

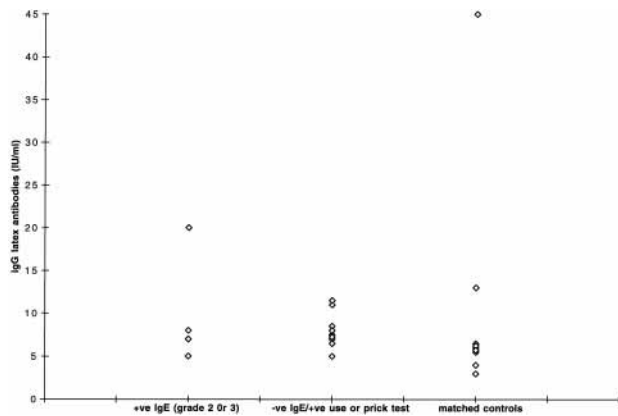


Fig. 1. Results of IgE and IgG latex RAST on latex-allergic, age-sex matched non-allergic, low IgE RAST-scoring individuals.

Patients and Methods

Following informed consent, sera for an IgG latex RAST was obtained from 4 out of 5 IgE RAST-negative patients who had strong histories of immediate-type hypersensitivity to latex products and were either latex glove 'use' or prick-test positive. 5 serum samples from similar IgE RAST-negative patients from Cardiff were also assessed. Sera was obtained from 9 age-sex matched controls without latex, rubber or tropical fruit sensitivities. 4 patients with low positive latex IgE RAST were also assessed.

Results

Fig. 1 shows the RAST results. IgG latex antibodies show no specificity for latex-allergic individuals. The concentration range of IgG latex antibodies or patient age are also non-discriminatory.

Discussion

The presence of IgG₄ in serum has been related to chronic antigen exposure in both atopic and non-atopic individuals (6). The subclasses of IgG latex antibodies, however, were not assessed in this study, as IgG₄ immunoblotting was not available. Further investigation could be directed at comparing immunoblot for latex against IgE and IgG. The consistent finding of IgG latex antibodies in our non-latex-sensitive individuals may reflect the increasing use of latex outside the hospital environment. A lack of specificity of IgG latex antibodies in our study suggests that the latex IgG RAST is not helpful when assessing IgE latex RAST-negative individuals who have a clinical history suggestive of immediate-type hypersensitivity to latex products.

References

1. Warshaw E M. Latex allergy. *J Am Acad Dermatol* 1989; 39: 1–24.
2. Kurup V P, Alenius H, Kelly K J et al. A 2-dimensional electrophoretic analysis of latex peptides reacting with IgE and IgG antibodies from patients with latex allergy. *Int Arch Allergy Immunol* 1996; 109: 58–67.
3. Akasawa A, Matsumoto K, Saito H et al. Incidence of latex allergy in atopic children and hospital workers in Japan. *Int Arch Allergy Immunol* 1993; 101: 177–181.
4. Higgins S M, Resnick A, Kurup V P et al. Latex-specific IgE and IgG antibodies in patients with latex sensitivity and age-matched controls. *J Allergy Clin Immunol* 1994; 93: 282.
5. Alenius H, Renunala T, Turjanmaa KJ, Palosuo T. Detection of IgE₄ and IgE antibodies to rubber proteins by immunoblotting in latex allergy. *Allergy Proc* 1992; 13: 75–77.
6. Aalberse R C, Van der Gaag R, Van Leeuwen J. Serological aspects of IgG₄ antibodies (I). *J Immunol* 1983; 130: 722–726.

Clinical relevance of positive patch test reactions to preservatives and fragrances

ANTON C. DE GROOT

Department of Dermatology, Carolus Ziekenhuis, PO Box 1101, 5200 BD's-Hertogenbosch, The Netherlands

Key words: clinical relevance; contact allergy; preservatives; fragrances; standardization. © Munksgaard, 1999.

"Evaluating the relevance of a reaction is the most difficult and intricate part of the patch test procedure, and is a challenge to both dermatologist and patient. The dermatologist's skill, experience and curiosity are crucial factors" (1).

