

The association between ambient air conditions (temperature and absolute humidity), irritant sodium lauryl sulfate patch test reactions and patch test reactivity to standard allergens

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To support the decision as to whether erythematous patch test reactions to allergens are irritant or allergic, sodium lauryl sulfate (SLS, 0.5% in water) has been added to the standard patch tests since July 1996 in the Dortmund Department of Dermatology. Data on 1600 patients patch tested up until June 2001, as well as standardized data on ambient temperature and humidity obtained by the German Meteorological Service, were included in a logistic regression analysis taking age, sex and atopy as potential confounders into account. The pattern of association was heterogeneous: while doubtful reactions to nickel sulfate were significantly associated with dry/cold weather conditions, but not with SLS reactivity, the opposite was observed for lanolin alcohol, benzocaine and *Myroxylon pereirae* resin (balsam of Peru). Doubtful reactions to other allergens, namely formaldehyde, fragrance mix or *p*-phenylenediamine, were associated with both factors. For several other allergens of the standard series, no distinct, significant pattern could be discerned. In conclusion, meteorological conditions and SLS reactivity independently contribute information on individual irritability at the time of patch testing, and both should be considered.

Key words: ambient humidity; ambient temperature; contact allergy; patch testing; skin irritation; sodium lauryl sulfate. © Blackwell Munksgaard, 2003.

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Sodium lauryl sulfate (SLS) is the most widely used irritant in studies assessing human skin irritability under various conditions. Recently, patch testing with SLS, with occlusive application for 1 or 2 days, parallel to diagnostic patch testing with allergen panels, has been introduced in a few centres. The aim was to grossly diagnose individual susceptibility to irritation at the time of patch testing, striving for a more valid interpretation of a doubtful patch test reaction to certain allergens, which are also marginal irritants under test conditions. In Dortmund, SLS 0.5% in water (aq.) has been tested routinely in consecutive patch test patients since July 1996. Results obtained in 1600 patients, up until June 2001, have already been presented, addressing the spectrum of SLS reactions and in particular the association between SLS reactivity and reactions [doubtful, weak positive and strong positive] to contact allergens (1).

Skin irritability, however, increases in winter (2), with prevailing low ambient temperature (*T*) and absolute humidity (*AH*), and indeed significantly increased reactivity to SLS in winter months has been found in our material (1), confirming previous findings (3). As it has also been found that wintry weather conditions render patients more prone to doubtful or weak-positive (possibly false-positive) patch test reactions at least to marginal irritants (4), the following questions have to be raised:

- (1) Whether the association between SLS reactivity and doubtful or (weak-) positive reactions to certain allergens (1) merely reflects the effect of ambient conditions, which also lead to increased SLS reactivity, or
- (2) Whether SLS reactivity additionally depends on other, e.g. individual susceptibility factors
- (3) possibly relevant to the interpretation of allergen patch test results.

If the latter hypothesis should hold true, it would be advisable to include SLS patch testing to assess the current degree of the patient's irritability, instead of merely relating it to prevailing weather conditions.

To examine these hypotheses in detail, a multi-factorial analysis of patch test data (SLS and allergens of the standard series), anamnestic data and environmental data (temperature and ambient humidity) was performed (Fig. 1), allowing for the quantification of the independent influence of these factors on the risk of – doubtful or irritant, weak-positive and (strong-) positive – patch test reactions.

Materials and Methods

Methods concerning testing with SLS (5), allergen patch tests, clinical data collection and analysis (1) have been reported previously. In the analyses presented here, reactions 3 days after application of patches (D3) were considered for both SLS (0.5% aq.) and the contact allergens of the German standard series tested throughout the whole study period (July 1 1996 to June 30 2001), including 1600 consecutive patients who gave their prior informed consent. In addition, meteorological data for Dortmund were obtained from the German Meteorological Service (Deutscher Wetterdienst, DWD, <http://www.dwd.de>), Offenbach, FRG, namely, the daily mean values of temperature (T) and relative humidity (RH) during the period mentioned. Due to temporary unavailability of measurements from the Dortmund weather station ($51^{\circ}30'N$, $7^{\circ}32'W$) for certain periods, data from the adjacent weather station of Hagen-Fley ($51^{\circ}24'N$, $7^{\circ}29'W$) were then used instead. Mean values were calculated from the 3 measurements taken at 07:30, 14:30 and 21:30 MET. Daily means of AH were calculated from the other

2 day mean values according to the following formula (6):

$$AH = \left(\frac{RH_T}{100} \right) SVP_T$$

where SVP_T is the saturated vapour pressure at a certain temperature T derived from the following formula:

$$SVP_T = C_1 \frac{C_2 T}{C_3 + T}$$

with the 3 constants being $C_1 = 6.11$ (for -50 to $100^{\circ}C$), $C_2 = 17.84$ (for -50 to $0^{\circ}C$) and 17.08 (for 0 – $100^{\circ}C$), $C_3 = 245.43$ (for -50 to $0^{\circ}C$) and 234.18 (for 0 – $100^{\circ}C$).

