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Skin irritability to sodium lauryl sulfate is associated with increased positive patch test reactions

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Conflict of interest

J.B., J.G. and J.S. have no conflicts of interests to declare. H.L. and W.U. have accepted honoraria for presentations or travel reimbursement from cosmetic and pharmaceutical industry associations, respectively. A.S. works as ad hoc consultant for cosmetic industry (associations) partly remunerated.

What's already known about this topic?

- Irritation and contact allergy follow a partly similar pathomechanism and lead to similar morphology, e.g., in patch testing.
- Doubtful, irritant, but also partly weak positive patch test reactions to allergens have been found to be associated with irritant reactions to 0. 25% sodium lauryl sulfate (SLS) in water
- Some studies have linked skin irritability as diagnosed with SLS to susceptibility to contact sensitisation

What does this study add?

- Skin irritability to SLS is associated with multiple positive reactions to patch tests of the baseline series. The risk of having one additional positive reaction increases by 22% in patients with an irritant reaction to SLS.
- It is apparent that further research beyond the mere analysis of patch test data is needed to disentangle the conflicting interpretations of irritant SLS reactions being indicative of false (weak) positive patch test reactions *versus* increased susceptibility to contact sensitisation

Abstract

Background

Since previous observations have indicated an interrelation between irritant and allergic skin reactions we have analysed data of synchronous allergen and SLS patch tests in terms of a relation between SLS-responsiveness and allergic patch test reactions.

Objectives

To analyse differences in terms of allergen specific and overall reaction profiles between patients with versus without an irritant reaction to SLS.

Methods

Clinical data of 26.879 patients patch tested from 2008 to 2011 by members of the IVDK network (www.ivdk.org) were analysed. After descriptive analyses, including the MOAHLFA index, the positivity ratio and reaction index, a negative binomial hurdle model was adopted to investigate the correlation between SLS-reactivity and positive patch test reactions.

Results

Men, patients aged ≥ 40 and patients with occupational background were overrepresented in the SLS-reactive group. Patients with an irritant reaction to SLS showed a higher proportion of weak positive reactions as well as more questionable and irritant reactions to contact allergens than patients not reactive to SLS. The risk of an additional positive patch test reaction increased by 22% for SLS-reactive patients as compared to SLS-negative ones.

Conclusion

The marked association between SLS-reactivity and the number of positive reactions in patch test patients may be due to non-specific increased skin reactivity at the moment of patch

testing only. However, increased SLS-reactivity could also be due to longer lasting enhanced skin irritability, which may have promoted (poly-) sensitisation. Further studies, e.g. with longitudinal data on patients repeatedly patch tested with SLS and contact allergens, are necessary.

Keywords: skin irritability, contact allergy, polysensitisation, patch test, SLS

Introduction

Patch testing is a well tried and tested diagnostic method to detect contact allergy.

Nevertheless, the procedure is not without some difficulties. One well-known problem is the distinction between irritant and weak allergic reactions in case of erythema and infiltration.

To aid this distinction the German Contact Dermatitis Group (DKG) decided to add sodium lauryl sulfate (SLS, 0.25% in water) to the German baseline patch test series. The rationale is that in case of an irritant reaction to this control, reactions to “difficult” allergens morphologically qualifying as weak positive reactions can more confidently be attributed to irritation – with appropriate consideration of various other aspects of the patch test ^{1,2}.

Thereby, each patient’s reactivity to SLS at the time of patch testing with the baseline series is routinely recorded by departments of dermatology that are members of the Information Network of Departments of Dermatology (IVDK) in Germany.

With regard to the pathogenesis of irritant and allergic skin reactions some observations indicate that mechanisms involved in both types of inflammation are related ¹. Current evidence indicates that epidermal barrier perturbation (due to irritation) may favour contact sensitisation due to increased allergen penetration. Moreover, the inflammatory cytokine background seems to augment sensitisation and elicitation, respectively³. Nagtegaal et.al², e.g. showed that enhanced SLS reactivity is associated with the presence of multiple allergies to fragrance chemicals. Similar results were demonstrated by Smith et al. when investigating colophony⁴.

