test in guinea pigs has shown no sensitization reaction in 20 animals which had been treated with 0.1% PG for intradermal induction (32). Even studies with 7 different methods (including guinea pig maximization test, split adjuvant test, optimization test, FCA test, open epicutaneous test, a test method according to Dossou and Sicard and a further modified induction method with the use of FCA, followed by a repeated occlusive application) could not show any sensitization with undiluted PG in groups of 8–20 animals (33, 34). In addition, negative results have been reported for a modified mouse ear swelling test with 100% PG in 19 BALB/c mice (35). A recent study revealed no sensitization in a local lymph node assay with PG up to 100%. Therefore no EC3 value could be estimated (36).

In summary, several predictive tests failed to detect any sensitizing properties of PG.

Analysis of IVDK Data, 1992–2002

Patients and methods

The multicentre project IVDK, an instrument of epidemiological surveillance of contact allergy, has been described in detail elsewhere (37, 38).

Briefly, patients with suspected allergic contact eczema, attending the contact allergy clinics comprising the multicentre project, are usually patch tested with the standard series of the German Contact Dermatitis Research Group (DKG)

and partially with additional series, depending on individual history. Patch tests are performed in accordance with current guidelines of the DKG (39) and international recommendations (40, 41). Patch test material is obtained from Hermal/Reinbek, Germany and applied for 24 hr or 48 hr. Readings are taken until at least 72 hr using the following gradings: neg, ?, +, ++, +++, irritant and follicular. The patch test results of every reading, a standardized history (comprising age, sex, atopic diseases, current and former occupation(s) and presumptive causal exposures), as well as final diagnosis, and site of dermatitis are assessed and documented. All data are regularly transferred to the data centre in Göttingen in an anonymized format.

Frequencies of sensitization (as percentage of patients tested) were calculated as crude proportions and as proportions standardized for sex and age (37), following current guidelines (42). The RI and the PR were calculated as further parameters to assess the diagnostic quality of a patch test preparation.

For comparison of the demographic characteristics of patients positive and non-positive to an allergen, the MOAHLFA index (37) is used. With the positive versus non-positive patch test reaction as outcome, a Poisson regression analysis is performed, quantifying the independent impact of the MOAHLFA factors on PG-sensitization risk by the prevalence ratio, accompanied by 95% confidence intervals (CI). Further information from the patient history, particularly the occupation of allergic and non-allergic patch test patients, is considered.

For data management and analysis, the statistical software package SAS 8.2 (SAS Institute, Cary, NC, USA) was used.

For this analysis, we included patients tested with PG additionally to the standard series between 1992 and 2002. In total, 45 138 patients (28 928 females and 16 210 males) have been tested with 20% PG in water.

Results

Out of these 45 138 patients, 1044 (2.3%; 632 females and 412 males) tested positively: 895 patients with a 1+ (2.0%), 129 patients with a 2+ (0.3%) and 20 patients (0.04%) with a 3+ reaction. In addition, 1083 doubtful, follicular or erythematous reactions (2.4%) and 271 explicitly irritant reactions (0.6%) have been observed (Table 3). Of the 895 1+ reactions, 114 (12.7%) were singular reactions to PG without any concomitant reaction to other substances. The RI was –0.14 and the PR 85.7%.

Table 3. Frequency of reactions to PG – all patients tested in 1992–2002; in 14 patients no valid type of reaction has been documented

	Frequency (%)
Negative	42 725 (94.68)
?	1041 (2.31)
Follicular	43 (0.10)
+	895 (1.98)
++	129 (0.29)
+++	20 (0.04)
Irritant reaction	271 (0.60)

Regarding the MOAHLFA index (Table 4), there are only little differences between patients with positive reactions and those with negative reactions to PG. The greatest difference was the high portion (27.2% versus 13.1%) of patients with leg dermatitis, which turned out to be the only significant risk factor, about doubling the risk of PG sensitization. The frequencies of hand and face dermatitis in PG-positive patients were lower than that in patch-test-negative patients (Table 4). In accordance with the unremarkable proportion of occupation-related cases, there were no distinctly different patterns of occupations in PG-positive versus -negative patients. With the exception of topical therapeutics, which have been quoted more frequently in the PG-sensitive group (43.0% versus 32.7% in the control group), no difference was found between the 2 groups (PG positive versus PG negative) with regard to the frequencies of the suspected causative exposures.