To provide for some smoothing out of sudden weather changes, and to cover the time period which is probably most likely to affect skin condition at the start of patch testing, moving averages of T , RH and AH on the first day of examination (start of patch testing) and the preceding 2 days were calculated and used in the analyses. Meteorological conditions during application of patches (D1 and D2) were not regarded as relevant because occlusion (by the test chambers) was assumed then to have an overwhelming influence on barrier function.

Logistic regression analysis was performed:

- (1) To quantify the association between SLS reactivity [as a dichotomous outcome 'irritant reaction' (any degree) versus 'no reaction'] and the environmental variables, controlling for the potentially confounding influence of age, sex and atopic dermatitis and
- (2) To assess the relationship between reactivity to contact allergens of the standard series (employing 3 different definitions of the outcome) and SLS reactivity, the environmental variables, age, sex and atopic dermatitis as explanatory variables. Only those allergens were considered which exhibited a prevalence of doubtful and weak-positive reactions of at least 1% each to avoid a situation of sparse data.

Results of the logistic regression analyses are reported as odds ratios (ORs), quantifying the degree of association between the outcome and the explanatory factor(s). Confidence intervals were calculated by the profile-likelihood method, which gives more reliable results than the standard Wald method, and offers an alternative to the computationally expensive exact analysis for moderately large sample sizes (7). Statistical analyses were performed with the SAS program package (version 8.2, SAS Institute, Cary, NC, USA).

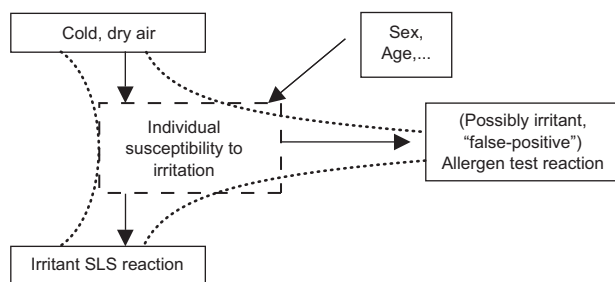


Fig. 1. Environmental and individual factors relevant for (unmeasurable) susceptibility to irritation and thus for – irritant, ‘false-positive’ – patch test reactivity. Arrows: presumable causal relationship, dotted lines: observed associations.