Prompted by abovementioned considerations and evidence, it appeared interesting to analyse IVDK data on skin irritability to SLS and positive patch test reactions to baseline series allergens.

Materials & Methods

For the present analysis patch test data filed by the Information Network of Departments of Dermatology, IVDK (www.ivdk.org) were retrospectively analysed. The IVDK is a group of 65 cooperating dermatological clinics in Germany, Austria and Switzerland interested in the epidemiology of contact allergy. The methods applied by the IVDK to collect and process patch test data were described previously⁵. Standardized test procedures, following international guidelines^{6,7}, are employed by all departments. All participants of the IVDK are members of the German Contact Dermatitis Research Group (DKG), which maintains the German baseline series of patch test allergens. In the study period this comprised 30 allergens and the irritant sodium lauryl sulphate (SLS) (Tab. 1).

Insert table 1 about here

SLS (0.25% in water) has been tested routinely since 2008, resulting in a data pool of 34.095 patients until December 2011. The reaction to SLS was regarded as “positive irritant” for this study if an irritant reaction of any degree was read at the first assessment on day two or at the second assessment on day three or four. SLS was regarded “negative” if all readings were negative (Tab. 2), according to⁸.

Insert table 2 about here

The reaction to an allergen was regarded as “positive allergic” if a weak, strong or extreme positive reaction was diagnosed on day three or, if exceptionally no day three reading was

available, at day four; all other reactions (doubtful, irritant or negative) were summarised as non-positive.

Beyond this common definition of an allergic patch test response, the individual reaction kinetic for each allergen from day 2 to day 3 or 4 was considered. A reaction with an increase of intensity is called a 'crescendo reaction', whereas a decrease is classified as 'decrecendo reaction'. If the first and the second reading yielded identical results a 'plateau reaction' was diagnosed. Preliminary analyses had shown that it is meaningful to consider 'robust' allergic reactions only, i.e. those with a plateau or crescendo time course. Patients with reactions to allergens that were read as irritant or questionable twice were excluded. The present analysis is thus restricted according to the algorithm shown in Fig. 1, resulting in a data pool of 26.879 patients.

Insert figure 1 about here

Regarding polysensitisation it is important to take into account only unrelated allergens.

Therefore allergic reactions to related allergens were counted as one reaction only. This applies to the following combinations: mercaptobenzothiazole and mercapto mix, thiuram mix and zinc diethyldithiocarbamate, fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, e.g., LyrallTM), formaldehyde and 2-bromo-2-nitropropane-1,3-diol.

The relation of the reactivity to SLS with polysensitisation was statistically analysed by use of a negative binomial hurdle regression model. A more detailed explanation regarding the choice of this very model is found in ⁹. The hurdle model allows estimation of both the odds ratio (OR) of having at least one allergic reaction and the risk of having multiple contact allergies, associated with "irritant positive" reactions to SLS and other factors.

For statistical analysis, the software R (version 2.15.3) was used (www.r-project.org).

Results

Overall, 22.1% of all patients patch tested had an irritant reaction to SLS, and in 18.3% of patients this was of a crescendo type (i.e., approximately 83% of all SLS reactions). The MOAHLFA index¹⁰ illustrates the distribution of important demographic and clinical characteristics of patients included, and of the subgroups defined by SLS reactivity (Tab. 4).

Insert table 4 about here

The odds ratios shown in table 4 describe the association between the single MOAHLFA factors and irritability by SLS. These odds ratios reveal that the factors male, occupational, age 40+ and hand were overrepresented in the subgroup with irritant SLS reaction, compared to the non-reactive group (OR > 1). A history of atopic eczema showed no association to SLS, the OR is 1. Leg and face dermatitis were inversely associated with SLS reactivity (OR < 1).

