

The impact of meteorological conditions on patch test results with 12 standard series allergens (fragrances, biocides, topical ingredients)

W. Uter, J. Hegewald, B. Kränke,* A. Schnuch,† O. Gefeller and A. Pfahlberg

Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, 91054 Erlangen, Germany

*Department of Dermatology, Medical University of Graz, Graz, Austria

†Information Network of Departments of Dermatology (IVDK) at the Georg August University, Göttingen, Germany

Summary

Correspondence

Wolfgang Uter.

E-mail: wolfgang.uter@rzmail.uni-erlangen.de

Accepted for publication

17 November 2007

Key words

allergic contact dermatitis, epidemiology, patch testing, weather

Conflicts of interest

None declared.

Background Fluctuating irritability of the skin induced by low ambient temperature and humidity may compromise the reproducibility of patch testing.

Objectives To assess the impact of temperature and absolute humidity at the time of patch testing on the occurrence of irritant or doubtful (IR/?), weak positive (+) and (strong) positive (++) reactions, respectively, among 12 allergens included in the German Standard Series.

Methods Analysis of clinical data collected in the surveillance network IVDK (<http://www.ivdk.org>) between January 1993 and December 2001 (n = 73 691 patients) combined with meteorological data obtained by the national services in Germany and Austria. Multinomial logistic regression analysis was used to estimate the risk associated with temperature, absolute humidity and vapour pressure, respectively, adjusted for sex, age, atopic dermatitis and duration of patch test application.

Results For low temperature and humidity, a relevant increase of IR/? reaction frequency was observed in the cases of paraben mix and (chloro-) methylisothiazolinone. Both IR/? and + reactions were significantly increased with respect to the allergens fragrance mix, oil of turpentine, methyldibromo glutaronitrile + phenoxyethanol and particularly formaldehyde, while ++/+++ reactions were hardly affected by weather conditions.

Conclusions The observed increase of IR/? reactions may be due to epidermal barrier function impairment. The impact of dry/cold weather on + reactions in terms of possibly false-positive reactions is restricted to few allergens. In the case of + reactions of unknown relevance, a re-test under warm conditions or verification tests such as the repeated open application test or the provocative use test may be recommendable.

Since its invention by Jadasson, the patch test (PT) has been refined and standardized regarding many methodological aspects.¹ However, the PT is still a diagnostic tool with limited validity and reliability. Among the factors potentially compromising the diagnostic performance of the PT, the impact of season has been the subject of several studies – under the hypothesis either that increased ultraviolet exposure during summer could reduce reactivity, or that winter conditions might diminish epidermal barrier function, leading to overall increased irritability and PT reactivity. The latter hypothesis, in particular, is supported both by clinical research and bioengineering methods,^{2–4} and by experimental studies.⁵

In accordance with this background, seasonal or monthly fluctuation of PT results has been identified by several (but not all) previous studies, e.g. that of Kränke and Aberer.⁶ One of the most detailed studies, moreover, identified particular seasonal patterns for different allergens.⁷ However, weather conditions may vary considerably within a month and particularly within a season. Hence, the previously used markers are very imprecise, and it is highly desirable to use actual exposure data instead. In a pilot study, the feasibility of combining meteorological data prevailing at the day of the PT with PT results has been demonstrated.⁸ The present study expanded this approach (i) by including a range of contact allergens

potentially occurring in cosmetics, toiletries and topical medications and (ii) by exploiting the availability of standardized meteorological data in an adequate spatial and temporal resolution. The objective of the present study was to examine the impact of meteorological conditions on different grades of PT reactions, addressing factors potentially contributing to non-reproducibility of the PT.