Materials and Methods

Contact Dermatitis and the American Journal of Contact Dermatitis back to 1990, Dermatosen back to 1994 and recent issues of the Journal of the American Academy of Dermatology were reviewed. Studies in which patch test-

ing was performed with standard series and/or supplemental allergens in unselected patients with suspected allergic contact dermatitis were evaluated for data on the clinical relevance of positive patch test reactions to fragrances and preservatives.

Results

Concept, evaluation and scoring of relevance

Only 3 articles specifically dealt with relevance (2–4). 1 was an abstract (2), the 2nd a review article also providing a schematic approach to the problem (3) and the 3rd

Table 1. Relevance of positive reactions to preservatives

Allergen	No. studies	Range "relevant" (%)				Ref.
		relevant	definite	probable	possible	
2-bromo-2-nitropropane-1,3-diol	3	42–45	3	14	32	(8, 9, 14)
chloroacetamide	1	20				(8)
<i>p</i> -chloro- <i>m</i> -cresol	1	40				(8)
chloroxylenol	2	90	8	32	24	(8, 9)
diazolidinyl urea	3	10–68	8–10	36–38	39–41	(8, 9, 15)
DMDM hydantoin	2	56	11–13	34–36	39	(8, 9)
formaldehyde	3	64–86	10	23	42	(8, 9, 11)
imidazolidinyl urea	2	54–58	10–15	31–34	34–43	(8, 9)
methyl(chloro)isothiazolinone	7	32–92	19–21	46–48	22–24	(8, 9, 16–20)
methyldibromo glutaronitrile	5	23–71	5–42	10–26	34	(8, 9, 10, 21, 22)
parabens	2	68	6	43	36	(8, 9)
quaternium-15	3	44–78	18	40	27	(8, 9, 23)
sorbic acid	2	40–70				(8, 24)
thimerosal	3	12–37	2	4	5	(8, 9, 25)

proposed a new relevance scoring system (4). In over 65% of all clinical studies evaluated, little or no data on relevance was provided. Even experts in the field sometimes reported quantitative patch test data without such information (5–7). When comparing studies that did address relevance, there was no uniform concept of its definition, how it should be evaluated and how scored. Sometimes, reactions were scored only as "relevant"; sometimes "past relevance" was also evaluated. In the 1992–1994 NACDG study, reactions were classified either as "present relevance" or "past relevance" (8), whereas in their 1994–1996 study, the terms "definite", "probable" and "possible" for current relevance were introduced (9). Investigators at the University of Louisville used "relevance definite", "relevance probable" and "relevance doubtful" (10).

Furthermore, the criteria of whether or not positive reactions should be considered relevant varied considerably. Sometimes, criteria were used that seemed questionable or even wrong. The NACDG, for example, considered a patch test reaction "relevant", "if the patient was exposed to circumstances in which skin contact with a material known to contain the putative allergen was likely to occur" (8). This may be considered too uncertain, leading to overestimated %s of relevance. In the publication thereafter of their 1994–1996 results (9), the same methodology of establishing relevance was used, but relevance was now subdivided into "current relevance *definite*", "current relevance *probable*", or "current relevance *possible*". When isn't relevance "possible"? For widespread allergens, such as preservatives and fragrances, contact will be very hard to rule out. In another American study, relevance was rated "doubtful", if there was no contact with the putative allergen, but "the patch test reaction appearance and timing suggested an allergic reaction" (10). Thus, the morphology of the patch test reaction was used for determining relevance. While morphology may be useful in assessing whether a patch test reaction is truly allergic, no firm conclusions can be drawn from its characteristics per se as to its relevance.

In another study, a reaction to formaldehyde was considered to be relevant in *every case* where formaldehyde

was demonstrated by analysis in 1 or more products brought in by the patients and applied at the site of dermatitis (11). A flaw in this study was that the amounts of formaldehyde present were not determined: the analytical methods used detected free formaldehyde at as low as 5 ppm, whereas the minimum eliciting threshold concentration may approach 250 ppm (12). The authors themselves admitted that relevance may thus have been overestimated, though still arrived at an 86% figure without mention of any clinical improvement on avoidance. In a recent study on fragrances (13), relevance was evaluated by asking prior to patch testing whether patients had ever experienced a rash from cosmetics and whether they had used perfumed cosmetics daily before the onset of their eczema. Apparently, no attention was paid to whether products had been applied to the sites of eczema, and no mention was made of the results of avoidance of fragranced products, both important criteria for relevance (3).