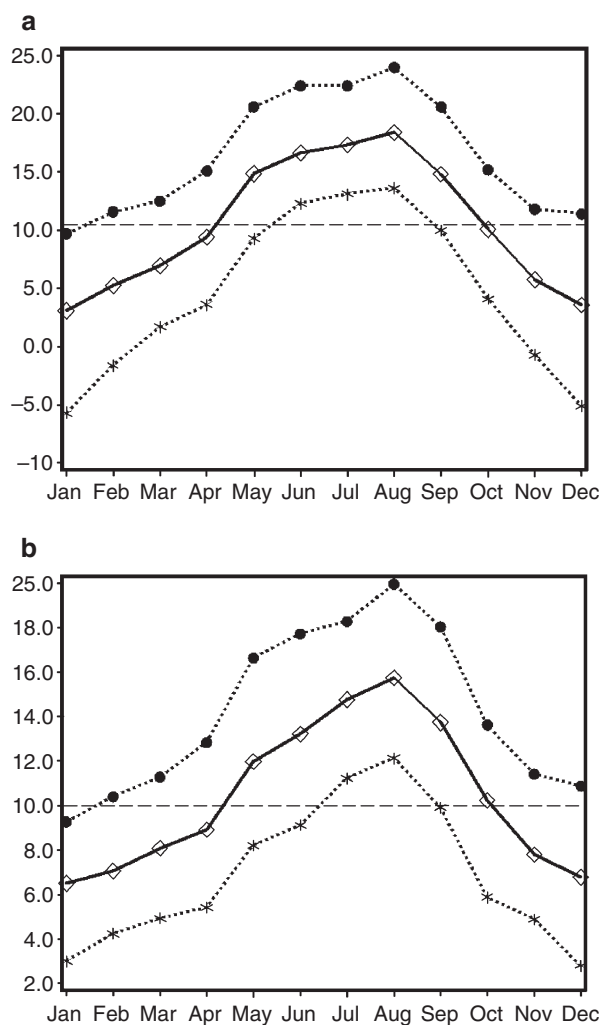


Fig. 2. (a) Seasonal variation of temperature (°C) in Dortmund, Germany, 1993–2001 (monthly mean, 5 and 95% percentiles). (b) Seasonal variation of absolute humidity (mg/l) in Dortmund, Germany, 1993–2001 (monthly mean, 5 and 95% percentiles).

Results

Of the 1600 patients, 668 (41.8%) had an irritant SLS-reaction at D3, which exceeded ++ in only 41 patients. Weather conditions displayed the typical seasonal variation of a temperate climate (Fig. 2). *T*, *RH* and *AH* were classified into ordinal variables according to the tertiles of the distribution in our data. Because of a strong correlation between

the climatic factors, in particular between *T* and *AH*, which have a functional relationship, the 3 factors were included in separate logistic regression models to avoid problems of colinearity. Results concerning the association with SLS reactivity are presented in Table 1, showing an approximately 50% increased chance of irritant SLS reactions under the condition of low *AH* and low *T*, but no association with *RH*. As outdoor *RH* was not related to skin irritation in this as well as previous analyses (8), this factor was disregarded in the subsequent multifactorial analyses.

The standard series was tested in 96% of the 1600 patients, namely 644 patients with and 892 patients without reaction to SLS. Detailed results for these subgroups, including the proportions of patients with erythematous (doubtful) or irritant reactions, with weak-positive (+) reactions and with strong-positive reactions (++ or +++) have already been reported (1). In Table 2, the results of the logistic regression analyses are presented – 1 analysis for each of the 3 outcomes, i.e. doubtful or irritant versus negative, weak positive versus negative and strong positive versus negative – and a set of these 3 analyses for SLS, *T* and the confounders, and SLS, *AH* and the confounders, respectively. Thus, for each allergen, 6 logistic regression models were built. The estimates for SLS refer to the model containing *T* and not *AH* [this made very little difference concerning the estimates for SLS (data not presented)]. As can be seen in Table 2, risk estimates could not be derived for the outcome ‘at least ++ reaction’ for some allergens, because this outcome was too rare for stable estimation of model parameters (data not shown).

Although the pattern of associations may appear irregular at first sight, certain phenomena can in fact be clearly observed (Table 2):

- (1) There is no significant association between irritant SLS reactivity and strong-positive patch test reactions to allergens.
- (2) In 8 of 15 allergens eventually included in the multifactorial analysis, a significant association between irritant SLS reactivity and doubtful or irritant allergen reactions was observed. In only 2 of these 8 allergens was a weak-positive

Table 1. Risk of irritant reaction to sodium lauryl sulfate (SLS) 0.5% aq., reading at D3, controlling for sex, age and atopic dermatitis – results of a logistic regression analysis

Tertile	Temperature		Relative humidity		Absolute humidity	
	°C	Odds ratio (95% CI*)	%	Odds ratio (95% CI*)	mg/l	Odds ratio (95% CI*)
Lowest	<7.4	1.50 (1.17–1.92)	<74.8	0.85 (0.67–1.09)	<8.1	1.44 (1.12–1.85)
Medium	7.4–13.0	1.41 (1.10–1.81)	74.8–82.9	0.95 (0.75–1.21)	8.1–11.8	1.24 (0.97–1.59)
Highest	>13.0	1.00 (reference)	>82.9	1.00 (reference)	>11.8	1.00 (reference)

*95% profile-likelihood confidence interval.

