

Patch testing with the irritant sodium lauryl sulfate (SLS) is useful in interpreting weak reactions to contact allergens as allergic or irritant

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Several contact allergens are tested at concentrations which might cause irritant reactions. In this study we investigated whether the reactivity to a standard irritant is useful in identifying subjects with hyperreactive skin yielding a higher rate of doubtful or irritant reactions. Sodium lauryl sulfate (SLS) 0.5% (aqua) was tested in addition to the standard series routinely for 5 years in the Department of Dermatology, Dortmund. For data analysis, we compared reactions at D3 to the standard series, the vehicle/emulsifier and preservative series and benzoyl peroxide to the reactions obtained with SLS. Proportions were standardized for age and sex. The association between reactivity to a certain allergen and SLS reactivity as a dichotomous outcome, controlled for age and sex as potential confounders, was assessed with logistic regression analysis. Results showed that of the 1600 tested patients, 668 (41.8%) had an irritant reaction to SLS which exceeded 2+ in only 41 patients. Seasonal variation was statistically significant, showing reduced SLS reactivity in summer vs. winter. Patients with irritant reactions to SLS showed significantly more erythematous reactions to the following 10 allergens of the standard series: fragrance mix, cobalt chloride, balsam of Peru (*Myroxylon pereirae*), lanolin alcohol, 4-phenylenediamine base (PPD), propolis, formaldehyde, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD), benzocaine, and 4-*tert*-butylphenol-formaldehyde resin. No significant differences regarding strong positive allergic reactions were observed. Concerning other allergens, significantly more erythematous reactions were observed in SLS-reactive patients to benzoyl peroxide, octyl gallate, cocamidopropyl betaine, Amerchol L-101, *tert*-butylhydroquinone, and triethanolamine. In the SLS-reactive group of patients, the reaction index was negative for 10 allergens of the standard series compared to only 5 in the SLS non-responder group. For the first time, this study, based on a large data pool, revealed a significant association between reactivity to the irritant SLS and erythematous reactions to certain allergens. With SLS as a marker for hyperreactive skin at hand, some of these reactions can now be classified as irritant more confidently, particularly if there is no history of exposure to the allergen.

Key words: contact allergy; erythematous patch test reactions; false-positive patch test reactions; irritant; patch testing; sodium lauryl sulfate; threshold. © Blackwell Munksgaard, 2003.

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Patch tests are performed to find out if the patient is allergic to the substances tested or not. An allergic patch test reaction is usually characterized by erythema, infiltration, papules and/or vesicles, depending on the reaction intensity. However, macular, purely erythematous reactions sometimes occur, which are mostly regarded as irritant reactions, but may reflect a weak contact sensitization in certain cases (1). Some allergens or allergen preparations, e.g. formaldehyde, lanolin alcohol,

or mercury salts are more likely than others to evoke erythematous reactions, leading to a negative reaction index (2). Potassium dichromate is also known to cause irritant reactions in human skin (3). In addition, some allergens such as benzalkonium chloride, benzoyl peroxide, octyl gallate, or propylene glycol may lead to crescendo-pattern irritant reactions with erythema and infiltration, which would commonly be classified as weak allergic reactions (+) (4–6).

The decision as to whether these reactions, as well as macular erythematous reactions, are allergic or irritant might be facilitated if an irritancy control test was available, performed separately together with the patch test. For this purpose, sodium lauryl sulfate (SLS) 0.5% aq. was patch tested in addition to the standard series in the Department of Dermatology of the Klinikum Dortmund and University of Witten/Herdecke, Germany, from 1996. A concentration of 0.5% aq. was chosen because previous own (unpublished) studies were in line with the findings of Wahlberg et al. (7) that, on the one hand, more than 90% of patients tested with SLS 1.0% aq. showed an irritant reaction and, on the other hand, only less than 25% reacted to SLS 0.1% aq., while about 40% reacted to SLS 0.5% aq. Thus, it seemed likely that this concentration might be the best to distinguish between patients prone to irritant patch test reactions and those who were not. After 5 years of routine patch testing with SLS, we analysed the results to answer the following questions:

Do patients with an irritant reaction to SLS 0.5% aq. generally have more strictly erythematous reactions to the allergen preparations tested than those without reaction to SLS?

Do patients with an irritant reaction to SLS 0.5% aq. have more macular erythematous reactions (i.e. ? reactions) or weak positive reactions (i.e. + reactions = erythema with infiltration and/or papules) to the above-mentioned problematic allergens than those patients not reacting to SLS?

In addition, we looked for seasonal variation in SLS reactivity, though this latter aspect will be addressed in more detail in a separate publication.

Materials and Methods

Patch tests were performed following international guidelines (1). Standard Finn Chambers on Scanpor (Epitest, Tuusula, Finland) were used as carrier. SLS (analytical grade) was purchased from Sigma Chemicals (Neuherberg, Germany) and diluted with water at 0.5%. Solutions were renewed every 3 months and stored together with the patch test materials at 4°C. 20 µL were pipetted onto the filter paper disc of the Finn Chamber. Exposure time was 2 days for both the contact allergens and the SLS. Tests were read at day 2 (D2) and D3. Reactions to allergens were documented in accordance with the recommendations of the ICDRG with slight amendments by the German Contact Dermatitis Research Group (DKG) (8). Test reactions to SLS were scored following the recommendations of the Standardization Group of the Euro-

Table 1. Scoring of test reactions to SLS

Symbol	Morphology
0	No reaction
1 +	Weak, spotty or diffuse erythema/scaling
2 +	Weak, good visible erythema/scaling
3 +	Moderate erythema
4 +	Strong erythema and/or minute epidermal defect
5 +	Very strong erythema with epidermal defect

pean Society of Contact Dermatitis (9) with our own slight amendments (see Table 1). Allergen preparations were obtained from Hermal, Reinbek, Germany.