Materials and methods

Clinical data

Since 1989, an expanding network of departments of dermatology in Germany, Austria and Switzerland has cooperated as the 'Information Network of Departments of Dermatology' (IVDK, <http://www.ivdk.org>) in the field of clinical research on contact sensitization (CS). Aims and operational procedures have been described in detail.⁹ In brief, the PT results, along with a standardized set of demographic and clinical data of all patients with suspected allergic contact dermatitis attending one of the participating centres, are collected and pooled in the Göttingen data centre in an anonymous format. The PT procedure follows current international guidelines¹ further amended by the German Contact Dermatitis Research Group,¹⁰ of which all IVDK partners are members. For the present retrospective analysis, standard series results from patients seen by one of the 28 Austrian and German IVDK departments of dermatology within a 30-km radius around a weather station maintained by the German Meteorological Service (Deutscher Wetterdienst, DWD), Offenbach, or the Austrian Central Institute for Meteorology and Geodynamics (Zentralanstalt für Meteorologie und Geodynamik, ZAMG), Vienna in the years 1993–2001 were examined.

The allergens of the standard series shown in Table 1 have been considered in this analysis focusing on cosmetic and topical drug allergens.

Meteorological data

Meteorological data were obtained from the DWD and the ZAMG, respectively. Both institutions maintain weather stations located throughout Germany and Austria. IVDK centres were paired with the closest available weather station. Occasionally, in larger cities like Munich or Berlin, multiple local IVDK centres were assigned to one weather station. The DWD calculated daily values of temperature (T) and relative humidity (RH) by averaging measurements at the weather station taken at three set times until March 2001, and from 24 hourly measurements thereafter. According to previous research, absolute humidity (AH), and not RH, is preferable for the analysis in terms of an association with irritant skin damage.^{11,12} Another past study has shown that vapour pressure (VP) also provides an appropriate representation of humidity.⁴ Therefore, AH and VP values were derived from T and RH values for the analysis with published formulae.^{13,14}

The 3 days preceding the PT, including the 2 days prior to PT application and the day of application, were regarded as most relevant. Therefore, 3-day moving averages of T, AH and VP were calculated and matched appropriately to the dates of PT application, similar to the study by Löffler and Happle.⁴ T, AH and VP were then (i) categorized according to the quartiles of the corresponding distribution and (ii) combined to a new variable with – theoretically – 16 levels, to address possible interaction between the effects of T and AH and T and VP, respectively. As some combinations are not possible for

Table 1 Twelve allergens of the standard series and the frequency of different grades of patch test reactions to these

Allergen	Test conc. (%)	No. tested	No. of reactions			Percentage + to +++
			IR/?	+	++/+++	
A Fragrance mix	8	61 085	2811	4878	2395	11·91
A Myroxylon pereirae resin (balsam of Peru)	25	61 128	2286	3964	1491	8·92
A Oil of turpentine	10	58 051	750	967	273	2·14
B Methyl dibromo glutaronitrile + phenoxyethanol 1 : 4 (e.g. Euxyl™ K 400)	1	29 428	580	904	344	4·24
B Paraben mix (a mixture of butyl-, ethyl-, methyl- and propylparaben in equal parts)	16	49 771	1040	581	131	1·43
B Formaldehyde ^a	1	61 217	2811	890	285	1·92
B Chloromethylisothiazolinone/methylisothiazolinone (e.g. Kathon™ CG) ^a	0·01	59 999	529	993	464	2·43
C Neomycin sulphate	20	61 178	592	1159	498	2·71
C Benzocaine	5	61 214	440	587	381	1·58
C Propolis	10	36 503	473	605	274	2·41
D Lanolin alcohols	30	61 216	1119	1856	591	4·00
D Cetostearyl alcohol	20	57 228	540	511	176	1·20

All allergens in petrolatum except where otherwise indicated: ^awater. A, fragrance allergens *sensu lato*; B, biocides; C, topical agents; D, emulsifiers; IR/?, irritant or doubtful; +, weak positive; ++/+++, (strong) positive reactions.

physical reasons, and hot and arid conditions are very rare in our temperate climate, only 10 of the 16 combinations proved relevant for the analysis.