In 396 cases, cofactors have been deemed to contribute to the skin reactions; in 166 of these cases (41.9% versus 19.4% in the control group), chronic venous deficiency has been noted (data on file). The association of a positive reaction to PG with leg dermatitis can also be shown by the Poisson regression analysis and the resulting prevalence ratio of 2.10 (Table 4).

Analysing the pattern of concomitantly positive patch test reactions to other allergens in PG-positive versus -negative patients, we found high (age- and sex-standardized) frequencies of concomitant reactions to the fragrance mix (31.0% versus 12.1%), Myroxylon pereirae resin (balsam of Peru; 27.8% versus 9.3%), lanolin alcohol (17.2% versus 4.6%), Amerchol L-101 (16.9% versus 4.8%), colophony (14.3% versus 4.2%), methylidibromo glutaronitrile/phenoxy-ethanol (1 : 4) (9.8% versus 3.7%), cetearyl alcohol (8.0% versus 1.2%), neomycine sulfate (6.8% versus 2.7%) and several other allergens, including potentially irritant patch test preparations such as phenyl mercury acetate (14.5%

Table 4. MOAHLFA index: frequency of characteristics in PG-positive versus -negative patients, and results of a Poisson regression analysis with a positive patch test reaction to PG as outcome, and the MOAHLFA factors as explanatory variables [additional sites included in the model to allow for full coding, the risk quantified with the prevalence ratio, accompanied by a 95% confidence interval (CI)]

Variable	Count (%)		Prevalence ratio (95% CI)
	Cases	Controls	
Men	412 (39.5)	15 798 (35.8)	1.12 (0.98–1.27)
Occupational dermatitis	117 (11.2)	6414 (14.5)	0.88 (0.70–1.10)
Atopic dermatitis	187 (17.9)	8385 (19.0)	1.14 (0.96–1.35)
Hand dermatitis	255 (24.4)	13 215 (30.0)	0.85 (0.66–1.12)
Leg dermatitis	284 (27.2)	5771 (13.1)	2.10 (1.64–2.73)
Face dermatitis	143 (13.7)	7530 (17.1)	0.80 (0.61–1.06)
Age ≥ 40 years	700 (67.0)	27 531 (62.4)	0.98 (0.85–1.14)

versus 6.5%) or cocamidopropyl betaine (11.1% versus 2.1%) (Table 5).

Discussion

Several aspects have to be discussed for the interpretation of the results presented here.

Irritancy and false-positive reactions

First of all, as outlined above, the relatively low RI is indicative of a (slightly) irritant test preparation, and some of the weak 'positive' reactions may be false positive. The low RI may be due to a high share of doubtful or irritant reactions in a subgroup of patients (genetically) more susceptible to irritants. This view is supported in part by the finding of an increased share of erythematous reactions to PG in patients with

an irritant reaction to 0.5% sodium lauryl sulfate (SLS), compared to patients without an SLS reaction (43). If this assumption holds really true, the low RI will not generally be indicative only of an irritant patch test preparation, but rather of this increased susceptibility in the patients tested. On the other hand, it cannot be excluded that doubtful (erythematous) reactions could indicate weak contact allergy. However, in view of the relatively high test concentration, this will presumably not often be the case.

Allergic reactions

An increased individual susceptibility to irritation may also be associated with allergic reactions. This presumptive increased susceptibility may not only be due to a reduced barrier function of the horny layer of the skin (i.e. enhanced