Table 2. Risk estimates [odds ratio (OR) with accompanying 95% confidence interval (CI)] for sodium lauryl sulfate (SLS) together with temperature and absolute humidity, concerning doubtful or irritant, weak-positive and strong-positive reactions to the contact allergens as respective outcomes

Allergen (n)	SLS			Temperature			Absolute Humidity		
	OR for irritant SLS reaction(95% CI)			OR for $T < 7.4^{\circ}\text{C}$ (95% CI)			OR for $AH < 8.1\text{ mg/l}$ (95% CI)		
	(reference: no SLS reaction)			(reference: $> 13.0^{\circ}\text{C}$)			(reference, $> 11.8\text{ mg/l}$)		
	?/IR	+	++/+++	?/IR	+	++/+++	?/IR	+	++/+++
Potassium dichromate 0.5% pet. (1515)	0.87 (0.43–1.70)	1.14 (0.60–2.17)	1.31 (0.70–2.45)	0.52 (0.23–1.13) 0.50 (0.21–1.11)	1.14 (0.51–2.63) 1.31 (0.60–2.97)	0.48 (0.22–0.99) 0.46 (0.21–0.97)	0.36 (0.14–0.84) 0.61 (0.28–1.27)	1.03 (0.48–2.23) 0.81 (0.36–1.81)	0.57 (0.27–1.19) 0.52 (0.24–1.08)
Cobalt chloride 1% pet. (1515)	1.63 (1.09–2.47)	0.83 (0.44–1.50)	0.69 (0.29–1.50)	1.26 (0.77–2.08) 1.03 (0.61–1.75)	0.67 (0.32–1.38) 0.95 (0.48–1.86)	0.89 (0.34–2.34) 1.30 (0.53–3.28)	1.35 (0.83–2.24) 0.94 (0.56–1.61)	0.68 (0.34–1.33) 0.50 (0.24–1.02)	1.03 (0.38–2.80) 1.35 (0.55–3.51)
Nickel sulfate 5% pet. (1511)	1.37 (0.79–2.38)	1.05 (0.64–1.70)	1.18 (0.77–1.79)	2.13 (1.07–4.46) 1.43 (0.68–3.11)	0.87 (0.49–1.55) 0.86 (0.48–1.53)	0.86 (0.53–1.39) 0.71 (0.42–1.19)	2.21 (1.09–4.77) 1.60 (0.76–3.51)	0.70 (0.39–1.26) 0.73 (0.42–1.29)	0.95 (0.59–1.53) 0.55 (0.32–0.93)
p-Phenylenediamine 1% pet. (1512)	2.41 (1.34–4.42)	2.30 (1.26–4.32)	1.74 (0.88–3.48)	2.17 (1.04–4.84) 1.48 (0.66–3.46)	1.21 (0.59–2.52) 0.95 (0.43–2.05)	0.70 (0.30–1.58) 0.78 (0.34–1.73)	1.78 (0.83–4.04) 1.76 (0.82–3.99)	1.38 (0.66–3.01) 1.18 (0.55–2.61)	0.55 (0.22–1.30) 0.87 (0.40–1.89)
/Thiuram mix 1% pet. (1519)	1.86 (0.83–4.25)	2.00 (0.83–4.99)	1.03 (0.42–2.44)	0.81 (0.32–2.05) 0.58 (0.20–1.58)	0.71 (0.25–1.93) 0.54 (0.17–1.59)	0.19 (0.03–0.72) 0.88 (0.35–2.15)	0.72 (0.27–1.85) 0.63 (0.23–1.66)	0.67 (0.22–1.97) 0.80 (0.28–2.25)	0.20 (0.03–0.79) 1.00 (0.40–2.46)
Neomycin sulfate 20% pet. (1521)	1.93 (1.02–3.76)	1.89 (0.91–4.03)	2.06 (0.65–7.09)	0.67 (0.30–1.49) 0.86 (0.40–1.83)	1.18 (0.47–3.02) 1.27 (0.52–3.21)	0.92 (0.25–3.37) 0.39 (0.06–1.85)	1.02 (0.39–2.65) 0.99 (0.47–2.11)	1.02 (0.39–2.65) 1.31 (0.55–3.26)	0.70 (0.13–3.09) 1.16 (0.30–4.75)