Statistical analysis was done at the data centre of the Information Network of Departments of Dermatology (IVDK) (10) using SAS 8.1. software (SAS Institute, Cary, NC, USA). Because SLS tests were performed to facilitate the final assessment of patch test results, and this assessment is usually done after the 2nd reading at D3, only patch test reactions of the allergens at D3 were evaluated. With the exception of benzoyl peroxide, all of the above-mentioned problematic allergens are part of the standard series or the vehicle/emulsifier and preservative series of the DKG. Thus, we focused our data analysis on these test series. The reaction index was calculated according to the formula of Brasch and Henseler (11).

The demographic characteristics of a patch test population, especially the distribution of age and sex as important surrogate markers for an array of actual exposures, influences the frequency of positive allergic reactions in this group (12, 13). One can expect this to apply not only to clear-cut allergic reactions, but also to strictly erythematous reactions. Thus, for comparison of reaction frequencies in patients with and without reaction to SLS, data on patch test results were directly age- and sex-standardized to the IVDK standard population, according to population-adjusted frequency of sensitization (PAFS) (12, 13). The standardized proportions are accompanied by their corresponding approximative 95% confidence interval (CI) (14).

Differences in crude proportions of reactions or population characteristics in disjunct subgroups of patients were tested for statistical significance using Fisher's exact test. A *P*-value of ≤ 0.05 was regarded as significant. The association between reactivity to a certain allergen [erythema only, +, or ++, +++ as dichotomous outcome (yes/no, respectively)] and SLS reactivity as a dichotomous exposure was assessed with logistic regression analysis, at the same time controlling for the influence of age and sex, which were included in the regression model as dichotomous variables. *P*-

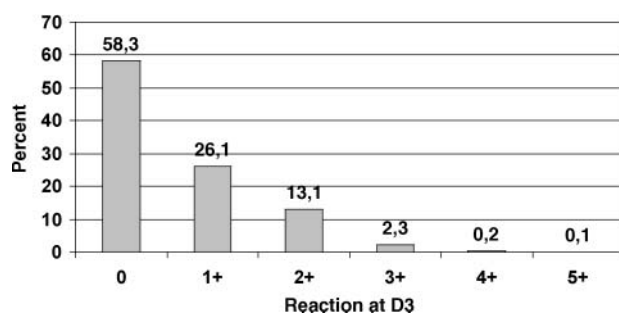


Fig. 1. Test reactions at D3 to SLS 0.5% aq. in 1,600 patients.

values of ≤ 0.05 for the influence of the beta coefficient representing SLS reactivity were considered significant.

Results

From 1 July 1996 to 30 June 2001, SLS 0.5% aq. was patch tested in 1600 consecutive patients. In the course of these 5 years, 31 patients had been tested twice, and one patient 3 times. In these cases, which accounted for 2% of the test population, the strongest SLS reactions and their associated reactions to contact allergens were selected for data analysis. The reactions to SLS 0.5% aq. at D3 are shown in Fig. 1. Of the patients tested, 668 (41.8%) had an irritant reaction, which exceeded 2+ in only 41 patients. In other words, 627 of the 668 reactions to SLS, i.e. 93.9%, had a score of 1+ or 2+. On the other hand, 932 patients (58.3% of the 1600 patients tested) did not react to SLS at all at D3.

Of the 1600 patients tested with SLS 0.5% aq., altogether 682 showed a reaction either at D2, or D3, or both. While 126 reactions were seen at D2, 668 reactions were observed at D3. Of the 556 reactions appearing de novo at D3, 537 raised from score 0 (no reaction) at D2 to score 1+ or 2+ (weak erythema and/or scaling). Additionally, 60 reactions became more intense from D2 to D3. Thus, the proportion of crescendo reactions to SLS was 90.3% (616 of 682). In contrast, only 15 reactions (2.2% of 682) followed a decrescendo pattern. The remainder, i.e. 51 reactions (7.5% of 682), had the same intensity at D2 and D3 (see Table 2).

The analysis of seasonal variation of SLS reactions revealed a reduced reactivity in summer or an increased reactivity in winter, respectively (see Table 3); this variation was statistically significant ($P = 0.009$).

A description of the test population and of the 2 subgroups of patients with and without irritant reaction to SLS at D3 using the MOAHLFA index (13) is given in Table 4. Among those reacting to

Table 2. Test reactions to SLS 0.5% aq. at D2 and D3 in 1600 patients

Reaction at D2	Reaction at D3						Total
	0	1+	2+	3+	4+	5+	
0	918	377	160	17	1	1	1474
1+	11	40	40	14	1	0	106
2+	3	1	9	5	—	—	18
3+	—	—	—	1	—	—	1
4+	—	—	—	—	1	—	1
Total	932	418	209	37	3	1	1600

SLS, there were significantly more men (50 vs. 41%; $P < 0.001$), and less patients with face dermatitis (13 vs. 17%; $P = 0.03$), compared to the non-reactors. The other items included in the MOAHLFA index did not differ significantly between the 2 groups. No significant differences were revealed by a comparison of these population characteristics between the 2 subgroups of patients with 1+ reaction to SLS and 2+ or more (data not shown in detail).