The results of relevance scoring

The results of relevance scoring in various studies providing adequate relevance data are presented in Table 1 (preservatives) and Table 2 (fragrances), the data in the columns "Definite", "Probable", and "Possible" being nearly all from 1 NACDG study (9). Few studies provided such relevance data, and there are striking differences in the relevance %s, both between different preservatives and between different studies on the same preservative. The new NACDG scoring system results in most reactions now being scored as "probably" or "possibly" relevant (9).

For fragrances, the same pattern can be recognized: few data, and a steep decline in relevance % when a more refined method of scoring is used. Correlation of a positive reaction to the fragrance mix with the clinical picture is often lacking and many such patients can tolerate perfumes and fragranced products (13). Between 50% and 65% of all positive reactions to the mix are deemed relevant, although this is often hard to prove (9, 26). Nevertheless, there is a highly significant association with a positive history (27). In fragrance mix allergic patients with concomitant positive reactions to their own

Table 2. Relevance of positive reactions to fragrances

Allergen	No. studies	Range "relevant" (%)				Ref.
		relevant	definite	probable	possible	
cinnamal	2	61	5	28	53	(8, 9)
balsam of Peru	3	49–55	6	19	50	(8, 9, 25)
fragrance mix	3	50–64	9	36	38	(8, 9, 25)

perfumes or scented products, relevance is highly likely, the fragrance mix appearing to be a good reflection of actual exposure (28). 1 or more of the constituents of the mix are present in nearly all deodorants (29), popular prestige perfumes (30), perfumes used in the formulation of other cosmetic products (13) and natural-ingredient-based cosmetics (31), often in levels high enough to cause allergic reactions (32, 33). Even despite this, absolute proof of relevance remains virtually impossible, as it is usually not known whether suspected products actually contain implicated fragrance allergens, and if in sufficient amounts to elicit dermatitis.

Conclusions and Recommendations

From this limited literature review, it would appear that the opening quote is right (1). Evaluating relevance is difficult and there is no consensus as to its definition, evaluation and scoring system. Only a small minority of authors address the issue at all, some of whom use questionable methods. Not surprisingly, the results of relevance scoring vary widely. It can thus be assumed that data are generally inadequate and presumably unreliable. More attention should therefore be focused on the relevance problem. To this end, we make following suggestions.

(i) Dermatologists-researchers should be made more aware of the problem.

(ii) Journal editors should pay more attention to the issue and inform authors of their responsibilities.

(iii) The excellent review article by Ale & Maibach (3) should be updated to highlight the issue again.

(iv) The ESCD or EECDRG should consider forming a Working Party to define and standardize the concept of relevance.

(v) Lists of possible exposures to standard allergens and/or national and international databases should be published by the ESCD or EECDRG and regularly updated.

(vi) Every effort should be made to facilitate the labelling of key fragrances in cosmetics and toiletries and the declaration of ingredients in household, hobby and industrial products.