Benzocaine 5% pet. (1518)	4.73 (1.80–14.70)	1.67 (0.59–4.84)	n.c.	0.64 (0.21–1.89) 0.72 (0.23–2.09)	3.56 (0.85–24.26) 3.19 (0.73–21.89)	n.c. n.c.	0.99 (0.32–3.14) 1.04 (0.34–3.28)	2.46 (0.52–17.33) 3.89 (0.96–25.90)	n.c. n.c.
Lanolin alcohols 30% pet. (1519)	2.14 (1.32–3.49)	1.55 (0.95–2.52)	n.c.	0.73 (0.41–1.31) 0.80 (0.45–1.43)	0.69 (0.38–1.25) 0.84 (0.47–1.48)	n.c. n.c.	0.70 (0.39–1.24) 0.69 (0.38–1.23)	0.76 (0.41–1.40) 0.97 (0.55–1.73)	n.c. n.c.
Cetearyl alcohol 20% pet. (1523)	1.17 (0.50–2.65)	0.99 (0.36–2.56)	n.c.	1.49 (0.55–4.25) 1.25 (0.44–3.60)	0.91 (0.27–2.93) 1.02 (0.32–3.13)	n.c. n.c.	2.05 (0.70–6.76) 2.03 (0.71–6.59)	0.89 (0.26–2.87) 0.90 (0.29–2.77)	n.c. n.c.
<i>Myroxylon peretiae</i> resin (balsam of Peru) 25% pet. (1520)	1.67 (1.12–2.50)	3.00 (1.83–5.01)	1.54 (0.82–2.91)	1.27 (0.81–2.02) 0.59 (0.34–1.01)	1.20 (0.67–2.18) 0.94 (0.51–1.73)	0.73 (0.34–1.56) 0.69 (0.32–1.45)	1.19 (0.75–1.90) 0.61 (0.36–1.03)	1.07 (0.57–2.04) 1.38 (0.77–2.53)	0.68 (0.31–1.42) 0.56 (0.25–1.19)
Fragrance mix 8% pet. (1515)	2.00 (1.39–2.87)	1.37 (0.89–2.10)	1.66 (0.93–2.95)	1.48 (0.93–2.38) 1.76 (1.12–2.80)	1.05 (0.63–1.75) 0.93 (0.54–1.57)	0.72 (0.35–1.43) 0.78 (0.39–1.55)	1.61 (1.01–2.62) 1.75 (1.11–2.81)	1.07 (0.64–1.81) 0.98 (0.58–1.65)	0.74 (0.37–1.44) 0.59 (0.28–1.17)
Colophonium 20% pet. (1518)	1.49 (0.79–2.83)	0.88 (0.43–1.72)	0.98 (0.45–2.08)	1.88 (0.89–4.26) 1.10 (0.46–2.66)	1.52 (0.69–3.44) 0.97 (0.40–2.33)	0.68 (0.26–1.71) 0.93 (0.38–2.25)	1.88 (0.89–4.26) 1.02 (0.42–2.47)	1.59 (0.73–3.59) 0.81 (0.32–1.97)	0.68 (0.26–1.71) 0.84 (0.35–2.02)
Formaldehyde 1% aq. (1520)	5.16 (2.06–15.68)	2.18 (0.77–6.59)	0.56 (0.08–2.49)	2.15 (0.72–7.87) 2.33 (0.77–8.60)	1.29 (0.36–5.13) 1.24 (0.33–5.06)	0.46 (0.02–4.88) 2.68 (0.57–18.95)	2.16 (0.72–7.92) 2.22 (0.73–8.18)	0.61 (0.18–1.94) 0.38 (0.08–1.40)	0.46 (0.02–4.92) 2.24 (0.47–15.88)
Ammoniated mercury 1% pet. (1524)	1.49 (0.73–3.07)	2.60 (1.15–6.24)	n.c.	2.80 (0.96–10.11) 4.01 (1.46–14.10)	0.73 (0.28–1.86) 0.57 (0.19–1.55)	n.c. n.c.	2.81 (0.97–10.16) 3.72 (1.35–13.06)	0.83 (0.33–2.08) 0.44 (0.14–1.25)	n.c. n.c.
Thimerosal 0.1% pet. (1519)	1.61 (0.81–3.25)	1.25 (0.63–2.46)	1.91 (0.59–6.28)	1.06 (0.45–2.57) 1.21 (0.52–2.90)	1.15 (0.47–2.86) 1.65 (0.72–3.98)	0.12 (0.01–0.68) 0.57 (0.15–1.91)	1.23 (0.49–3.22) 1.74 (0.75–4.36)	1.13 (0.48–2.69) 1.16 (0.50–2.76)	n.c. n.c.