Multifactorial analysis

As simple bivariate analyses of the association between meteorological conditions and the pattern of PT reactions might be confounded, adjusted multifactorial analyses were additionally performed. The following factors were considered as potential confounders in all models: (i) atopic eczema (past or current vs. none), (ii) the duration of application (24 vs. 48 h), (iii) age (≤ 40 vs. > 40 years, according to IVDK standards¹⁵) and (iv) sex. Multinomial logistic regression was used to examine the relationship between T, AH and VP, respectively, and the PT results. PT readings at the third day served as the dependent variable, where irritant or doubtful (IR/?), weak positive (+) and (strong) positive (++)/+++ reaction readings were compared with negative reactions (reference group), respectively. T, AH and VP were examined in separate models (marginally) in the four categories mentioned. Additionally, the 10 relevant categories of T combined with AH, and T combined with VP, respectively, were examined in a combined exposure variable (see above) in two separate models for each allergen. To examine a possible interaction effect between T and AH (VP), each significant risk estimate of a combination variable of T and AH (VP) was compared with the two respective marginal estimates of T and AH (VP), respectively. Large increases (or decreases in the case of lowered risk estimates) of the risk estimates of the combined variable over the individual factors would indicate that the factors interact (additively or multiplicatively) to amplify the effects of exposure.

Results

A total of 73 691 patients was patch tested in the study period in the centres included. The proportion of females was 63.1%; 40.7% were aged 40 years or less. Past or current atopic eczema was noted in 17.5%. The PT was applied for 24 h in 38% and for 48 h in the remainder. The frequency of PT reactions is shown in Table 1. Evidently, the fragrance mix is the leading allergen, while positive reactions to cetostearyl alcohol, benzocaine, formaldehyde and the paraben mix were relatively rare, ranging between 1% and 2%. The mixture of methylidibromo glutaronitrile and phenoxyethanol 1 : 4 (MDBGN + PE) at a 1% test concentration was included in the German Standard Series only in January 1997, and propolis in June 1999, explaining the lower number of patients tested with these allergens. During the study period, the seasonal variation of meteorological variables typical for a temperate climate was observed. In the northern (southern) part of the study region, the median summer (April–September) T was 15.0 °C (15.9 °C) and the median winter (October–March) T was 4.6 °C (4.5 °C). Median RH was 73% (71%) in summer and 83% (83%) in

winter, with overall variability largely similar between North and South.

As a first step of assessing the relationship between meteorological factors and PT reactions, a bivariate analysis of the proportion of IR/?, + and ++/+++ reactions in the four classes of AH is presented (Fig. 1). Corresponding analyses with T and VP, respectively, yielded very similar results and are thus not presented here. The analyses show that in the cases of some allergens (e.g. fragrance mix, formaldehyde, paraben mix), reactions, particularly of the IR/? type, display a distinct association with AH, while other allergens such as lanolin alcohols, propolis and benzocaine were not associated with the weather conditions.

The 12 allergens were analysed in five separate multinomial logistic regression analyses each as described above; results in full detail are presented in Hegewald.¹⁶ In this paper, the presentation is restricted to marginal model results for AH, as VP and T, respectively, yielded very similar results. Table 2 shows the results of the marginal model in terms of risk estimates for the most extreme (dry) exposure category. No significant effect of weather conditions on any type of PT reaction was noted for benzocaine, propolis, lanolin alcohols and cetostearyl alcohol. Neomycin sulphate exhibited a peculiar pattern in that risk was reduced in drier/colder weather, compared with more humid/warmer conditions. In all other seven allergens, a more or less marked increase mainly of IR/?, less often of + reactions, was found. Only in the case of the fragrance mix were ++/+++ reactions also significantly over-represented in the two coldest and driest categories, respectively. The analysis of interaction did not yield evidence of a general, consistent interaction effect between T and AH (VP).

Discussion

For the first time, a detailed analysis of the pattern of association between meteorological conditions, namely, T, AH and VP, and different grades of PT reactions to a set of important allergens has been performed. Apparently, PT results are relatively stable across the weather conditions of the central European climate for most allergens, at least in terms of morphologically positive (presumably allergic) results in the range of + to +++ reactions. In this context, a very limited increase in risk of up to 20% (odds ratio ≤ 1.20) should probably be regarded as nonrelevant, even if significant, as with fragrance mix. Focusing on significant and relevant associations gives reassurance that PT results can be regarded as fairly reliable in this respect.