Table 1 also shows the percentage of positive reactions to an allergen in patients with versus without an irritant reaction to SLS. Positive reactions to most of the allergens were associated with an irritant SLS reaction. Only patients with positive reactions to mercapto mix and nickel sulfate showed a slightly lower frequency of SLS-reactivity.

In most allergens the majority of positive reactions were weak positive (+) (Tab. 5). Almost equal percentages of weak and moderate/strong positive reactions were elicited by nickel sulfate, bufexamac and epoxy resin. Columns 6-13 of table 5 reveal a relation between the likelihood of + reactions and SLS reactivity: Patients with an irritant reaction to SLS were more likely to have a weak positive reaction to an allergen than those displaying a negative SLS result. This tendency is expressed by the odds ratios (OR) shown in table 5: a value >1 indicates weaker positive patch test reactions in the SLS-reactive patients. Odds ratios >1 were calculated for 23 out of 29 allergens for the relation between SLS reactivity and a weak positive patch test reaction.

Insert table 5 about here

The Positivity Ratio (PR) (Fig.2), describes the share of weak positive reactions among all positive reactions obtained with an allergen ¹¹. Patients with an irritant reaction to SLS at the time of patch testing were more likely to have a weak positive reaction to an allergen than patients not reactive to SLS. A sign test confirmed this trend ($p < 0.001$).

Insert figure 2 about here

The Reaction Index (RI) relates the numbers of irritant and doubtful reactions to an allergen to the number of positive reactions elicited by this allergen ¹². In our test population we found that for all allergens the RI was lower for patients with an irritant SLS reaction than for those without SLS-reactivity (Fig.3) ($p < 0.001$). This means that patients with an irritant SLS reaction showed more often an irritant or questionable reaction to an allergen than patients without an irritant SLS reaction. Moreover, for all allergens the RI was positive for patients without an irritant SLS reaction, while it was negative for some allergens in the SLS positive group.

Insert figure 3 about here

Figure4 shows the relation between positive reactions and SLS reactivity. Higher numbers of positive reactions were clearly related to a higher likelihood of SLS-irritability.

Insert figure 4 about here

In individuals without any positive reaction to the patch test SLS reactivity occurred in 20.3% which is below the average responsiveness of 22.1% within the entire group of patients evaluated. For individuals with three or more positive reactions to the baseline series, the percentage of irritant SLS reactions was 29.3%. The association between SLS reactivity and positive reactions is confirmed by a hurdle model (Tab. 6).

Insert table 6 about here

SLS reactivity thus increased the odds of having positive reactions by 33%. The risk of having one additional positive reaction increased by 22% in patients with an irritant reaction to SLS compared to patients without SLS reactivity.

Discussion

Two main pathways can lead to eczematous skin reactions: irritation and allergic mechanisms. The fact that both aetiologies lead to largely similar skin lesions on morphological, histopathological and molecular levels³ reveals the close relation between irritant and allergic eczema, including shared pathophysiological mechanisms³. Experimental data also indicated that skin contact irritation can enhance the development of allergic contact dermatitis¹³. In this case one should expect a relation between skin irritability and the capacity to acquire contact sensitisation. However, in the non-experimental study of this relationship, e.g. based on routine data as in our analysis, the validity of the diagnosis of contact sensitisation based on a (weak) positive patch test reaction is to some extent problematic, as this may be sensitive to the very fact studied, i.e. irritability, as discussed below.

SLS is probably the best-trying irritant in research on skin irritability^{14,15}. It was established as a test substance helpful to quantify skin irritability¹⁵⁻¹⁷ and to identify a propensity to irritant patch test reactions¹⁸. Löffler et al.⁸ found that SLS-irritability is associated with a lower RI: Patients with a positive SLS reaction showed more questionable or irritable reactions to allergens of the standard series. This is in agreement with our findings. The fact that in patients reactive to SLS at the time of patch testing the RI was lower for all contact allergens than in non-responders to SLS indicates that at least at the time of patch testing these patients had not only a higher susceptibility to SLS but to other agents as well. Obviously this group

of patients had – at least temporarily – generally enhanced skin susceptibility for a broad spectrum of unrelated chemicals.