Table 5. Allergens (top 20) for cases and controls

Substance	Cases		Controls	
	Number tested (%)	Standardized (%)	Number tested (%)	Standardized (%)
Propylene glycol	1044 (100)	100	44 081 (0.0)	0.0
Fragrance mix	1011 (32.8)	31.0	42 874 (12.7)	12.1
Balsam of Peru	1006 (32.2)	27.8	42 906 (10.4)	9.3
Lanolin alcohol	1010 (19.8)	17.2	42 990 (5.1)	4.6
Amerchol L-101	1017 (19.7)	16.9	42 431 (5.3)	4.8
Nickel(II) sulfate *6H ₂ O	1006 (17.3)	20.8	42 702 (14.9)	16.7
Colophony	1008 (15.1)	14.3	42 933 (4.3)	4.2
Phenyl mercury acetate	945 (13.8)	14.5	39 151 (6.6)	6.5
MDBGN	613 (12.6)	11.6	22 698 (5.1)	4.7
MDBGN + 2-phenoxyethanol	998 (11.4)	9.8	41 463 (4.0)	3.7
Cocamidopropyl betaine	1012 (10.9)	11.1	42 146 (2.1)	2.1
Cetearyl alcohol	1006 (10.2)	8.0	42 808 (1.4)	1.2
Potassium dichromate	1011 (8.5)	8.6	42 947 (4.4)	4.4
Neomycine sulfate	1010 (8.3)	6.8	42 970 (3.0)	2.7
p-Phenylene diamine (free base) (CI 76060)	1010 (8.1)	7.5	42 821 (4.4)	4.4
Oil of turpentine	978 (8.1)	7.6	42 182 (2.3)	2.2
Formaldehyde	1011 (7.8)	7.8	43 029 (1.7)	1.6
(Chloro-)Methyl isothiazolinone (MCI/MI)	1014 (7.5)	7.1	42 985 (2.4)	2.4
Cobalt (II) chloride *6H ₂ O	1013 (7.2)	8.3	42 878 (5.2)	5.6
tert-Butylhydroquinone	1029 (7.2)	6.1	43 068 (1.8)	1.6

penetration of a xenobiotic), but also due to the complex set of biochemical events accompanying it, e.g. release of tumour necrosis factor (TNF)- α , which is one of the unspecific signals for sensitization. Such an individual susceptibility might be explained by the association between irritancy and TNF- α polymorphism (44).

The high share of concomitant reactions to some other substances, which are partly regarded as weak allergens, may also be the consequence of a higher (inherent) susceptibility of certain individuals to irritants and (!) contact allergens. In an induction study, by using different concentrations of 2,4-dinitrochlorobenzene (DNCB), patients with pre-existing polysensitization were to be sensitized more easily than individuals with sensitization to only 1 single allergen (45). Such an (genetically) increased susceptibility has been suggested to be causative (in part) for polysensitization in patients with a special genotype in TNF- α as one of the cytokines that are involved in the pathogenesis of allergic contact eczema (46).

The association between PG sensitization and lower leg (stasis) dermatitis/venous ulcer goes along with concomitant reactions to allergens known to be associated with chronic venous disease as well, such as lanolin alcohol, cetearyl alcohol and neomycine sulfate. Sensitization is not only facilitated by their extensive use as ingredients of topicals in chronic venous disease, but also by an immunostimulant effect of the chronic, partly inflammatory disease. Although up to now, PG has not been found to be an important contact allergen in chronic venous disease, and positive reactions to PG have been reported in 2 studies in 4 of 50 patients and in 9 of 359 patients (2.5%) with leg ulceration (tested concentration 10% in water and 5% in pet., respectively) (47, 48). In a further small study, 3 of 36 patients with chronic venous insufficiency reacted positively to 5% PG in pet. (49). According to a recent publication, positive reactions to the relatively high concentration of 30% aqueous PG have been observed in 7 of 52 patients with leg ulcerations (50). Tavadia et al. (51) found only 4 positive reactions (2%) in 200 leg ulcer patients tested, which seems a very low frequency, compared to the 47 fragrance mix or 33 lanolin alcohol-positive cases. Among 457 stasis dermatitis patients tested with 5% PG in pet., only 3 patients (0.7%) showed a positive response (52). 2360 of our patients tested were affected by stasis dermatitis or ulcer cruris, and 90 patients (3.8% of this particular subgroup) showed a positive reaction to PG.

The role of (non-specific) inflammation

The observation that contact allergy to PG was often associated with leg dermatitis seems interesting for the following 2 reasons:

- (1) Leg dermatitis, possibly aggravated by leg ulcers, was shown to be a predisposing risk factor for sensitization to contact allergens in general, even to substances with a proven weak-sensitization potency, such as emulsifiers (51, 53–55).
- (2) From a theoretical point of view, leg dermatitis, as a chronic inflammatory skin disease, may contribute to the inflammatory signals necessary to mount a full immunological response.