References

1. Wahlberg J E. Patch testing. In: Rycroft R J G, Menné T, Frosch P J (eds): *Textbook of contact dermatitis*, 2nd edition. Berlin, Heidelberg: Springer-Verlag, 1995: 239–268.
2. Bruze M. What is a relevant contact allergy? *Contact Dermatitis* 1990; 23: 224–225.
3. Ale S I, Maibach H I. Clinical relevance in allergic contact dermatitis. *Dermatosen* 1995; 43: 119–121.
4. Lachapelle J-M. A proposed relevance scoring system for positive allergic patch test reactions: practical implications and limitations. *Contact Dermatitis* 1997; 36: 39–43.
5. Schnuch A, Geier J. Die häufigsten Kontaktallergene im Jahr 1994. *Dermatosen* 1995; 43: 275–278.
6. Menné T, Frosch P J, Veien N K, Hannuksela M, Björkner B, Lachapelle J-M et al. Contact sensitization to 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (MCI/MI). *Contact Dermatitis* 1991; 24: 334–341.
7. Jacobs M-C, White I R, Rycroft R J G, Taub N. Patch testing with preservatives at St John's from 1982 to 1993. *Contact Dermatitis* 1995; 33: 247–254.
8. Marks J G Jr, Belsito D V, DeLeo V A, Fowler J F Jr, Fransway A F, Maibach H I et al. North American Contact Dermatitis Group standard tray patch test results (1992 to 1994). *Am J Contact Dermatitis* 1995; 6: 160–165.
9. Marks J G Jr, Belsito D V, DeLeo V A, Fowler J F Jr, Fransway A F, Maibach H I et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998; 38: 911–918.
10. Jackson J M, Fowler J F. Methylchloroisothiazolinone (Euxyl K400): a new and important sensitizer in the United States? *J Am Acad Dermatol* 1998; 38: 934–937.
11. Trattner A, Johansen J D, Menné T. Formaldehyde concentration in diagnostic patch testing: comparison of 1% with 2%. *Contact Dermatitis* 1998; 38: 9–13.
12. Flyvholm M-A, Hall B M, Agner T, Tiedemann E, Greenhill P, Vanderveken W et al. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. *Contact Dermatitis* 1997; 36: 26–33.
13. Johansen J D, Rastogi S C, Andersen K E, Menné T. Content and reactivity to product perfumes in fragrance mix positive and negative eczema patients. *Contact Dermatitis* 1997; 36: 291–296.
14. Frosch P J, White I R, Rycroft R J G, Lahti A, Burrows D, Camarasa J G, Ducombs G et al. Contact allergy to bronopol. *Contact Dermatitis* 1990; 22: 24–26.
15. Hectorne K J, Fransway A F. Diazolidinyl urea: incidence of sensitivity, patterns of cross-reactivity and clinical relevance. *Contact Dermatitis* 1994; 30: 16–19.
16. Marks J G Jr, Moss J N, Parno J R, Adams R M, Belsito D V, DeLeo V A et al. Methylchloroisothiazolinone/methylisothiazolinone (Kathon CG) biocide: second United States multicenter study of human skin sensitization. *Am J Contact Dermatitis* 1993; 4: 87–89.
17. Hasson A, Guimaraens D, Condé-Salazar L. Patch test sensitivity to the preservative Kathon CG in Spain. *Contact Dermatitis* 1990; 22: 257–261.
18. Foussereau J. An epidemiological study of contact allergy to 5-chloro-3-methyl isothiazolinone/3-methyl isothiazolinone in Strasbourg. *Contact Dermatitis* 1990; 22: 68–70.
19. Macháčová J, Kalenský J, Vocilková A. Patch test sensitivity to Kathon CG in Prague. *Contact Dermatitis* 1990; 22: 189–190.
20. Marks J G Jr, Moss J N, Parno J R, Fowler J F Jr, Storrs J, Belsito D V et al. Methylchloroisothiazolinone/methylisothiazolinone (Kathon CG) biocide – United States