In contrast, IR/? reactions are observed more frequently under dry and cold conditions among several allergens. Apparently, an impaired epidermal barrier function under these ambient conditions^{2–5} renders the skin more vulnerable to the (very) slight irritating effect many allergens may exert under PT conditions. Formaldehyde exhibits the strongest association, and chloromethylisothiazolinone/methylisothiazolinone (MCI/MI) also shows a marked increase in risk of IR/? reactions in dry and/or cold conditions. This could indicate that

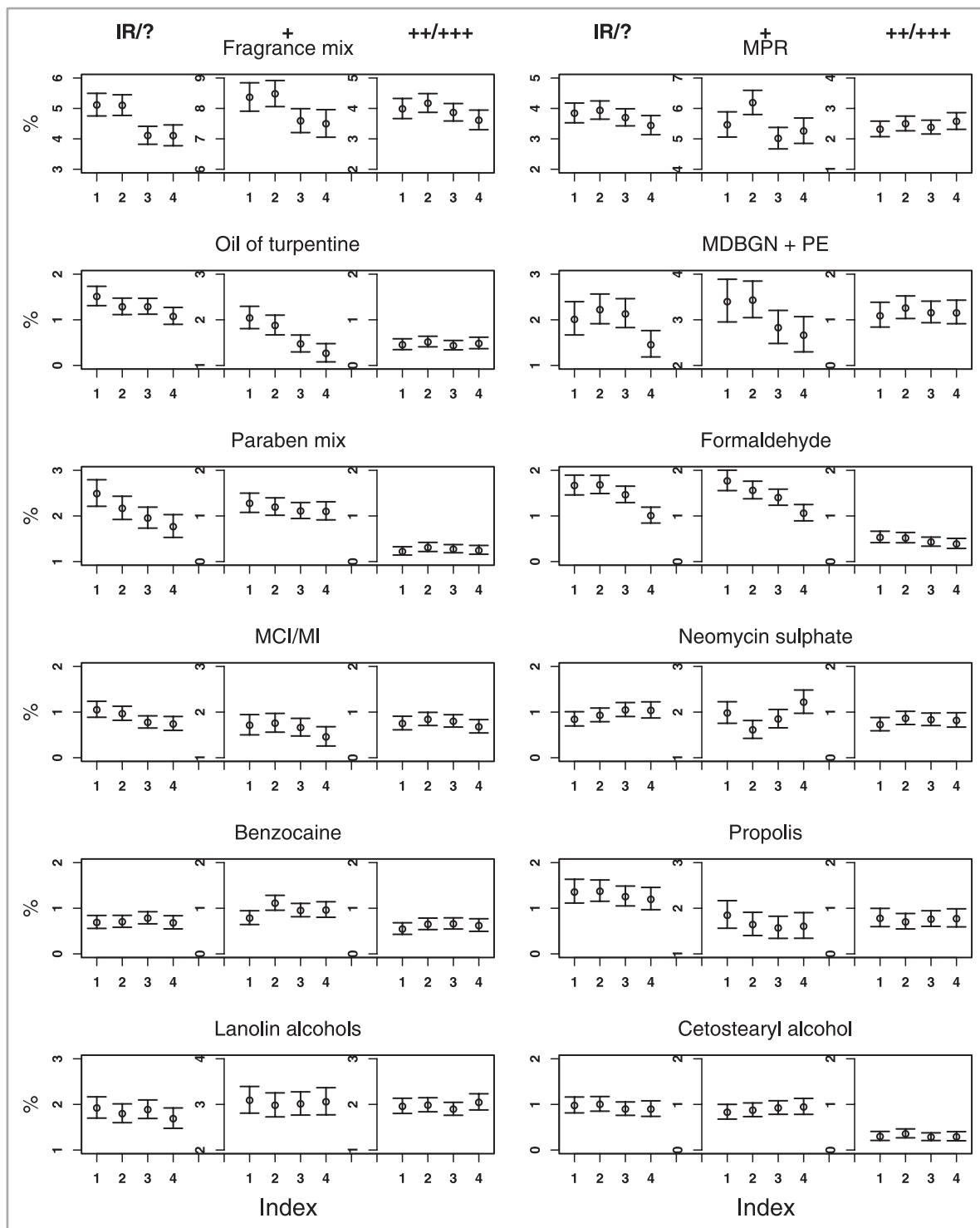


Fig 1. Distribution of irritant or doubtful (IR/?), weak positive (+) and (strong) positive (++) reactions to 12 allergens with 95% confidence intervals in the classes of absolute humidity: 1, $\leq 5 \text{ g m}^{-3}$; 2, > 5 to 7 g m^{-3} ; 3, > 7 to 10 g m^{-3} ; 4, $> 10 \text{ g m}^{-3}$. MCI/MI, chloromethylisothiazolinone/methylisothiazolinone; MPR, *Myroxylon pereirae* resin; MDBGN + PE, methyldibromo glutaronitrile + phenoxyethanol.

water-based allergen preparations are more seasonally dependent than petrolatum-based test materials or, conversely, that petrolatum as PT vehicle partly counteracts¹⁷ the impairment of the epidermal barrier function caused by dry/cold ambient conditions.

Interestingly, lanolin alcohols, well known to cause nonspecific, i.e. irritant, reactions, did not exhibit weather-dependent variation of any of the reaction classes (IR/?, +, ++/+++). Presumably, the mechanism of irritation by lanolin alcohol and related substances is (i) different from that of other

