

Another look at seasonal variation in patch test results

A multifactorial analysis of surveillance data of the IVDK*

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There is conflicting evidence concerning seasonal variability of patch test results and no evidence concerning the influence of season on weak-positive, possibly false-positive, irritant reactions, which was analysed in the present study. Data collected in the German Information Network of Departments of Dermatology (IVDK) 1992 to 1997 were combined with external environmental data on temperature and absolute humidity in Germany, and bivariate as well as logistic regression analyses performed concerning the association between reactivity to selected allergens and air temperature and absolute humidity on the respective days of patch testing. Between 39,239 and 41,629 patients had been tested with the 4 allergens considered here. Only formaldehyde exhibited a distinct increase in questionable or irritant as well as weak-positive reactions associated with dry, cold weather. Methylchloroisothiazolinone/methylisothiazolinone and lanolin alcohol showed only a weak, and epoxy resin no, association with climatic conditions. The results indicate that weak-positive reactions, at least to formaldehyde as a prototype of an allergen which is at the same time a marginal irritant, may sometimes be irritant rather than allergic. Patients showing these should be re-tested to improve the poor reproducibility observed with this allergen.

Key words: allergic contact dermatitis; patch testing; seasonal variation; false-positive reactions; formaldehyde; epoxy resin; methylchloroisothiazolinone/methylisothiazolinone; lanolin alcohol.
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Seasonal variation of patch test results has been described by a number of authors, in particular, a potential loss of positive reactions during summer has been postulated (1–3), at least for some allergens (4). A recent experimental study found that mice reacted more strongly to 2,4,6-trinitrochlorobenzene (TNCB) if housed in low ambient humidity (5). Other authors, however, did not find a notable influence of season on patch test results,

namely, the variability of proportions of positive reactions across different periods (6–8). Dooms-Goossens et al. in particular did not find any influence of UV light – a possible enhancer of the epidermal barrier due to light hardening as well as a potential immunomodulator – in their careful study utilising external data to approximate UV exposure of patients in the days prior to patch testing (6).

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However, some authors found increased irritability even of skin not exposed to climate conditions during the winter season in bioengineering studies (9, 10). Thus, the possibility has to be additionally considered that increased irritability may interfere with patch testing during the winter season, at least for those allergens that are at the same time marginal irritants, possibly resulting in false-positive reactions and thus contributing to seasonal variation. We therefore analysed the association between meteorological factors previously found to be important for the pathogenesis of irritant hand dermatitis (11) and patch test reactivity, namely weak-positive reactions to marginal irritants.

Materials and Methods

The Information Network of Departments of Dermatology (IVDK) is a multicentre institution serving epidemiological surveillance of contact allergy. It has been already described in detail (12–14; <http://www.ivdk.gwdg.de>); briefly, patch test data and a standardized history of all patients patch tested in the participating centres are entered into a computer and transferred to the data centre in Göttingen for pooled analysis. The time period covered by this analysis is January 1992 to April 1997. The analysis of the respective sensitizations was based on test readings at D3 following ICDRG criteria. For data management and analysis, the statistical software package SAS 6.12 (SAS Institute, Cary, NC) was used.

For the following analyses, a panel of allergens from the standard series was considered, including lanolin alcohol in petrolatum and formaldehyde in water (as marginal irritants with presumably different modes of action), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI, another water-based allergen) and epoxy resin (as a control allergen not suspected to be irritating when tested at 1% in petrolatum).

As a 1st step, the distribution of weak-positive (+) reactions and of (strong)-positive (++) and (+++) reactions, respectively, per month was analysed to obtain some rough idea of any possible association between season and patch test reactivity (results see Figs. 1, 2). Results are depicted in the format of star plots, which is particularly suitable for the representation of data that show cyclical variation: the centre represents zero and the outer circle the maximum value found among the classes, which form the rays of the star, the length of which denotes the respective mean proportion of reactions per month, in this case.