Table 5 gives an overview of the test reactions to allergens of the standard series in the total test population, and in patients with and without reaction to SLS, respectively. The standard series was tested in 96% of the patients, namely 644 patients with, and 892 patients without, reaction to SLS. Patients with reaction to SLS showed significantly more erythematous reactions to the following 10 allergens: fragrance mix (11.8 vs. 6.6%; $P < 0.0001$), cobalt chloride (9.8 vs. 5.4%; $P = 0.0094$), balsam of Peru (7.9 vs. 5.5%; $P = 0.0425$), lanolin alcohol (7.0 vs. 3.2%; $P = 0.0020$), 4-phenylenediamine base (PPD) (6.1 vs. 2.5%; $P = 0.0017$), propolis (3.6 vs. 1.0%; $P = 0.0149$), formaldehyde (3.3 vs. 0.6%; $P = 0.0007$), *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD) (2.6 vs. 0.7%; $P = 0.0173$), benzocaine (2.4 vs. 0.6%; $P = 0.0065$), and 4-*tert*-butylphenol-formaldehyde resin (1.7 vs. 1.0%; $P = 0.0478$). In patients with an irritant reaction to SLS, significantly more weak positive reactions (i.e. +) to the following 3 allergens of the standard series were observed: balsam of Peru (7.6 vs. 2.8%; $P < 0.0001$), 4-phenylenediamine base (PPD) (4.3 vs. 2.3%; $P = 0.0229$), and ammoniated mercury (2.4 vs. 1.3%; $P = 0.0288$). No significant differences concerning strong positive allergen reactions (i.e. ++ or +++) were observed.

Table 6 shows the test reactions obtained with the ointment base and preservative series, which was tested in 67.6% of the patients, namely 441 patients with, and 641 patients without, reaction to SLS. Additionally, data on benzoyl peroxide were added in this table. With this test series, significantly more erythematous reactions were observed in patients reacting to SLS with the following 6 allergen prep-

Table 3. Seasonal variation in reactions to SLS 0.5% aq. at D3. The sum of patient count is more than 1600 in this table due to re-testing of 32 patients within the study period, but not always within the same quarter of the year

Reaction to SLS	Spring (March, April, May)		Summer (June, July, Aug)		Autumn (Sep, Oct, Nov)		Winter (Dec, Jan, Feb)	
	No.	%	No.	%	No.	%	No.	%
1 + to 5 +	168	41	131	35	175	43	199	46
0	239	59	248	65	231	57	234	54
Total	407	100	379	100	406	100	433	100

Table 4. MOAHLFA index of the study population, and patients with (n = 668) and without (n = 932) reaction to SLS 0.5% aq. at D3

	Patients tested		Reaction to SLS			
	n = 1600		n = 932		1+ to 5+ n = 668	
	n	%	n	%	%	%
Male	721	45%	384	41%	337	50%
Occupational dermatitis	348	22%	195	21%	153	23%
Atopic dermatitis	356	22%	194	21%	162	24%
Hand dermatitis	519	32%	293	31%	226	34%
Leg dermatitis	214	13%	129	14%	85	13%
Face dermatitis	245	15%	158	17%	87	13%
Age ≥ 40 years	1018	64%	584	63%	434	65%

arations: benzoyl peroxide (22.1 vs. 7.7%; $P = 0.0064$), octyl gallate (14.1 vs. 7.2%; $P < 0.0001$), cocamidopropyl betaine (9.8 vs. 6.7%; $P = 0.0115$), Amerchol L-101 (5.5 vs. 3.7%; $P = 0.0457$), *tert*-butylhydroquinone (3.8 vs. 1.7%; $P = 0.0043$), and triethanolamine (1.9 vs. 0.2%; $P = 0.0357$). With propylene glycol, more erythematous reactions were also seen in SLS reactors (3.6 vs. 1.8%); however, this difference was not significant ($P = 0.0611$). With the following 2 allergens, significantly more weak positive reactions (i.e. +) were observed in patients reacting to SLS: phenylmercuric acetate (4.8 vs. 2.2%; $P = 0.0340$), and bromonitropropanediol (2.2 vs. 0.5%; $P = 0.0275$). Due to the small sample size, results for benzoyl peroxide were not significant (12.6 vs. 3.4%; $P = 0.0573$).

Due to a limited number of allergen reactions, and a quasi-complete separation of data points used in the logistic regression analysis, the significance of differences between patients with and without reaction to SLS could not be computed for some allergens (see Table 6).

Discussion

To our knowledge, this is the first study assessing the association between irritant patch test reactivity to SLS and patch test reactions to an array of allergens in a large number of patients. Of the 1600 patients tested with SLS 0.5% aq., 42% showed an irritant reaction at D3. These reactions most probably indicate increased irritability of the skin.

In patients reacting to SLS, significantly more

erythematous reactions were observed with several allergen preparations which are known for their tendency to evoke erythematous and/or (delayed) irritant reactions, namely formaldehyde, lanolin alcohol, Amerchol L-101, cobalt chloride, octyl gallate, cocamidopropyl betaine, and benzoyl peroxide. A similar trend was seen with propylene glycol. The coincidence of SLS reactions and macular erythematous reactions to allergen preparations in these patients is a strong argument in favour of the interpretation of these erythematous reactions as irritant phenomena, and not weak allergic reactions. However, we certainly do not want to imply that all erythematous reactions to the tested allergens would be irritant and therefore diagnostically meaningless. Every experienced allergologist knows patients in whom there is a big discrepancy between the severity of clinical picture and the patch test reaction. Major influencing factors are the degree of sensitization, exposure time and mode (open, occlusive, single, repetitive), skin condition, body region and other cofactors (ultra-violet light, friction, temperature). Local irritants may contribute to the manifestation of the dermatitis and lead to a suprathreshold allergic contact dermatitis even when the sensitization level is quite low (e.g. in hand dermatitis).