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of patch test reactions (vs. no reaction) from marginal models with the driest of four categories of 3-day moving averages of absolute humidity ($\leq 5 \text{ g m}^{-3}$) vs. the most humid ($> 10 \text{ g m}^{-3}$)

	IR/?		+		++/+++	
	OR	95% CI	OR	95% CI	OR	95% CI
Fragrance mix	1.31	1.17–1.47	1.15	1.05–1.25	1.15	1.01–1.30
Myroxylon pereirae resin	1.17	1.03–1.34	1.07	0.97–1.18	0.94	0.80–1.10
Oil of turpentine	1.42	1.14–1.77	1.63	1.34–1.99	0.96	0.67–1.37
MDBGN + PE	1.43	1.09–1.86	1.29	1.05–1.58	0.96	0.69–1.34
Paraben mix	1.47	1.22–1.77	1.16	0.91–1.48	0.93	0.54–1.61
Formaldehyde	1.69	1.36–2.09	1.69	1.37–2.08	1.37	0.96–1.96
MCI/MI	1.45	1.12–1.88	1.20	0.98–1.45	1.11	0.83–1.47
Neomycin sulphate	0.83	0.65–1.07	0.92	0.77–1.08	0.92	0.70–1.22
Benzocaine	1.05	0.79–1.40	0.93	0.64–1.08	0.91	0.66–1.24
Propolis	1.17	0.88–1.54	1.18	0.93–1.50	1.05	0.73–1.49
Lanolin alcohols	1.17	0.98–1.40	1.04	0.91–1.20	0.96	0.76–1.22
Cetostearyl alcohol	1.15	0.89–1.48	0.91	0.70–1.19	1.05	0.67–1.67

Models were adjusted for sex, atopic dermatitis, duration of application and age. Significant risk estimates are shown in bold.

MDBGN + PE, methyldibromo glutaronitrile + phenoxyethanol; MCI/MI, chloromethylisothiazolinone/methylisothiazolinone; IR/?, irritant or doubtful; +, weak positive; ++/+++, (strong) positive reactions.

allergens or model irritants and (ii) not subject to meteorological influences.