As a 2nd step, day mean values of temperature and relative humidity, measured in the Hannover

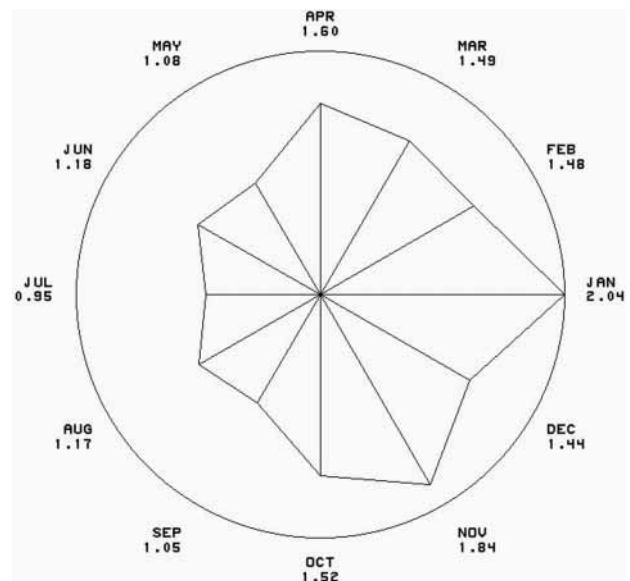


Fig. 1. Monthly variation of + reactions to formaldehyde (1% in water), 1992–1997 with proportions of reactions per month given.

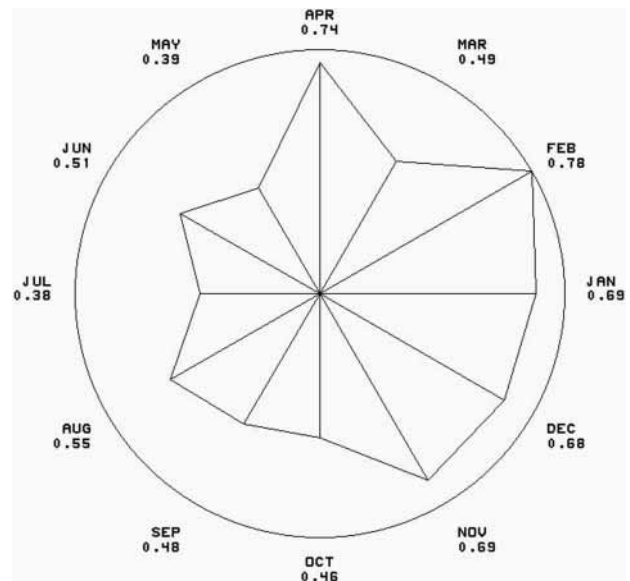


Fig. 2. Monthly variation of ++ to +++ reactions to formaldehyde (1% in water), 1992–1997 with proportions of reactions per month given.

weather station, were obtained from the German Meteorological Service (*Deutscher Wetterdienst*, Department of Medical Meteorology, Freiburg, Germany). Absolute humidity was calculated from temperature, saturated vapour pressure and relative humidity (11, 15). Monthly means and ranges of temperature and absolute humidity were calculated in order to assess the degree of variation of the meteorological parameters within each of the 12 months (Table 1).

Table 1. Variation of meteorological parameters within months, years 1992 to 1997, weather station of Hannover

Month	Temperature (°C)			Absolute humidity (mg/l)		
	min.	mean	max.	min.	mean	max.
Jan.	-16.9	1.3	13.0	1.3	5.9	11.2
Feb.	-13.5	2.7	16.0	1.6	6.3	13.3
Mar.	-3.4	5.7	16.8	3.1	7.2	13.8
Apr.	-1.6	10.2	25.9	4.0	8.9	20.3
May	5.6	15.1	27.8	6.2	12.2	24.4
June	9.6	17.5	29.4	8.8	14.2	25.2
July	11.5	20.2	33.6	9.4	16.1	28.4
Aug.	11.3	19.4	37.1	9.8	16.0	31.6
Sep.	6.3	14.4	23.9	8.2	13.4	22.3
Oct.	2.2	10.2	19.2	4.6	10.7	18.9
Nov.	-6.3	5.6	13.4	3.3	8.0	13.2
Dec.	-16.0	1.9	12.6	1.4	6.3	12.3