A patch test on normal back skin with the allergen in petrolatum is a good diagnostic tool but far from perfect. Many recommendations for patch test concentrations in this vehicle are based on small series of patients. Quantitative testing and validation by repeated open application or other ex-

Table 5. Patch test reactions at D3 to allergens of the standard series in the total test population, and in the subgroups of patients with and without reaction to SLS 0.5% aq. at D3

Allergen	Patients tested <i>n</i> = 1536	Reaction to SLS							
		0				1+ to 5+			
		<i>n</i> = 892	<i>n</i> = 644				<i>n</i> = 644		
	% pos. ¹ [95%-CI]	% ery. ² [95%-CI]	% + ³ [95%-CI]	% + +, + + + ⁴ [95%-CI]	RI ⁵	% ery. ² [95%-CI]	% + ³ [95%-CI]	% + +, + + + ⁴ [95%-CI]	RI ⁵
Potassium dichromate 0.5 0.5% pet.	5.1 [4.0–6.3]	1.8 [1.0–2.7]	2.1 [1.2–3.0]	2.5 [1.4–3.6]	0.3	2.4 [1.0–3.8]	3.0 [1.6–4.5]	2.9 [1.5–4.4]	0.5
4-Phenylenediamine base 1% pet.	5.6 [4.3–6.8]	2.5* [1.3–3.6]	2.3* [1.2–3.4]	2.1 [1.1–3.1]	0.3	6.1* [3.8–8.4]	4.3* [2.6–6.0]	2.9 [1.5–4.3]	0.2
Thiuram mix 1% pet.	2.8 [2.0–3.7]	1.4 [0.6–2.2]	0.9 [0.3–1.5]	1.2 [0.5–1.9]	0.3	2.2 [0.9–3.4]	2.1 [0.8–3.4]	2.0 [0.7–3.2]	0.3
Neomycin sulfate 20% pet.	2.4 [1.6–3.1]	1.6 [0.8–2.5]	1.2 [0.5–1.9]	0.5 [0.0–1.1]	0.0	3.5 [1.8–5.1]	2.3 [1.2–3.4]	1.0 [0.2–1.9]	0.0
Cobalt chloride 1% pet.	6.3 [4.9–7.7]	5.4* [3.7–7.1]	4.3 [2.8–5.8]	2.8 [1.6–4.0]	0.0	9.8* [7.0–12.6]	3.2 [1.5–4.8]	2.0 [0.6–3.4]	–0.4
Benzocaine 5% pet.	1.5 [0.9–2.1]	0.6* [0.0–1.2]	0.8 [0.2–1.4]	0.2 ⁶ [0.0–0.4]	0.3	2.4* [1.1–3.8]	1.2 [0.3–2.2]	0.9 ⁶ [0.2–1.5]	0.0
Nickel sulfate 5% pet.	15.4 [13.4–17.5]	2.4 [1.3–3.5]	5.8 [4.1–7.5]	9.7 [7.5–12.0]	0.6	3.2 [1.6–4.8]	5.1 [3.2–7.0]	10.0 [7.1–12.9]	0.5
Colophony (colophonium) 20% pet.	4.4 [3.3–5.5]	2.3 [1.2–3.4]	2.3 [1.3–3.3]	2.3 [1.2–3.3]	0.4	2.7 [1.5–3.9]	2.4 [1.0–3.8]	1.9 [0.8–3.0]	0.1
<i>N</i> -Isopropyl- <i>N'</i> - phenyl-4-phenyl enediamine (IPPD) 0.1% pet.	0.5 [0.1–0.9]	0.7* [0.1–1.2]	0.1 ⁶ [0.0–0.2]	0.4 [0.0–0.9]	–0.3	2.6* [1.1–4.1]	0.2 ⁶ [0.0–0.5]	0.2 [0.0–0.4]	–0.6
Lanolin alcohol 30% pet.	5.3 [4.2–6.5]	3.2* [2.1–4.3]	3.7 [2.5–4.9]	0.9 ⁶ [0.3–1.5]	0.2	7.0* [4.9–9.2]	5.6 [3.6–7.6]	0.8 ⁶ [0.2–1.5]	0.0
Mercapto mix 1% pet.	0.8 [0.3–1.2]	0.7 [0.1–1.3]	0.2 ⁷ [0.0–0.5]	0.6 [0.1–1.2]	0.3	1.5 [0.3–2.8]	0.4 ⁷ [0.0–0.8]	0.2 [0.0–0.6]	–0.2
Epoxy resin 1% pet.	0.8 [0.3–1.3]	0.8 [0.2–1.4]	0.2 [0.0–0.5]	0.3 ⁶ [0.0–0.6]	–0.3	1.9 [0.7–3.1]	0.9 [0.0–1.9]	0.4 ⁶ [0.0–0.8]	–0.3
Myroxylon Pereirae resin (balsam of Peru) 25% pet.	7.2 [5.9–8.5]	5.5* [4.0–7.0]	2.8* [1.7–3.8]	2.3 [1.3–3.3]	0.0	7.9* [5.7–10.0]	7.6* [5.4–9.8]	2.8 [1.4–4.1]	0.1
4- <i>tert</i> -Butylphenol- formaldehyde resin 1% pet.	1.2 [0.7–1.7]	1.0* [0.2–1.7]	0.4 [0.0–0.9]	0.5 [0.1–0.9]	0.1	1.7* [0.6–2.7]	0.9 [0.2–1.6]	0.6 [0.1–1.2]	0.0
Formaldehyde 1% aq.	1.9 [1.1–2.8]	0.6* [0.0–1.1]	0.7 [0.1–1.4]	1.0 [0.2–1.8]	0.4	3.3* [1.7–4.9]	1.8 [0.5–3.0]	0.4 [0.0–1.1]	–0.3
Fragrance mix 8% pet.	10.1 [8.4–11.7]	6.6* [4.9–8.4]	5.6 [4.0–7.1]	3.2 [1.9–4.5]	0.1	11.8* [9.1–14.5]	7.6 [5.2–9.9]	4.4 [2.5–6.3]	–0.1
Ammoniated mercury 1% pet.	2.3 [1.5–3.2]	1.6 [0.7–2.5]	1.3* [0.4–2.2]	0.7 [0.1–1.3]	–0.1	3.1 [1.5–4.8]	2.4* [1.1–3.7]	0.3 [0.0–0.7]	0.0
Oil of turpentine 10% pet.	1.7 [1.0–2.4]	1.2 [0.4–1.9]	1.3 [0.4–2.1]	0.3 [0.0–0.6]	0.1	1.4 [0.4–2.3]	0.8 [0.0–1.6]	1.0 [0.2–1.8]	0.1
(Chlor)methyl- isothiazolinone 0.01% aq.	2.8 [1.9–3.7]	0.6 ⁶ [0.2–1.1]	2.2 [1.2–3.3]	0.3 [0.0–0.6]	0.5	1.3 ⁶ [0.5–2.0]	2.3 [1.1–3.5]	0.8 [0.0–1.5]	0.3
Paraben mix 16% pet.	0.7 [0.3–1.1]	2.1 [1.1–3.0]	0.5 ⁶ [0.1–0.9]	0.3 ⁶ [0.0–0.6]	–0.4	2.9 [1.3–4.5]	0.5 ⁶ [0.0–1.1]	0.1 ⁶ [0.0–0.3]	–0.5
Cetostearyl alcohol 20% pet.	1.2 [0.7–1.8]	1.2 [0.5–1.8]	1.0 [0.4–1.6]	0.3 ⁶ [0.0–0.6]	0.0	1.8 [0.6–3.0]	1.2 [0.3–2.2]	0.0 ⁶ [0.0–0.0]	–0.2
Thimerosal 0.1% pet.	3.7 [2.6–4.8]	1.4 [0.6–2.2]	2.4 [1.3–3.5]	0.9 [0.2–1.6]	0.2	3.0 [1.4–4.6]	3.1 [1.5–4.8]	1.2 [0.2–2.3]	0.1
Zinc diethyldithio- carbamate 1% pet.	0.5 [0.1–0.9]	0.0 ⁶ [0.0–0.0]	0.3 [0.0–0.7]	0.2 ⁶ [0.0–0.4]	1.0	0.6 ⁶ [0.1–1.2]	0.6 [0.0–1.4]	0.1 ⁶ [0.0–0.3]	–0.1
Methyldibromo glutaronitrile/ 2-Phenoxyethanol 1% pet. ⁷	2.1 [1.1–3.1]	1.0 [0.3–1.8]	1.1 [0.3–2.0]	0.4 [0.0–1.0]	0.1	2.0 [0.2–3.8]	1.6 [0.5–2.8]	1.3 [0.0–3.0]	0.3
Propolis 10% pet. ⁷	1.6 [0.5–2.7]	1.0* [0.0–2.2]	0.7 [0.0–1.7]	0.4 [0.0–0.9]	0.0	3.6* [0.9–6.3]	1.9 [0.0–4.2]	0.7 [0.0–1.6]	–0.3