In many instances, topical administration of a contact allergen alone is apparently sufficient to trigger the induction or upregulation of cytokines necessary for the effective induction of sensitization. Under these conditions of exposure, the chemical itself causes sufficient cutaneous inflammation and irritation and hence production of proinflammatory cytokines. However, chemicals that alone do not provoke proinflammatory changes may fail to induce sufficient cytokine responses (56). Furthermore, endosomal processing (MHC peptide ligand formation) and Langerhans' cell activation is dependent of inflammatory stimuli (57, 58). The intimate relationship between irritation and sensitization was further substantiated by studies with the contact allergen DNCB together with the irritant SLS in mice (59). At high (irritant) doses of DNCB, SLS did not impact the levels of immune activation induced by the allergen. However, at lower (non-irritant) concentrations of DNCB, responses were augmented by SLS, which is thought to provide the necessary exogenous inflammatory stimuli. It was proposed that the chemical irritancy of a hapten activates the innate immune system, an activation step necessary for development of specific immunity in the skin (60).

The concept referring to the necessary 'danger signals' (61) is supported by clinical observation. For example, patients sensitized to colophony have shown a reduced irritant threshold to SLS as compared to healthy, nonatopic volunteers (62), and patients with a lower threshold of sensitivity to SLS seem to be more susceptible to elicitation (and sensitization?) to weak allergens (43). In addition, allergens negative in a patch test were able to elicit a positive patch test reaction when applied in combination (63). In summary, a certain level of skin irritation seems to be required for the induction of a sensitization. Chemicals that fail to trigger sufficient local

cytokine production may (in the absence of additional exogenous stimuli) be unable to realize their full potential as allergens.

With regard to PG, it may be concluded that despite obviously being endowed with a certain irritative property, it rarely causes sensitization and would need further enhancing cofactors, such as increased individual susceptibility or pre-existing dermatitis.

Exposure, occupational contact

In most cases of (presumptive) sensitization to PG, skin contact with PG-containing topical medicaments or cosmetic products has been considered causative. We found a high proportion of concomitant reactions to the fragrance mix and balsam of Peru (31% versus 12.1% and 27.8% versus 9.3%, respectively). This finding could be indicative of additional exposure to fragrances in topical care products and possibly topical therapeutics. The concomitant reactions to lanolin alcohol, Amerchol L-101, cetearyl alcohol, neomycine sulfate and possibly methylidibromoglutaronitrile are most likely also due to the exposure to topical care products or topical therapeutics. Other frequent concomitant reactions may be due to the presumptive susceptibility to irritants (for example, phenyl mercury acetate or cocamidopropyl betaine).

There were no further areas of exposure in which the groups of PG-positive and -negative patients differed. This holds also true for occupational exposure, because there is almost no difference regarding the documented occupations in the 2 groups.

Conclusions

- (1) According to the analysis of IVDK patch test and other clinical data, neither occupation nor any special exposures were identified as risk factors for PG contact allergy.
- (2) The negative RI and the high PR of PG tested 20% in water supports the view that responses observed at this concentration may be indicative of a slightly irritant preparation and a low sensitization potential of PG.
- (3) Apparently, many of the weak positive reactions (i.e. 1+ reactions), that is >80% of all positive reactions, must be interpreted as false positive, because of the slightly irritant potential of the test preparation.
- (4) Moreover, weak positive reactions might predominantly reflect individual susceptibility to a

substance rather than a general property of the substance itself.

(5) The majority of the remaining positive reactions, probably to be interpreted as allergic, seem to be due to exposure to PG in topical therapeutics and/or cosmetic preparations.

(6) In about one-sixth of the cases, the positive reactions are correlated to a predisposing skin disease, i.e. leg dermatitis in chronic venous disease.

(7) Taking into account the negative experimental findings in animals and the high level of exposure to PG in the population, the low frequency of positive reactions to non-irritant PG concentrations in patch-tested patients indicates a very low sensitization potential in humans.

(8) The risk for sensitization to PG on uncompromised skin seems to be extremely low.

(9) The diagnosis of PG contact sensitization should not be based on a positive patch test reaction alone, but only on a combination of anamnestic information and, preferably, validation tests.

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