Next, values of temperature and absolute humidity were individually matched to each patient according to the 1st day of the patch test. Subsequently, these 2 metric variables were categorized in a 4 scale ordinal variable, representing the respective quartiles of the distribution. For further analyses, temperature and absolute humidity were additionally combined in 1 variable with, accordingly, 16 theoretically possible values. A logistic regression analysis was conducted to obtain estimates of the association between the outcome (+ reactions to the different allergens mentioned, addressing ++/+++ and ?/IR reactions alternatively in some instances) and the climatic exposure variables (combined and individually), at least for those 10 exposure combinations with sufficient sample size. Confidence intervals are calculated by means of the profile likelihood method. The highest category for temperature, absolute humidity, and for the combination of both, respectively, was chosen as the respective reference group.

Results

The patch test population comprised 46,887 patients tested in 27 centres. Of these, 34.9% were male, 15.5% suffered from occupational dermatitis, 18.5% from previous or current atopic dermatitis; the site affected was hand in 30.0%, leg in 7.9% and face in 14.9%. Altogether 56.2% of patients were 40 years or older – summarising the population characteristics according to the MOAHLFA index (16).

The monthly distribution of + and ++/+++ reactions, respectively, is depicted in Figs. 1 and 2 for formaldehyde. While for + reactions seasonal variation can be clearly recognized, the distribution of stronger reactions to this allergen does not seem to follow this pattern as clearly.

Meteorological conditions considered here

showed seasonal variation (Table 1) typical for central Europe, with low temperatures and low absolute humidity in December, January and February, and relatively high temperatures and water content of the atmosphere particularly around July and August. Temperature and absolute humidity were strongly correlated (Pearson correlation coefficient: 0.927, $p < 0.0001$).

The number of patients exposed to different classes of temperature (row sums), absolute humidity (column sums), and the combined exposure variable (cells) is shown in Table 2. Some combinations of temperature and humidity did not occur (a combination of high absolute humidity and low temperature is not possible for physical reasons (15)), and 2 cells were too sparsely populated and thus not considered in further multifactorial analyses.

The monthly distribution of those patient characteristics which are both potentially relevant for skin irritability (17) and may also be season dependent, and could thus confound the analysis between meteorological factors and reactivity, was analysed: while sex was distributed quite uniformly around the year, patients of age 40 and above were seen somewhat more often in summer than in winter. The strongest seasonal variation was noted with atopy (history of previous or current atopic dermatitis), with a proportion below 17% from May through to August, and above 18% from September to April, with more than 20% in December and January.

Results of logistic regression analyses, including effect estimates of all exposure combinations with sufficient sample size, are presented in Table 3. As a potential confounder, a positive history of atopic dermatitis was always included in the model, while the dichotomized age variable and sex were not included in final models, because (i) they were not associated with significantly de- or increased risk, (ii) they did not alter the other risk estimates (as a hint to possible confounding) and (iii) did not improve model fit. Exposure time to patches is either 24 h (in 10 centres seeing 44.3% of patients) or 48 h in the remaining centres and patients, respectively. It is an interesting additional explanatory factor and was thus additionally considered in logistic regression analysis. The goodness of fit was good to excellent for most models (see footnotes for Tables 3a–c).

Weak-positive reactions to formaldehyde occurred almost 2× as often during cold and dry meteorological conditions, than during warm and humid weather (Table 3a). Marginal estimates – i.e., unadjusted for the effect of the other meteorological variable – displayed a dose-response gradient for absolute humidity and for temperature. If

Table 2. Distribution of exposure classes among 46,887 patients tested in the years 1992 to 1997

Temp. (°C)	Absolute humidity (mg/l)				Row sums
	up to 6.5	>6.5 to 9.3	>9.3 to 13.0	>13.0	
up to 4.1	9805	1733	0	0	11,538
>4.1 to 9.5	1671	7854	2288	0	11,813
>9.5 to 15.4	85 ^{a)}	1550	8467	1685	11,787
>15.4	0	88 ^{a)}	1572	10,089	11,749
column sums	11,561	11,225	12,327	11,774	46,887

^{a)} Disregarded in further analyses due to very small cell count.