Table 5. continued

Allergen	Patients tested <i>n</i> = 1536	Reaction to SLS							
		0				1+ to 5+			
		<i>n</i> = 892				<i>n</i> = 644			
	% pos. ¹ [95%-CI]	% ery. ² [95%-CI]	% + ³ [95%-CI]	% ++, +++ ⁴ [95%-CI]	RI ⁵	% ery. ² [95%-CI]	% + ³ [95%-CI]	% ++, +++ ⁴ [95%-CI]	RI ⁵
Bufexamac 5% pet. ⁷	1.0 [0.3–1.7]	1.1 [0.2–2.1]	0.3 [0.0–0.7]	0.7 [0.0–1.5]	–0.1	0.8 [0.0–2.3]	0.7 [0.0–1.6]	0.3 [0.0–0.7]	0.6
Mercaptobenzothiazole 2% pet.	0.9 [0.4–1.3]	0.4 [0.0–0.9]	0.3 [0.0–0.7]	0.7 ⁶ [0.2–1.2]	0.5	0.9 [0.0–1.9]	0.6 [0.1–1.2]	0.0 ⁶ [0.0–0.0]	0.2

¹% pos. = age- and sex-standardized percentage of positive reactions (+, ++, +++) to the allergen. ²% ery. = age- and sex-standardized percentage of erythematous reactions to the allergen. ³% + = age- and sex-standardized percentage of weak positive reactions, i.e. + only, to the allergen. ⁴% ++, +++ = age- and sex-standardized percentage of strong positive reactions, i.e. ++ or +++ to the allergen. ⁵RI = reaction index. ⁶Significance of difference between patients with and without reaction to SLS not calculable due to quasi-complete separation of data points in the logistic regression analysis. ⁷Reduced count of patch tests because allergen was not part of the standard series during the whole study period. *Difference between patients with and without reaction to SLS significant; *P* < 0.05.