We also found an augmented SLS reactivity in men, in patients aged over 40 years and in patients tested because of occupational dermatitis. Some previous studies showed differing results regarding the relation of SLS reactivity to sex and age with no consistent trend^{16,19}, however, our findings are in accordance with^{18,20}. Our results are based on the largest SLS dataset analysed so far. The data of^{18,20} confirm a higher SLS reactivity in patients older than 40, whereas¹⁶ described no increase of SLS-reactivity with increasing age. Occupational dermatitis is a known risk factor for contact allergy. In our analysis it was associated with SLS reactivity as well. This correlation between SLS-reactivity and occupational dermatitis may reflect generally increased skin irritability in patients who develop occupational contact dermatitis. We found no different SLS-reactivity in patients with and without a history of atopic dermatitis. This is surprising because patients with atopic dermatitis are more prone to develop eczema than others^{21,22}. The reason for not finding a relation of irritability and atopic dermatitis in our study may be that the evaluated tests were strictly performed during a period of quiet skin with no eczema. As the SLS-test is a parameter which evaluates the acute skin irritability, an inactive atopic dermatitis is not correlated with an increased reaction to SLS²³.

So far research into skin irritability and sensitisation to contact allergens has yielded inconclusive results^{1,2,24,25}. An enhanced skin irritability and multiple positive reactions were seen in patients with polysensitisation to fragrances². Individuals with contact allergy to three or more fragrance chemicals showed a significantly higher SLS-reactivity (to 1 and 1.5%, respectively). However, no further data have been published hitherto.

To fill this gap we analysed the association between SLS-irritability and (multiple) positive patch test results to the contact allergens of the German baseline series. As described

previously by our group ⁸, we showed that patients reactive to 0.25 % SLS at a point of time when their skin was considered to be in a “quiet” state tend to have more positive patch test reactions than patients not responding to this SLS-exposure. In addition, there were more weak allergic reactions in SLS-positive patients. Two alternative explanations can be discussed:

1st: The SLS-test shows increased skin susceptibility just at the time of patch testing. Patients with positive SLS reaction and multiple positive reactions to contact allergens therefore developed these positive reactions merely because of a temporarily enhanced SLS-reactivity at the very time of testing. Indeed we found a decreased RI and an increased PR which may reflect unspecific increased skin reactivity. This may lead to a higher share of all non-negative patch test reactions. In detail: not only the irritant reactions are increased in SLS positive patients, but also doubtful reactions may increase to +. Even a ++ reaction in a SLS-negative patient may be seen as a +++-reaction in the same patient if he is in a state of higher skin reactivity revealed by a positive reaction to SLS. If this scenario was true, the consequence would be that if an irritant reaction to 0.25 % SLS occurs at the time of patch testing the patch test results (at least the weak positive reactions, and in particular to those allergens which are marginally irritating) have to be considered not valid because the transiently increased responsiveness had caused somewhat exaggerated reactions.

2nd: The irritant reaction to SLS at the moment of patch testing is not only a snapshot of a current, transient state, but also relates to previous and longer lasting enhanced skin irritability. Proceeding on the assumption that in the general population a positive response to 0.25 % SLS occurs only during limited periods of time in an individual person, the chance that a person is tested within a time slot of his positive SLS-responsiveness clearly increases with extended intervals of such SLS-susceptibility in a person; at least if the time point of testing is randomly chosen within a phase of clinically “quiet” skin. This was the case in our