Table 3a. Relative risk estimates for + reaction to formaldehyde (1% in water) associated with different exposure classes, controlled for atopic dermatitis and patch test exposure time; outcome positive in 669 out of 41,629 patients (1.61%); 268 patients with ++ and +++ reactions disregarded

Temp. (°C)	Absolute humidity (mg/l)				Marginal estimates: temperature ^{a)}
	up to 6.5	>6.5 to 9.3	>9.3 to 13.0	>13.0	
up to 4.1	1.91 (1.50–2.44)	1.69 (1.10–2.53)	–	–	1.86 (1.49–2.34)
>4.1 to 9.5	1.64 (1.05–2.48)	1.42 (1.08–1.86)	1.51 (1.00–2.20)	–	1.46 (1.15–1.85)
>9.5 to 15.4	–	1.91 (1.23–2.88)	1.40 (1.07–1.83)	1.22 (0.74–1.91)	1.43 (1.13–1.82)
>15.4	–	–	0.91 (0.50–1.54)	1.00 (ref.)	

marginal estimates^{b)}:

abs. humidity 1.81 (1.45–2.28) 1.49 (1.18–1.89) 1.31 (1.04–1.67) 1.00 (ref.)

Goodness-of-fit statistic: $p=0.80^a$, $p=0.95^b$, $p=0.87$ (combined exposure variable).

Table 3b. Odds ratios for ++ or +++ reaction to formaldehyde, controlled for atopic dermatitis and patch test exposure time; outcome positive in 268 out of 41,629 patients (0.64%)

Temp. (°C)	Absolute humidity (mg/l)				Marginal estimates: temperature ^{a)}
	up to 6.5	>6.5 to 9.3	>9.3 to 13.0	>13.0	
up to 4.1	1.16 (0.81–1.68)	0.42 (0.13–1.02)	–	–	1.08 (0.76–1.52)
>4.1 to 9.5	1.72 (0.95–2.95)	1.25 (0.85–1.82)	0.95 (0.48–1.71)	–	1.28 (0.92–1.79)
>9.5 to 15.4	–	1.09 (0.50–2.10)	0.80 (0.52–1.21)	0.84 (0.37–1.66)	0.88 (0.61–1.27)
>15.4	–	–	0.94 (0.41–1.87)	1.00 (ref.)	

marginal estimates^{b)}:

abs. humidity 1.31 (0.94–1.82) 1.12 (0.79–1.58) 0.87 (0.61–1.24) 1.00 (ref.)

Goodness-of-fit statistic: $p=0.63^a$, $p=0.23^b$, $p=0.94$ (combined exposure variable).

Table 3c. Odds ratios for ? (questionable) or IR (irritant) reaction to formaldehyde, controlled for atopic dermatitis and patch test exposure time; outcome positive in 791 of 41,629 patients (1.91%)

Temp. (°C)	Absolute humidity (mg/l)				Marginal estimates: temperature ^{a)}
	up to 6.5	>6.5 to 9.3	>9.3 to 13.0	>13.0	
up to 4.1	1.77 (1.42–2.21)	1.04 (0.65–1.60)	–	–	1.56 (1.27–1.92)
>4.1 to 9.5	1.65 (1.11–2.29)	1.38 (1.06–1.72)	1.16 (0.78–1.67)	–	1.29 (1.04–1.59)
>9.5 to 15.4	–	0.85 (0.49–1.39)	1.38 (1.09–1.76)	1.28 (0.84–1.89)	1.24 (1.00–1.54)
>15.4	–	–	1.29 (0.82–1.89)	1.00 (ref.)	

marginal estimates^{b)}:

abs. humidity 1.62 (1.33–1.99) 1.17 (0.94–1.45) 1.25 (1.02–1.54) 1.00 (ref.)

Goodness-of-fit statistic: $p=0.90^a$, $p=0.94^b$, $p=0.96$ (combined exposure variable).

stronger allergic reactions (papulo-vesicular) were considered, the 2 meteorological factors were not associated with a significantly increased risk (Table 3b). However, if questionable (erythematous) or irritant reactions are modelled as outcome, dry/cold ambient air is a significant risk factor again. Irritant or questionable patch test reaction to formaldehyde was the only outcome of those assessed for which atopic dermatitis was a significant risk

factor (OR 1.31, 95% CI: 1.11–1.55). Additionally, 48-h patch test exposure was a significant independent risk factor for this outcome (OR 2.59, 95% CI: 2.19–3.06).