posure tests have been published for only a few allergens (15–21). When the new patch test system on the basis of a gel on plastic sheets (TRUE Test™, Pharmacia, Uppsala, Sweden) was developed, intensive work was invested in standardization by finding the adequate test concentration (22, 23). With some allergens, e.g. the fragrance mix and particularly cobalt chloride, this test system produced less doubtful and irritant reactions in comparison to the conventional system with allergens in petrolatum (24). Formaldehyde is another instructive example. Initially, it was tested at 2% aq. and lowered to 1% aq. because of the problem of irritancy (16). The fragrance mix of Larsen (25) was reduced from 16 to 8% to obtain false-positive reactions less frequently. As discussed elsewhere, this concentration is still too high (26, 27). Patients with a doubtful reaction to 8% fragrance mix have a positive fragrance history in only 18.6%, compared to 88.9% for 3 + reactions (26% for 1 + reactions and 47.0% for 2 + reactions, respectively).

These lengthy considerations are a necessary background to interpret our data appropriately. Our goal was to investigate whether the reactivity to a standard irritant such as SLS might be associated with the reactivity to allergens in the problem zone of weak positive or doubtful/irritant reactions. One limitation of our data is the fact that we have not further studied those equivocal patch test reactions with serial dilution tests, ROAT or other exposure tests in order to differentiate true sensitizations from irritancy. This would have been possible in principle, but requires very cooperative patients. Nevertheless, our results are stimulating and gain support from various findings.

Based on numerous publications on SLS, the important facts can be summarized as follows. It is an anionic detergent which readily penetrates the stratum corneum and at low concentrations influences

lipid synthesis. This increases the transepidermal water loss even when there is no clinical reaction. SLS induces intercellular adhesion molecules and cytokine release (particularly IL-8), up-regulates integrin receptors and affects Langerhans cells. When patch tested at 0.5–1.0%, there is marked interindividual variation ranging from no response to a strong vesicular reaction. Various influencing factors have been established: age, race, anatomical site, season and climate. There is no clear sex difference. Patients with dry skin, particularly those with previous or active atopic dermatitis, have been shown to exhibit an increased response to SLS. Individual hyperreactivity is genetically determined (twin studies, skin type, UVB sensitivity) but can also develop on the basis of an acute dermatitis (several types), on a certain body location or after recent contact with irritants (reviewed by 9, 28).

Björnberg (29) pointed out many years ago that reactivity to SLS and other irritants depends on the condition of the skin – in the acute stage reactivity was higher than after healing of hand eczema. Therefore, it is generally accepted that patch testing in the acute stage of an eczema should not be performed, because of the possibility of frequent false-positive reactions. In practice, a compromise is often necessary because the eczema persists or is ameliorated only to a subacute stage despite various therapeutic efforts. In this situation, weak positive reactions are often obtained which later on cannot be reproduced. This is one scenario where the SLS test could be useful: a temporary hyperreactive state would presumably be detected by a positive reaction to 0.5% SLS.

The list of contact allergens with a higher representation in the SLS-positive group gains some support from publications regarding this problem. The following contact allergens of the standard series are often discussed regarding an irritant po-

Table 6. Patch test reactions at D3 to allergens of the ointment base and preservative series and benzoyl peroxide in the total test population, and in the subgroups of patients with and without reaction to SLS 0.5% aq. at D3