analysis and therefore one can argue that in average in our group of SLS-positive patients the time intervals with SLS susceptibility were probably longer (also in the past, and thus potentially relevant for (poly-)sensitisation) than in the SLS-negative group. On this understanding one can then hypothesize that prolonged skin irritability as diagnosed with SLS favours contact sensitisation (and possibly elicitation). However, even if the irritant SLS reactions were an expression of a generally elevated skin irritability, the possibility still exists that (weak) positive patch test reactions in these individuals are not true allergic, but false-positive, in particular to “problematic”, marginally irritating patch test preparations, probably less so to baseline series allergens, and less so if employing rigid criteria for a positive reaction as in our analysis. Hence, no conclusive evidence can be found in this matter if not verification tests for positive patch test reactions such as the ROAT are employed.

The idea that irritation can promote contact sensitisation is not entirely new. In this context it was suggested that irritation is a physiologically needed stimulus for inducing LC maturation²⁶. A plenitude of factors is functionally involved in Langerhans cell migration that contribute to the inflammatory response triggered by irritants as well as by contact antigens^{27,28}. It is also well known that a safe distinction between eczema due to irritation and eczema due to contact allergy is virtually impossible unless allergen-specific T-lymphocytes are demonstrated within the lesion³. In a mouse model with 2,4-dinitrofluorobenzene it was shown that contact irritation with this hapten conditions the development and severity of allergic contact dermatitis¹³. The second interpretation discussed above is in line with our results and may supply circumstantial evidence that in humans irritation may also promote contact sensitisation.

The fact that most contact allergens possess some inherent irritant properties supports the idea that allergen-related irritation could prompt functional danger signals that pave the way for both the sensitisation and elicitation phase of a contact allergy. Irritant and allergen danger

sensing is interconnected within the innate immune system by stimulation of Toll-like receptors that recognize danger associated molecular patterns²⁹⁻³¹. Furthermore, there is a genetic association between a low irritant threshold and allergic contact dermatitis as both conditions are associated with TNF polymorphisms^{32,33}. With regard to the impact of irritation it is noteworthy that nickel allergy is a special case. A unique immunological feature of nickel is its direct stimulation of the human Toll-like receptor 4³⁴. This activation is effective regardless of any concurrent irritation. Our findings now show that in contrast to nearly all other allergens nickel contact allergy is not associated with a low threshold to SLS. This result nicely relates to the hypothesis that the direct activation of Toll-like receptor 4 by nickel can promote sensitisation to nickel even in absence of additional 'irritant' stimuli.

We are quite aware of some limitations that are applicable to our analysis. SLS is an approved irritant with well-known effects but other irritants can trigger and better represent irritation by other mechanisms^{35,36}. Therefore a relation to SLS-reactivity is not necessarily representative for all types of irritants or irritability in general. Furthermore, our analysis was based on an assessment of skin irritability at one point of time only and it is known that skin irritability can vary in the course of time and with the season of year^{37,38}, although evidence is relatively scarce. Especially longitudinal studies with repeated measurements of skin irritability and patch testing in the same persons should be done. The practical importance of an interdependence between skin irritability and susceptibility to contact sensitisation - for instance in an occupational setting - will justify such an effort.

Authors' contribution

Judith Schwitulla performed the data analyses and wrote the manuscript together with Jochen Brasch and Wolfgang Uter. Axel Schnuch, Johannes Geier and Harald Löffler contributed to the discussion of results. All authors critically reviewed the manuscript and approved the final, submitted version.