The association between weak-positive reactivity to lanolin alcohol (in 890 of 40,931 patients, i.e., 2.17%) and the meteorological variables was not quite as marked as for formaldehyde. Patch test exposure time of 48 h was a significant risk factor

for this type of reaction (OR 1.91, 95% CI: 1.65–2.22). Epoxy resin (+ reactions in 247 of 41,601 patients, i.e., 0.60%) showed random variation of reactivity, with marginal estimates around 1, and without a consistent pattern for the combined exposure variable. MCI/MI, which had been chosen as the only other allergen of the standard series tested in water for comparison with formaldehyde, again displayed a subtle association between weak positive reactivity and temperature and absolute humidity, respectively, with a significantly elevated risk for the lowest combined category (OR 1.35, 95% CI: 1.07–1.70). The goodness of fit statistic indicated very good model fit when using the combined exposure variable (p -values between 0.87 and 0.99).

Discussion

Patch testing is more than a century old, and there still is no other diagnostic technique that could replace it for routine diagnosis of delayed type hypersensitivity, despite some drawbacks. One of the drawbacks is only moderate reproducibility of positive results for some allergens, while most other allergens appear to cause well-reproducible reactions according to recent studies, e.g., (18), in contrast to a previous study with quite devastating results (19). Several individual factors (such as atopy, excited skin, i.e., a state of non-specifically increased skin reactivity) as well as exogenous factors (exposure to UV light, [topical] drugs, and season) are suspected, and partly proven, to influence patch test results (20, pp. 239–268). Some of the variation, especially in weak positive test results (erythema, infiltrate, possibly even crescendo pattern), could also be attributed to the fact that some allergens are at the same time marginal irritants and can cause test reactions which mimic allergic reactions. It is well known that the propensity of the skin to develop subclinical or clinically visible irritation depends on both individual and environmental factors, individual variation possibly being more pronounced (10). Thus, *some* of the seasonal variation of patch test results previously observed may be due to the fact that the proportion of false-positive irritant reactions increases during winter.

The present study explores this issue by 1st assessing variation of patch test reactivity in the months of the year and then by linking actual exposure data (on temperature and absolute humidity) with individual patch test results. Relative humidity was omitted from the panel of potential risk factors, as previous work has shown no significant association with skin irritation (11). While the commonly used (2–4, 7, 8) representation of

exposure to varying weather conditions by month of the year does give some hint as to the influence of the respective meteorological conditions, variation of weather conditions within these gross time categories is substantial, as shown in Table 1, at least in the temperate climate prevailing in central Europe. Thus, it is much preferable to use actual exposure data instead of a gross approximation.

This study is, to our knowledge, the 1st study to address the influence of temperature and humidity on patch test reactivity, based both on a large data pool of patients and standardized meteorological measurements with sufficient temporal resolution. The use of day mean values of the 1st day of examination instead of, e.g., mean values of the whole week preceding the patch test seems appropriate, as (i) reactions to cold and dryness seem to occur fairly rapidly (21), (ii) day-to-day variation of these variables is usually not extreme and would at any rate not often result in classification into a different category and (iii) previous preliminary analyses of the Prevention of Occupational Skin Disease in Hairdressers (POSH) study material (11) did not reveal differences between these 2 alternatives with regard to predicting irritation risk (unpublished results).

However, despite this achievement, we are fully aware of the possibility of insufficient *spatial* resolution limiting the sensitivity of our analysis. Weather conditions are not completely homogeneous within Germany, even though it is a relatively small country. Additionally, the extent of outdoor activities and exposure to indoor air conditioning (which is, however, uncommon in German private households, but sometimes encountered in the work environment) will modify climatic conditions on the individual level. As a consequence, nondifferential exposure misclassification will have biased risk estimates downward (attenuation bias). The fact that, despite this, a clear increase in risk is seen for formaldehyde gives additional weight to the assumption of a true relationship.