Weather-dependent variation of IR/? reactions thus appears plausible, but is not a grave concern. In contrast, weather-dependent variation of + reactions must be regarded as critical for the reliability of the PT, as these are normally interpreted as indicative of CS and thus have grave individual implications. Misclassification must indeed be suspected, because it is not conceivable that true weather-dependent variation of the individual CS elicitation threshold should exist, and just regarding a few allergens. In this context, the slight, but very consistent, elevation of the risk not only of +, but also of ++/+++ PT reactions to the fragrance mix under dry/cold conditions could be due to the additive sorbitan sesquiolate. This emulsifying agent may enhance penetration, and subsequent reactions of any degree, especially under atmospheric conditions inducing subtle barrier impairment.

The fact that the increase of + reactions largely parallels the increase of IR/? reactions strongly points to the possibility that at least some of the + reactions are also irritant (false-positive). However, without employing verification tests such as the repeated open application test (ROAT) or the provocative use test (PUT)¹ it is not possible to decide whether false-positive reactions increase during dry/cold conditions, or whether false-negative reactions occur more frequently under warm/humid conditions.

Regarding the meteorological data, some exposure misclassification due to geographical mismatch may have happened. However, its effect is probably not severe, considering that variation over time is much more marked than spatial variation. While most people spend a large part of their daily life indoors, and not outdoors, especially in winter, previous studies have shown that the weather does affect skin regions normally covered by clothes, such as the upper arm.² Moreover,

winter outdoor air, which is typically cold, and has a moderate to high RH but a low AH, will impact the indoor environment of people, lessening the indoor AH (and, in fact, the indoor RH). Indeed, a fairly strong correlation between outdoor and indoor AH has been found, the latter being inversely correlated to the air exchange rate of the building.¹⁸ As exposure misclassification is most likely nondifferential, i.e. not related to the outcome, we would expect it to bias all risk estimates towards the null (unity), but not to distort the relative effect of the weather conditions on the different PT outcome classes.

Comparing marginal risk estimates of T, AH and VP, only minute differences were found. This is not surprising, given the strong correlation between the factors. Hence, it does not really matter which factor is considered, and future analyses might as well concentrate on the observation of one factor – keeping in mind that this will also more or less represent the other exposure factors.

In conclusion, for most of the allergens analysed here, PT performance is relatively stable across temperate central European weather conditions. However, some allergens, including MDBGN + PE, MCI/MI, formaldehyde and oil of turpentine, possibly lead to false-positive reactions under cold/dry conditions and should thus probably be re-tested under warm conditions. Alternatively, verification tests such as the ROAT or PUT should be performed, particularly in cases of + reactions of unknown relevance. The increase of IR/? reactions to several allergens is in line with other evidence on the impairment of epidermal barrier function under winter weather conditions. Hence, when patch testing allergens with largely unknown inherent irritating potential, and especially patients' own materials such as (adequately diluted) shampoos, cutting fluids, etc., a possibly lowered threshold for irritation must be considered when interpreting the PT reactions.

Acknowledgments

The study was funded by the Adolf-Rohrschneider foundation, University of Erlangen-Nürnberg, and the Society for the Advancement of Biostatistics and Epidemiology Erlangen-Nürnberg. The following members of the Information Network of Departments of Dermatology (IVDK) contributed data to this analysis (in alphabetical order): Aachen (H. Dickel, S. Erdmann), Berlin Charité (B. Laubstein, T. Zuberbier), Berlin UKRV (J. Grabbe, T. Zuberbier), Berlin B.-Frank. (B. Tebbe, R. Treudler), Dortmund (P.J. Frosch, B. Pilz, C. Pirker, R. Herbst), Dresden (G. Richter, R. Aschoff), Erlangen (K.-P. Peters, T.L. Diepgen, M. Fartasch, M. Hertl, V. Mahler), Essen (H.-M. Ockenfels, U. Hillen), Göttingen (T. Fuchs, J. Geier), Graz (W. Aberer, B. Kränke), Halle (G. Gaber, D. Lübke), Hamburg (M. Kiehn, D. Vieluf, R. Weißbecher), Heidelberg (A. Schulze-Dirks, M. Hartmann, U. Jappe), Homburg/Saar (F.A. Bahmer, P. Koch), Jena (M. Gebhardt, A. Bauer, W. Wigger-Alberti, M. Kaatz, S. Schliemann-Willers), Kiel (J. Brasch), Lübeck (K.P. Wilhelm, J. Kreusch, J. Grabbe), Mainz (D. Becker), Marburg (I. Effendy, H. Löffler), München LMU (F. Enders, F. Rueff, B. Przybilla), München TU (J. Rakoski), München-Schwabing (M. Agathos), Nürnberg (I. Müller), Osnabrück [W. Uter, S.M. John, H.J. Schwanitz (deceased), N. Schürer], Tübingen (G. Lischka), Ulm [H. Gall (deceased), P. Gottlöber, G. Staib], Wuppertal (O. Mainusch, J. Raguz).