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Table 1: Allergens of the European Baseline Series 2008-2011 used in this study with its patch test concentration. Patients with positive reactions to the respective allergen were stratified into those with and those without irritant reaction to SLS with the absolute number (n) indicated in the columns. Moreover, the percentage of positive reactions among all patients tested in the 2 subgroups is presented (%). The odds ratio (OR) (with its 95% confidence interval) specifies the odds of having an allergic reaction given an irritant SLS reaction. All allergens in petrolatum, except where indicated: * water

	Conc. (%)	SLS +		SLS -		OR	95% CI
		n	%	n	%		
(Chloro-) Methylisothiazolinone ¹ 3:1	0.01*	231	3.9	536	2.6	1.54	[1.32;1.8]
Bufexamac	5	57	1	191	0.9	1.05	[0.78;1.42]
Cetearyl alcohol	20	63	1.1	152	0.7	1.47	[1.09;1.97]
Methyldibromoglutaronitrile	0.2	202	3.4	458	2.2	1.58	[1.33;1.86]
Fragrance Mix I	8	570	9.6	1518	7.2	1.36	[1.23;1.5]
Epoxy resin	1	99	1.7	302	1.4	1.16	[0.92;1.46]
Formaldehyde	1*	102	1.7	147	0.7	2.47	[1.92;3.19]
Potassium dichromate	0.5	212	3.6	587	2.8	1.28	[1.09;1.51]
Cobalt chloride hexahydrate	1	296	5	955	4.6	1.1	[0.96;1.26]
Colophony	20	247	4.2	710	3.4	1.24	[1.07;1.43]
Mercaptobenzothiazole	2	32	0.5	114	0.5	0.99	[0.67;1.47]

¹ Mixture of 5-Chloro-2-methyl-isothiazol-3(2H)-one and 2-Methylisothiazol-3(2H)-one

N-Isopropyl-N'-phenyl-p-phenylenediamine	0.1	56	0.9	132	0.6	1.5	[1.1;2.06]
Nickel sulfatehexahydrate	5	814	13.7	2973	14.2	0.96	[0.88;1.04]
p-tert. Butylphenol formaldehyde resin	1	33	0.6	93	0.4	1.25	[0.84;1.87]
Paraben mix	16	60	1	129	0.6	1.65	[1.21;2.24]
<i>Myroxylonperei</i> (Balsam of peru)	25	531	8.9	1399	6.7	1.37	[1.24;1.52]
Propolis	10	176	3	433	2.1	1.45	[1.21;1.73]
Oil of turpentine	10	174	2.9	346	1.7	1.8	[1.5;2.16]
Thiuram mix	1	132	2.2	385	1.8	1.21	[0.99;1.48]
Lanolin alcohols	30	205	3.5	442	2.1	1.66	[1.4;1.96]
Zink diethyldithiocarbamate	1	32	0.5	89	0.4	1.27	[0.85;1.9]
Mercapto mix (without MBT)	1	31	0.5	125	0.6	0.87	[0.59;1.3]
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (e.g. Lyr TM)	5	140	2.4	376	1.8	1.32	[1.09;1.61]
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	0.5	68	1.1	138	0.7	1.75	[1.31;2.34]
<i>Canangaodorata</i> (YlangYlang Oil)	10	55	0.9	130	0.6	1.5	[1.09;2.06]
<i>Jasminum</i> spp. (Jasmin absolute)	5	30	0.5	101	0.5	1.05	[0.7;1.58]
<i>Santalum album</i> (Sandalwood oil)	10	29	0.5	82	0.4	1.25	[0.82;1.91]
Fragrance mix II	14	380	6.4	845	4	1.63	[1.44;1.84]
Compositae mix	5	101	1.7	260	1.2	1.38	[1.09;1.74]
Compositae mix II	5	3	0.1	9	0	1.18	[0.32;4.35]
Sodium lauryl sulfate	0.25*						

Table 2: Scoring of irritant patch test reactions to SLS according to Löffler et al.⁸

Symbol	Description	Qualification
0	No reaction	Negative
1	Very weak/slight erythema or scaling (spotty or diffuse)	Doubtful
2	Weak/slight erythema, scaling, oedema or roughness	Weak
3	Moderate erythema, scaling, oedema or roughness or weak/slight erosions, vesicles or fissures	Moderate
4	Strong erythema, scaling, oedema or roughness, or clear erosions, vesicles or fissures	Strong
5	As 4, with necrotic areas	Very strong/caustic