Compared with the general problem of random error in ascertaining exposure on the ecological (environmental), but also on the individual level, a more serious threat to the validity of epidemiological results would be *differential* exposure misclassification, i.e., classification errors that are not independent of the outcome status (patch test reaction). This can be excluded in the present study, because meteorological data had been collected in retrospect and were obtained from an institution independent of any of the patch test centres.

A mirror image of differential exposure misclassification would be differential misclassification of the outcome, if the observers' judgements of test reactions were biased by some notion on the influ-

ence of cold, dry weather on patch test reactions to formaldehyde in particular (but not to other allergens). However, this can largely be ruled out, as previous reports have not given any indication on this particular relationship, and also the participation of a large number of observers would considerably dilute the influence of 1 or more observers with such an unlikely notion, anyway. In contrast, the association between atopy and questionable or irritant reactivity to formaldehyde may not be unbiased, albeit plausible: observers may have been more inclined to classify a reaction as irritant if they knew the patient was atopic, whereas in other equivocal cases they could have classified this reaction as weak positive, for instance. Whether a similar bias has influenced our results concerning a significant positive association between 48-h patch test exposure time and questionable/irritant reactions to formaldehyde and weak-positive reactions to lanolin alcohol, respectively, can only be a matter of speculation. The interesting question as to whether 48-h exposure to lanolin alcohol yields more true weak-positive reactions (greater sensitivity) or more false weak positive reactions (reduced specificity), compared to 24-h exposure, cannot be addressed in this study.

There is no evidence for an influence of cold, dry ambient air in a range actually observed in central Europe on patch test reactivity to epoxy resin – probably because all at least erythematous, infiltrated reactions are true allergic reactions and thus not influenced by seasonal fluctuations in skin irritability, compared to false-positive (truly irritant) reactions observed with a few other allergens, namely formaldehyde. This observation seems to be contradictory to experimental results with TNCB in mice (5); however, Hosoi et al. did not address susceptibility (i.e., the proportion of animals sensitized under varying exposure conditions) directly, but measured the *strength* of the allergic reaction. Also, housing conditions with a very low ambient humidity rarely encountered in our temperate winters were used (10% relative humidity at 21 to 25°C used in the study equals 2.5 to 3.2 mg/l absolute humidity). These more extreme conditions may have compromised epidermal barrier function even further and thus have led to an exaggerated reactivity to TNCB during sensitization and elicitation – in this animal species.

The random variation of reactivity to epoxy resin across seasons also adds further evidence to the notion that UV-induced immunosuppression or barrier enhancement found in a central European summer do not substantially alter patch test reactivity (4, 6), as far as this can be assessed on an epidemiological, as opposed to an experimen-

tal, level, whereas hotter (e.g., subtropical) climates may have some influence (3, 7, 8).

Concerning the other allergens, evidence from this study is rather weak that climatic conditions exert a major effect on reactivity to lanolin alcohol and MCI/MI. However, there is most likely a true relationship between dry, cold ambient air and patch test reactivity – namely, infiltrated, erythematous reactions without vesicles, to be interpreted as irritant reactions – to formaldehyde. This view is based on the following 2 observations: (i) the increase in risk for + patch test reactions parallels the increase in risk for frank irritant or questionable reactions, and (ii) unequivocally positive (in the sense of allergic) reactions, i.e. papulo-vesicular reactions, do not display this seasonal pattern. The occurrence of presumably false-positive + reactions, increasing in winter, could be an explanation for the often observed poor reproducibility of positive patch test reactions to formaldehyde (18), together with other factors that may affect patch test reproducibility.

Conclusion

The present study demonstrates that formaldehyde, as a prototype of an allergen that is at the same time a marginal irritant, exhibits marked variation of the proportions of irritant, questionable and weak-positive patch test reactions, which parallels seasonally varying temperature and absolute air humidity. As a consequence, test results for formaldehyde should be interpreted with caution during winter, and patch testing should possibly be repeated in summer in case of questionable or weak-positive reactions, or validated by serial dilution testing. We regard this unprecedented study as a 1st step in the systematic analysis of the influence of environmental factors on patch test reactivity, with the ultimate aim of further improving patch test standardization.

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