References

- 1 Wahlberg JE, Lindberg M. Patch testing. In: *Contact Dermatitis* (Frosch PJ, Menné T, Lepoittevin JP, eds). Berlin: Springer-Verlag, 2006; 365–90.
- 2 Agner T, Serup J. Seasonal variation of skin resistance to irritants. *Br J Dermatol* 1989; **121**:323–8.
- 3 John SM, Uter W. Meteorological influence on NaOH irritation varies with body site. *Arch Dermatol Res* 2005; **296**:320–6.
- 4 Löffler H, Happle R. Influence of climatic conditions on the irritant patch test with sodium lauryl sulphate. *Acta Derm Venereol* (Stockh) 2003; **83**:338–41.
- 5 Hosoi J, Hariya T, Denda M *et al.* Regulation of the cutaneous allergic reaction by humidity. *Contact Dermatitis* 2000; **42**:81–4.
- 6 Kränke B, Aberer W. Seasonal influence on patch test results in Central Europe. *Contact Dermatitis* 1996; **34**:215–16.
- 7 Hjorth N. Seasonal variation in contact dermatitis. *Acta Dermatol Venereol* (Stockh) 1967; **47**:409–18.
- 8 Uter W, Geier J, Land M *et al.* Another look at seasonal variation in patch test results. A multifactorial analysis of surveillance data of the IVDK. Information Network of Departments of Dermatology. *Contact Dermatitis* 2001; **44**:146–52.
- 9 Uter W, Schnuch A, Geier J *et al.* The epidemiology of contact dermatitis. The Information Network of Departments of Dermatology (IVDK) in Germany. *Eur J Dermatol* 1998; **8**:36–40.
- 10 Brasch J, Becker D, Aberer W *et al.* Contact dermatitis. *J Dtsch Dermatol Ges* 2007; **5**:943–51.
- 11 Cooper MD, Jardine H, Ferguson J. Seasonal influence on the occurrence of dry flaking facial skin. In: *The Environmental Threat to the Skin* (Marks R, Plewig G, eds). London: M. Dunitz, 1992; 159–64.
- 12 Uter W, Gefeller O, Schwanitz HJ. An epidemiological study on the influence of season (cold and dry air) on the occurrence of irritant skin changes of the hands. *Br J Dermatol* 1998; **138**:266–72.
- 13 Schubert A. *Aspirations-Psychrometertafel des Deutschen Wetterdienstes*. Braunschweig: F. Vieweg, 1976.
- 14 Zmarsly E, Kuttler W, Pethe H. *Meteorologisch-klimatologisches Grundwissen*, 2nd edn. Stuttgart: Eugen Ulmer, 2002.
- 15 Schnuch A. PAFS: population-adjusted frequency of sensitization. (I). Influence of sex and age. *Contact Dermatitis* 1996; **34**:377–82.
- 16 Hegewald J. *Meteorological Influences on Epicutaneous Contact Allergy Testing*. Erlangen: University of Erlangen-Nürnberg (doctoral thesis), 2006.
- 17 Lodén M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *Am J Clin Dermatol* 2003; **4**:771–88.
- 18 Emenius G, Svartengren M, Korsgaard J *et al.* Building characteristics, indoor air quality and recurrent wheezing in very young children (BAMSE). *Indoor Air* 2004; **14**:34–42.