Allergen	Patients tested <i>n</i> = 1082	Reaction to SLS							
		0				1 + to 5 +			
		<i>n</i> = 641				<i>n</i> = 441			
	%pos. ¹ [95%-CI]	% ery. ² [95%-CI]	% + ³ [95%-CI]	% + +, + + + ⁴ [95%-CI]	RI ⁵	% ery. ² [95%-CI]	% + ³ [95%-CI]	% + +, + + + ⁴ [95%-CI]	RI ⁵
Propylene glycol 20% aq.	2.1 [1.1–3.0]	1.8 [0.8–2.9]	1.5 [0.5–2.6]	0.6 [0.1–1.1]	0.0	3.6 [1.6–5.6]	1.0 [0.1–1.9]	1.0 [0.0–2.1]	–0.3
Polyethylene glycol ointment as is	0.4 [0.0–0.9]	0.1 ⁶ [0.0–0.3]	0.1 ⁶ [0.0–0.3]	0.3 ⁶ [0.0–0.8]	0.3	0.4 ⁶ [0.0–0.9]	0.5 ⁶ [0.0–1.0]	0.0 ⁶ [0.0–0.0]	0.2
Triethanolamine 2.5% pet.	0.1 [0.0–0.2]	0.2* [0.0–0.6]	0.1 ⁶ [0.0–0.3]	0.0 [0.0–0.0]	–0.5	1.9* [0.4–3.5]	0.1 ⁶ [0.0–0.3]	0.0 [0.0–0.0]	–0.8
tert.-Butylhydroquinone 1% pet.	1.7 [1.0–2.4]	1.7* [0.6–2.7]	1.5 [0.6–2.5]	0.6 ⁶ [0.1–1.1]	0.1	3.8* [2.2–5.4]	0.7 [0.0–1.5]	0.4 ⁶ [0.0–1.0]	–0.6
Benzalkonium chloride 0.1% pet.	0.2 [0.0–0.5]	0.5 [0.0–1.1]	0.1 ⁶ [0.0–0.4]	0.0 [0.0–0.0]	–0.6	0.9 [0.1–1.7]	0.4 ⁶ [0.0–0.9]	0.0 [0.0–0.0]	–0.4
Chloroacetamide 0.2% pet.	0.9 [0.4–1.3]	0.5 [0.0–0.9]	0.7 [0.1–1.2]	0.4 ⁶ [0.0–0.8]	0.4	0.9 [0.0–2.1]	0.4 [0.0–0.9]	0.2 ⁶ [0.0–0.6]	0.0
Phenylmercuric acetate 0.05% pet.	3.6 [2.4–4.8]	7.7 [5.4–9.9]	2.2* [1.0–3.4]	0.6 [0.0–1.2]	–0.5	8.0 [5.2–10.9]	4.8* [2.5–7.0]	0.2 [0.0–0.6]	–0.3
Diazolidinyl urea 2% pet.	0.6 [0.2–1.0]	0.4 ⁶ [0.0–0.9]	0.3 ⁶ [0.0–0.5]	0.2 ⁶ [0.0–0.4]	0.4	0.5 ⁶ [0.0–1.2]	0.6 ⁶ [0.0–1.3]	0.3 ⁶ [0.0–0.7]	0.3
Bromonitropropanediol 0.5% pet.	1.6 [0.8–2.4]	0.5 [0.0–1.1]	0.5* [0.0–1.2]	0.5 ⁶ [0.0–1.1]	0.2	0.8 [0.0–1.6]	2.2* [0.8–3.7]	0.0 ⁶ [0.0–0.0]	0.5
Amerchol L-101 50% pet.	4.2 [3.2–5.1]	3.7* [2.4–4.9]	3.3 [2.1–4.4]	0.9 ⁶ [0.3–1.4]	0.1	5.5* [3.7–7.3]	3.2 [1.7–4.6]	1.2 ⁶ [0.4–1.9]	–0.1
Cocamidopropyl betaine 1% aq.	1.2 [0.5–2.0]	6.7* [4.6–8.7]	0.8 [0.1–1.5]	0.0 [0.0–0.0]	–0.8	9.8* [6.9–12.7]	1.8 [0.2–3.4]	0.0 [0.0–0.0]	–0.8
Coconut diethanolamide 0.5% pet.	0.3 [0.0–0.6]	0.9 [0.0–1.9]	0.2 [0.0–0.5]	0.0 [0.0–0.0]	–0.3	1.9 [0.3–3.4]	0.4 [0.0–1.0]	0.0 [0.0–0.0]	–0.6
Octyl gallate 0.3% pet.	1.2 [0.6–1.8]	7.2* [5.0–9.4]	1.3 [0.5–2.1]	0.0 [0.0–0.0]	–0.6	14.1* [10.6–17.6]	1.1 [0.2–2.0]	0.0 [0.0–0.0]	–0.8
Quaternium-15 1% pet.	0.7 [0.2–1.2]	0.3 [0.0–0.6]	0.6 ⁶ [0.0–1.2]	0.4 ⁶ [0.0–0.7]	0.5	0.3 [0.0–0.7]	0.3 ⁶ [0.0–1.0]	0.1 ⁶ [0.0–0.3]	0.0
Imidazolidinyl urea 2% pet.	0.5 [0.1–0.9]	0.2 ⁶ [0.0–0.5]	0.5 ⁶ [0.0–0.9]	0.0 ⁶ [0.0–0.0]	0.6	0.3 ⁶ [0.0–1.0]	0.2 ⁶ [0.0–0.6]	0.3 ⁶ [0.0–0.7]	0.6
DMDM Hydantoin 2% aq.	0.6 [0.0–1.2]	0.5 [0.0–0.9]	0.3 ⁶ [0.0–0.9]	0.3 ⁶ [0.0–0.9]	–0.3	1.2 [0.0–2.4]	0.5 ⁶ [0.0–1.5]	0.0 ⁶ [0.0–0.0]	–0.7
Sorbic acid 2% pet.	0.3 [0.0–0.5]	0.1 ⁶ [0.0–0.3]	0.1 ⁶ [0.0–0.4]	0.0 [0.0–0.0]	0.0	0.3 ⁶ [0.0–0.6]	0.5 ⁶ [0.0–1.0]	0.0 [0.0–0.0]	0.2
Triclosan 2% pet.	0.1 [0.0–0.3]	0.6 [0.1–1.2]	0.0 ⁶ [0.0–0.0]	0.0 [0.0–0.0]	–1.0	0.5 [0.0–1.5]	0.3 ⁶ [0.0–0.8]	0.0 [0.0–0.0]	0.3
Chlorhexidine digluconate 0.5% aq.	0.0 [0.0–0.0]	0.1 ⁶ [0.0–0.3]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	–1.0	1.3 ⁶ [0.0–2.5]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	–1.0
Benzyl alcohol 1% pet.	0.1 [0.0–0.3]	0.2 ⁶ [0.0–0.6]	0.2 ⁶ [0.0–0.5]	0.0 [0.0–0.0]	0.0	0.0 ⁶ [0.0–0.0]	0.0 ⁶ [0.0–0.0]	0.0 [0.0–0.0]	
Sodium benzoate 5% pet.	0.1 [0.0–0.3]	0.0 ⁶ [0.0–0.0]	0.2 ⁶ [0.0–0.6]	0.0 [0.0–0.0]	1.0	0.2 ⁶ [0.0–0.6]	0.0 ⁶ [0.0–0.0]	0.0 [0.0–0.0]	–1.0
Benzoyl peroxide 1% pet ⁷	9.4 [5.2–13.6]	7.7* [3.2–12.3]	3.4 [0.5–6.3]	3.1 [0.0–6.3]	–0.1	22.1* [12.3–32.0]	12.6 [4.1–21.0]	2.3 [0.0–5.5]	–0.4