- multicenter study of human skin sensitization. *Am J Contact Dermatitis* 1990; 1: 157–161.
21. De Groot A C, De Kock P A J J M, Coenraads P J, Van Ginkel C J W, Jagtman B A, Van Joost Th et al. Methyl dibromoglutaronitrile is an important contact allergen in The Netherlands. *Contact Dermatitis* 1996; 34: 118–120.
 22. De Groot A C, Bruynzeel D P, Coenraads P J, Crijns M B, Van Ginkel C J W, Van Joost Th et al. Frequency of allergic reactions to methyl dibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane) in The Netherlands. *Contact Dermatitis* 1991; 25: 270–271.
 23. Parker L U, Taylor J S. A 5-year study of contact allergy to quaternium-15. *Am J Contact Dermatitis* 1991; 2: 231–234.
 24. Ramsing D W, Menné T. Contact sensitivity to sorbic acid. *Contact Dermatitis* 1993; 28: 124–125.
 25. Brasch J, Geier J, Gefeller O. Dynamic patterns of allergic patch test reactions to 10 European standard allergens. *Contact Dermatitis* 1996; 35: 17–22.
 26. Frosch P J, Pilz B, Burrows D, Camarasa J G, Lachapelle J-M, Lahti A, Menné T, Wilkinson J D. Testing with the fragrance mix – is the addition of sorbitan sesquiolate to the constituents useful? *Contact Dermatitis* 1995; 32: 266–272.
 27. Johansen J D, Andersen T F, Veien N, Avnstorp C, Andersen K E, Menné T. Patch testing with markers of fragrance contact allergy. Do clinical tests correspond to patients' self-reported problems? *Acta Dermato-venereologica* 1997; 77: 149–153.
 28. Johansen J D, Rastogi S C, Menné T. Exposure to selected fragrance materials. A case study of fragrance-mix-positive eczema patients. *Contact Dermatitis* 1996; 34: 106–110.
 29. Rastogi S C, Johansen J D, Frosch P J, Menné T, Bruze M, Lepoittevin J P, Dreier B, Andersen K E, White I R. Deodorants on the European market: quantitative chemical analysis of 21 fragrances. *Contact Dermatitis* 1998; 38: 29–35.
 30. Johansen J D, Rastogi S C, Menné T. Contact allergy to popular perfumes; assessed by patch test, use test and chemical analysis. *Br J Dermatol* 1996; 135: 419–422.
 31. Rastogi S, Johansen J D, Menné T. Natural ingredients based cosmetics. Content of selected fragrance sensitizers. *Contact Dermatitis* 1996; 34: 423–426.
 32. Johansen J D, Andersen K E, Menné T. Quantitative aspects of isoeugenol contact allergy assessed by use and patch tests. *Contact Dermatitis* 1996; 34: 414–418.
 33. Johansen J D, Andersen K E, Rastogi S C, Menné T. Threshold responses in cinnamic-aldehyde-sensitive subjects: results and methodological aspects. *Contact Dermatitis* 1996; 34: 165–171.

Occupational allergic contact dermatitis from epoxy resin used to restore window frames

REBECCA C. BROOKE AND MICHAEL H. BECK

Contact Dermatitis Investigation Unit, The Dermatology Centre, University of Manchester Section of Dermatology, Hope Hospital, Salford M6 8HD, UK

Key words: restoration; conservation; bisphenol A; epoxy resin; allergic contact dermatitis; occupational; carpentry; joinery. © Munksgaard, 1999.

It is fashionable to retain "character features" in older properties, and mandatory in the UK, to maintain original materials in buildings of historical interest. Consequently, fillers based on epoxy resins have been developed, which can be used in rotten wooden window-frames to avoid replacement.

Case Reports

Case no. 1

A man had worked for 11 years as a joiner, repairing window frames. 4 weeks after a change in work practices, from making new frames to replacing rotten parts of the old frame with an epoxy-resin-based filler, which involved mixing the resin and hardener, he developed a rash on the right hand which rapidly spread to the left, and subsequently the face, chin and eyelids. He was moved back to his old job, but developed a flare some weeks later when working in the vicinity of others using the epoxy resin. He responded to oral and topical corticosteroids from his general practitioner. On questioning, he reported 5 other people from his works similarly affected.

Case no. 2

This man had been a joiner for 40 years. 12 months prior to patch testing, an epoxy resin system had been introduced so that repair of old window frames could be carried out in situ. The work involved scraping out all rotten wood, then sealing and remoulding the frame using a 2-part epoxy resin. He gradually developed a rash, initially on the wrists, which spread to the fingertips, hands, face and legs.

Both patients were patch tested to the European standard series, an epoxy resin series and their own work materials (Table 1).

Table 1. Positive patch test results

	Case no. 1	Case no. 2
epoxy resin (standard series)	+++	++
phenylglycidylether	++	++
2,4,6-tris(dimethylaminomethyl)phenol (0.5% pet.)	–	++
own resin (0.5% pet.)	++	++