Table 3: MOAHLFA index of the total test population and in the subgroups of patients with (SLS+) and without (SLS-) irritant reactions to SLS in absolute (n) and relative (%) numbers. The last columns show the odds ratio (OR) with its 95% confidence interval of having an irritant reaction to SLS compared to a negative one given the respective MOAHLFA factor

	Total		SLS +		SLS -		OR	95% CI
	n	%	n	%	n	%		
Male	9808	36.5	2552	43.0	7256	34.6	1.42	[1.34;1.51]
Occupational	4119	15.3	1170	19.7	2949	14.1	1.50	[1.39;1.62]
Atopic Eczema	5334	19.8	1179	19.9	4155	19.8	1.00	[0.93;1.07]
Site: Hand	7483	27.8	1823	30.7	5660	27.0	1.20	[1.13;1.28]
Site: Leg	2999	11.2	617	10.4	2382	11.4	0.90	[0.82;0.99]
Site: Face	4452	16.6	934	15.7	3517	16.8	0.93	[0.86;1.01]
Age 40+	1931	71.9	4483	75.5	14833	70.8	1.27	[1.19;1.36]
	7							

Table 4: Weak (+) and strong/extreme (+++/+++) allergic reactions in the whole data set and in patients with (SLS+) and without (SLS-) an irritant reaction to SLS in absolute numbers (n) and percent (%). Further the odds ratio (OR) of having a weak allergic reaction compared to a strong allergic reaction given an irritant SLS-reactivity

					Total	SLS +				SLS-				OR
	+		++/+++			+		++/+++		+		++/+++		
	n	%	n	%		n	%	n	%	n	%	n	%	
(Chloro-) Methylisothiazolinone 3:1	504	65.7	263	34.3	767	151	65.	80	34.	353	65.	183	34	0.9
Bufexamac	129	52	119	48	248	31	54.	26	45.	98	51.	93	48	1.1
Cetearyl alcohol	165	76.7	50	23.3	215	48	76.	15	23.	117	77	35	23	0.9
Methyldibromoglutaronitrile	527	79.8	133	20.2	660	179	88.	23	11.	348	76	110	24	2.4
Fragrance Mix I	141	67.6	676	32.4	2088	396	69.	174	30.	101	66.	502	33	1.1
Epoxy resin	203	50.6	198	49.4	401	63	63.	36	36.	140	46.	162	53	2.0
Formaldehyde	179	71.9	70	28.1	249	70	68.	32	31.	109	74.	38	25	0.7
Potassium dichromate	563	70.5	236	29.5	799	155	73.	57	26.	408	69.	179	30	1.1
Cobalt chloridehexahydrate	846	67.6	405	32.4	1251	196	66.	100	33.	650	68.	305	31	0.9