Controlled for atopic dermatitis, sex and age. Significant associations are given in bold.
n.c. = not calculable.

allergen reaction additionally associated with SLS reactivity. One more allergen, ammoniated mercury, had a unique pattern of a strong association between SLS reactivity and weak-positive, but not doubtful/irritant allergen reaction.

- (3) Concerning *T* and *AH*, similar risk estimates can be derived with regard to their association with the different grades of allergen reactions.
- (4) If in rare instances a significant association between *T* or *AH* and very strong positive allergen reactions can be observed, it is inverse, i.e. very strong patch test reactions to allergens are less likely to occur in a lower range of *T* or *AH*.
- (5) There is no significant association between either *T* or *AH* and weak-positive allergen reactions in our data.
- (6) A significantly increased risk of doubtful/irritant reactions to a number of allergens is found with low temperature or dry air. This includes nickel sulfate, *p*-phenylenediamine (PPD), fragrance mix and ammoniated mercury. The last allergen again displays a peculiar pattern, in that only the medium range of *T* and *AH*, is significantly associated with doubtful/irritant patch test reactivity.
- (7) Potassium dichromate is a unique allergen in our analysis, because the risk of doubtful/irritant patch test reactions is significantly reduced, rather than elevated, in dry ambient air, which parallels a (non-significant) effect of temperature. This means, conversely, that a high *AH*, which we have chosen as reference here, significantly increases the risk of doubtful/irritant patch test reactions to dichromate in petrolatum.

Discussion

Patch testing, a technique more than a century old, is still the 'gold standard' in the diagnosis of specific allergic contact sensitization. The reading of patch tests, however, is not without its pitfalls, because the relationship between morphology and interpretation (as irritant versus allergic) is difficult. For instance, erythematous, infiltrated and possibly papular patch test reactions, which are interpreted as weak-positive, i.e. allergic, according to international conventions (9), may well be irritant rather than allergic, which has been demonstrated for a number of allergens. In fact, even pure irritants such as SLS are able to mimic patch test reactions which could be regarded as typically allergic, including a crescendo between D2 and D3 (10) (if the observer is blind to the substance).

The interpretation of patch test reactions to certain problematic allergens would greatly benefit from a simple, reliable and valid criterion indicating increased irritability. Because previous studies had demonstrated an association between SLS reactivity and a presumable state of increased irritability, namely, in subjects with active irritant contact dermatitis (11) and later in active atopic dermatitis (12), SLS had been added to the standard patch test series in Dortmund. Our results indicate that indeed a significant association between irritability, defined as an irritant reaction to SLS 0.5% aq. applied under occlusion for 2 days, and doubtful reactions, and partly also with weak-positive reactions, can be found. Conversely, unequivocally positive patch test reactions, graded as ++ or +++, are not associated with SLS reactivity, as would be expected from our hypothesis. Interestingly, this association cannot be found for all allergens, which may be due to the fact that (i) doubtful reactions in the case of these other allergens are weak allergic rather than irritant reactions (ii) different mechanisms of irritation may exist, which are not represented by SLS and (iii) the power of our study was limited. The limited size of the study has also rendered the estimate for the association between *T* and *AH*, respectively, and doubtful/irritant reactivity to formaldehyde previously found (4) – albeit not adjusted for SLS reactivity – non-significant.

As the readings of both the SLS irritation test and the panels of contact allergens were performed synchronously, and the observer was not blind to the SLS test result when grading reactions to allergens and vice versa, it is theoretically possible that the classification of allergen reactions as irritant rather than otherwise was affected by the irritability information of the patient as presented by the SLS reaction, biasing risk estimates for SLS for the outcome doubtful/irritant allergen reaction. However, explicit irritant reactions, which were combined with doubtful reactions in our analysis, were observed only 2× (1× to formaldehyde and 1× to fragrance mix). In contrast, the doubtful reaction, which was observed abundantly, is a purely morphological category (erythema only) without interpretation as allergic or irritant by definition. Hence, an interpretational bias should have played no role.

Coming back to the initial question as to whether it appears necessary to include SLS or whether as much information on irritability could be gathered by simply taking ambient air conditions into account when reading the patch tests, 3 situations can actually be distinguished:

- (1) Only dry/cold meteorological conditions, but not SLS reactivity, are associated with an increased proportion of doubtful/irritant reactions (nickel sulfate).
- (2) Both dry/cold meteorological conditions and SLS reactivity are independently associated with an increased proportion of doubtful/irritant reactions (PPD, fragrance mix, possibly formaldehyde, although the effect of *T* and *AH* is borderline).
- (3) Only SLS reactivity, but not dry/cold meteorological conditions, is associated with an increased proportion of doubtful/irritant reactions (cobalt chloride, neomycin sulfate, benzocaine, lanolin alcohol and *M. pereirae* resin). In other words, SLS has a significant influence independent of weather conditions, which is supposedly explained by individual factors.

In conclusion, both meteorological conditions and SLS reactivity independently contribute information on individual irritability at the time of patch testing, and should both be taken into account.

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