¹% pos. = age- and sex-standardized percentage of positive reactions (+, + +, + + +) to the allergen. ²% ery. = age- and sex-standardized percentage of erythematous reactions to the allergen. ³% + = age- and sex-standardized percentage of weak positive reactions, i.e. + only, to the allergen. ⁴% + +, + + + = age- and sex-standardized percentage of strong positive reactions, i.e. + + or + + +, to the allergen. ⁵RI = reaction index. ⁶Significance of difference between patients with and without reaction to SLS not calculable due to quasi-complete separation of data points in the logistic regression analysis. ⁷Count of patients tested = 219. *Difference between patients with and without reaction to SLS significant; *P* < 0.05.

tential at the test concentration used: potassium dichromate, cobalt chloride, lanolin alcohol, formaldehyde, fragrance mix, mercury salts, rubber accelerators. In the vehicle/emulsifier and preservative series, these are: propylene glycol, triethanolamine, benzalkonium chloride, phenylmercuric acetate,

Amerchol L-101, cocamidopropyl betaine, octyl gallate and benzoyl peroxide (4, 5, 30–32). In some but not all of these allergens, there was an association of erythematous reactions with the SLS reactivity in this study. If all reaction indices are compared regarding the 2 groups of SLS reactivity, the

number of allergens with a negative RI is higher in the SLS-reactive group than in the non-responders (10 vs. 5 for the standard series, 13 vs. 10 for the other allergens). This lends further support to the hypothesis that in the SLS-reactive group there is an overrepresentation of doubtful/irritant reactions. Weak reactions to 0.5% potassium dichromate are often non-reproducible and represent irritancy rather than contact allergy. The concentration has not been lowered to 0.375% because too many true sensitizations would be missed with this concentration (3). In our study, however, there was only a trend, but no significant difference between the SLS reactors and non-reactors. This might be explained by the relatively small effective sample size of this study. Although data of 1600 patients were analysed, one has to be aware that only up to 15% of these showed a positive reaction and only up to 12% showed an erythematous reaction to an individual allergen. Thus, the contribution of patients to the study results, in terms of statistical power and precision, is much smaller than the total number of patients tested suggests. This fact is reflected by the relatively wide 95% CIs calculated for the proportion of erythematous and positive reactions and explains why only some of the observed differences were statistically significant.

On the other hand, a good correlation between the reactivity to SLS and *any* contact allergen with an irritant potential cannot be expected. Björnberg (29) has pointed out that the irritancy of one irritant cannot be predicted by another one. In Björnberg's large series of 11 chemically different irritants, the correlation was weak. For SLS a significant relationship was established only for NaOH. However, in a similar study on healthy volunteers, Frosch (26) and Frosch & Wissing (33) found a significant relationship between SLS and NaOH, ammonium hydroxide, DMSO, quaternium-1, croton oil, kerosene and the minimal erythema dose of a UVB light source. Löffler reported a significant relationship between the irritancy of SLS and dithranol, but not between SLS and tretinoin (34, 35). This can be explained by differences in the pathogenetic mechanisms of irritants differing regarding solubility, penetration, release of cytokines, etc. (for review see 36). This might also apply to some of the allergens which are tested at the border of irritancy. Therefore, other irritants (like nonanoic acid?) may have to supplement SLS in order to assess the inflammatory capacity of an individual in a more reliable way.

A further aspect of hyperreactive skin has recently been promoted by Smith et al. (37). They reported an increased response to SLS in the group of patients allergic to colophony (colophonium) in comparison to healthy nonatopic control subjects.

They hypothesized that individuals with enhanced susceptibility to skin irritation would also be more liable to develop allergic skin reactivity. Although the difference between the 2 groups was significant, this could have been due to disease still being active in the patient group and considerable differences regarding age and size of control group (42 vs. 30 years; 23 patients vs. 237 controls). This observation awaits further confirmation by more detailed studies. Nevertheless, it would be in line with the assumption that a subgroup of patients with contact dermatitis is more reactive to chemicals with an irritant and/or allergic potential. Some allergens are also potent irritants and might thus elicit an irritant and/or an allergic contact dermatitis at a higher frequency in individuals with (SLS) hyperreactive skin, in comparison to more resilient subjects.

As can clearly be seen from Table 3, there are seasonal differences in SLS reactivity. This corresponds to the results of a study on the dependence of irritant contact dermatitis on weather conditions performed in hairdresser apprentices (38). In that study, it was shown that low temperature and humidity were positively associated with irritant hand dermatitis. However, according to a careful experimental study by Basketter et al. (39), interindividual variation is probably more pronounced than seasonal variation in testing with SLS. In our analysis, the only significant differences concerning individual patient characteristics as associated with SLS reactivity were found to be male sex and face dermatitis.

In conclusion, and in answer the 2 main questions posed above, patch testing with SLS 0.5% aq. as a marker of skin irritability in addition to the standard series facilitates the interpretation of patch test readings, because macular erythematous test reactions to problematic allergens can be interpreted more confidently as irritant in the presence of a positive reaction to SLS. This even more so, if there is no history and no known exposure to the allergen. However, due to the relatively small sample size, a larger study is needed to confirm the observed positive association between reactivity to SLS and irritant erythematous reactions to allergen preparations. Currently, the German Contact Dermatitis Research Group (DKG) is conducting a multicentre study on this subject.

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