Colophony	555	58	402	42	957	143	57.	104	42.	412	58	298	42	0.9
							9		1					9
Mercaptobenzothiazole	95	65.1	51	34.9	146	27	84.	5	15.	68	59.	46	40	3.6
							4		6		6		.4	5
N-Isopropyl-N'-phenyl-p-phenylendiamine	96	51.1	92	48.9	188	31	55.	25	44.	65	49.	67	50	1.2
							4		6		2		.8	8
Nickel sulfatehexahydrate	191	50.4	187	49.6	3788	431	52.	383	47.	147	49.	149	50	1.1
	1		7				9		1	9	7	4	.3	4
p-tert. Butylphenol formaldehyde resin	86	68.3	40	31.7	126	25	75.	8	24.	61	65.	32	34	1.6
							8		2		6		.4	4
Parabens mix	165	87.3	24	12.7	189	53	88.	7	11.	112	86.	17	13	1.1
							3		7		8		.2	5
<i>Myroxylonpereiarae</i> (Balsam of peru)	155	80.5	377	19.5	1930	436	82.	95	17.	111	79.	282	20	1.1
	3						1		9	7	8		.2	6
Propolis	481	79	128	21	609	148	84.	28	15.	333	76.	100	23	1.5
							1		9		9		.1	9
Oil of turpentine	403	77.5	117	22.5	520	139	79.	35	20.	264	76.	82	23	1.2
							9		1		3		.7	3
Thiuram mix	291	56.3	226	43.7	517	76	57.	56	42.	215	55.	170	44	1.0
							6		4		8		.2	7
Lanolin alcohols	556	85.9	91	14.1	647	184	89.	21	10.	372	84.	70	15	1.6
							8		2		2		.8	5
Zink diethyldithiocarbamate	90	74.4	31	25.6	121	27	84.	5	15.	63	70.	26	29	2.2
							4		6		8		.2	3
Mercapto mix (without MBT)	107	68.6	49	31.4	156	23	74.	8	25.	84	67.	41	32	1.4
							2		8		2		.8	
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (e.g. Lyrat™)	358	69.4	158	30.6	516	93	66.	47	33.	265	70.	111	29	0.8
							4		6		5		.5	3
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	155	75.2	51	24.8	206	55	80.	13	19.	100	72.	38	27	1.6
							9		1		5		.5	1
<i>Canangaodorata</i> (YlangYlang Oil)	137	74.1	48	25.9	185	41	74.	14	25.	96	73.	34	26	1.0
							5		5		8		.2	4
<i>Jasminum</i> spp. (Jasmin absolute)	108	82.4	23	17.6	131	26	86.	4	13.	82	81.	19	18	1.5
							7		3		2		.8	1
<i>Santalum album</i> (Sandalwood oil)	87	78.4	24	21.6	111	25	86.	4	13.	62	75.	20	24	2.0
							2		8		6		.4	2
Fragrance mix II	902	73.6	323	26.4	1225	287	75.	93	24.	615	72.	230	27	1.1
							5		5		8		.2	5
Compositae mix	209	57.9	152	42.1	361	68	67.	33	32.	141	54.	119	45	1.7
							3		7		2		.8	4
Compositae mix II	7	58.3	5	41.7	12	3	100	0	0	4	44.	5	55	--
											4		.6	

Table 6: Odds ratio (OR) of having at least one and relative risk (RR) of one additional allergic reaction, respectively. The first column (%) shows the prevalence of the factor. The hurdle model has additionally been adjusted for the number of allergens tested.

	%	OR	95% CI	RR	95% CI
SLS (pos.)	23.75	1.33	[1.25 ; 1.42]	1.22	[1.14 ; 1.3]
Sex (f)	63.17	1.72	[1.63 ; 1.81]	1.09	[1.02 ; 1.17]
Atopic dermatitis (yes)	20.48	1.17	[1.1 ; 1.25]	1.22	[1.14 ; 1.32]
Age < 34 (Ref)	20.31	1	-	1	-
34-47	21.9	1.34	[1.24 ; 1.45]	1.19	[1.08 ; 1.31]
48-61	28.07	1.24	[1.15 ; 1.33]	1.46	[1.33 ; 1.6]
≥62	29.72	1.04	[0.96 ; 1.12]	1.56	[1.41 ; 1.71]
Season (winter)	51.68	1.35	[1.26 ; 1.45]	1.18	[1.09 ; 1.28]

Figure 1: Exclusion criteria and remaining number of patients for the analysis

Figure 2: Positivity ratios of the different allergens for patients with (SLS+) and without (SLS-) an irritant reaction to SLS.

Figure 3: Reaction indices of the different allergens for patients with (SLS+) and without (SLS-) an irritant reaction to SLS.

Figure 4: Percentages of patients with irritant (SLS+) and negative (SLS-) reactions to SLS within groups of patients having zero, one, two or three and more positive reactions to contact allergens





