

# Contact allergens in shoe leather among patients with foot eczema

A. M. VAN COEVORDEN<sup>1</sup>, P. J. COENRAADS<sup>1</sup>, H. H. PAS<sup>1</sup> AND P. G. M. VAN DER VALK<sup>2</sup>

<sup>1</sup>Department of Dermatology, Groningen University Hospital, Groningen, <sup>2</sup>Department of Dermatology, University Medical Centre St. Radboud, Nijmegen, the Netherlands

Some patients with relapsing foot eczema and a shoe leather allergy, who fail to show positive results with standard series and shoe wear screening tray patch testing, do not respond to the use of hypoallergenic shoe leather. We assume that relevant allergens are present in hypoallergenic shoe leather. We described an experiment to demonstrate the presence of these allergens. Alcoholic extracts were made of green, black and undyed hypoallergenic shoe leather, and the extracts were fractionated by paper chromatography. The resulting chromatograms were cut into 16 equal paper disks and patch tests were performed with extracts and the paper chromatography fractions. Positive reactions were seen to all extracts and to fractions of all types of leather. From analysis of the pattern of positive patch tests we concluded that leather-related allergens (e.g. tanning agent) and dyes were present in hypoallergenic shoe leather. In these cases, alternatives to shoe leather should be sought, for instance wooden or plastic shoes.

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Allergic contact eczema of the feet from shoe materials is fairly common (1). If footwear eczema is diagnosed, further classification can be complicated, as many factors should be considered. There are four major factors that may influence footwear eczema: allergy, atopy, friction and occlusion (including hyperhidrosis).

Some patients with nonatopic foot eczema are patch test negative to the European standard series and our shoe wear screening series, but demonstrate positive patch test reactions to their own shoe leather. In our experience, these patients can be characterized by frequent exacerbations of a relatively therapy-resistant foot eczema, even when using, as recommended, hypoallergenic leather. This could be explained by the absence of a relevant allergen (or several allergens) from the standard and shoe series, which are present in hypoallergenic leather. Another explanation would attribute the positive patch test reactions to non-specific reactions, e.g. irritation.

We designed an experiment to demonstrate the presence of potential allergens in hypoallergenic shoe leather.

## Patients and Methods

### Subjects

Group 1 consisted of 18 patients with foot eczema, patch test positive to their own hypoallergenic shoe leather without clinical or anamnestic suspicion of an atopic diathesis. A control group of 8 patients with foot eczema not reacting to hypoallergenic shoe leather was formed (group 2). Every patient seen in a 2-year period at our out-patient clinics with foot eczema was eligible for inclusion; with inclusion depending on the patient's consent. 15 healthy members of the hospital staff formed the 2nd control group (group 3).

### Materials

Alcohol extracts were made from 3 unused samples of widely used hypoallergenic, chromate-free and unfinished shoe leather (Allergosan®), only differing in colour (green, black and undyed). This extract was made by adding alcohol (ethanol 100%) to each type of leather in a 10:1 ratio. After 2 h in an ultrasonic bath, the fluid was pipetted and

centrifuged for 10 min at 10000 r.p.m. The supernatant was further concentrated by vacuum evaporation at a maximum temperature of 50°C. Alcohol 100% was added and the solution was centrifuged for 20 min at 13000 r.p.m. Processing of 2 g of leather resulted in 5.00 mL of extract, which was stored in the dark at 5°C. (Methods supplied by Prof. A. Goossens, Leuven, Belgium.)

The extracts were separated by means of paper chromatography, and the paper-base was cut into 16 equal fractions. (Chromatograph designed and assembled at Department of Dermatology, Groningen, the Netherlands.) These fractions were numbered 1–16, with number 1 at the base of the chromatogram.

### Procedures

All patients and controls were patch tested with the crude alcohol extracts, and petrolatum as a negative control. 12 patients from group 1 were also patch tested with the 3 series of 16 fraction-containing chromatography paper-discs. 6 patients from this group refused further testing because of the discomfort associated with patch testing. Patch tests with the fractions were not performed on the subjects from groups 2 and 3, since they did not react to hypoallergenic shoe leather.

Patch test readings were done at day 2 and at day 3, in compliance with the International Contact Dermatitis Research Group (ICDRG) guidelines.

This study was conducted in accordance with the Helsinki Declaration of 1975, and later revisions. Informed consent was obtained.

### Results

No patients or controls reacted to the patch tests with the petrolatum control.

10 of the 18 (56%) patients in group 1 (foot eczema attributable to leather) showed positive patch test reactions to the alcoholic leather extracts after 3 days. Positive patch tests were found to green leather in 8 patients, black leather in 8 patients and undyed leather in 5 patients. 1 subject in group 2 (foot eczema not attributable to hypoallergenic leather) showed a positive reaction to the green leather extract. None of the controls in group 3 showed any reaction to the extracts. There were no irritant reactions.

None of the 6 patients who refused further patch testing with the fractions showed reactions to the extracts. Of the 12 patients who were patch tested with the fractions, 6 (50%) had positive reactions to the fractions made of the green leather extract, 4 (33%) to the fractions made of black

Table 1. Results of patch tests with paper chromatography fractions, performed on 12 patients from group 1

| Fraction no. | No. of patients with a positive reaction to fractions made of |               |                |
|--------------|---------------------------------------------------------------|---------------|----------------|
|              | Black leather                                                 | Green leather | Undyed leather |
| 1–7          | 0 patients                                                    | 0 patients    | 0 patients     |
| 8            | 1                                                             | 0             | 0              |
| 9            | 1                                                             | 1             | 0              |
| 10           | 3                                                             | 1             | 0              |
| 11           | 4                                                             | 2             | 0              |
| 12           | 3                                                             | 4             | 0              |
| 13           | 3                                                             | 4             | 1              |
| 14           | 3                                                             | 5             | 2              |
| 15           | 3                                                             | 4             | 2              |
| 16           | 1                                                             | 2             | 2              |
| Total        | 4                                                             | 6             | 2              |

leather extract and 2 (17%) to the fractions made of undyed leather extract. Most reactions were to fractions 14 and 15, but also to the fractions just proximal to these. All reactions were to fractions in the distal part of the chromatogram, forming a continuous sequence for every type of leather (see Table 1 and Fig. 1). Only patients who demonstrated positive reactions to the extracts showed positive reactions to the fractions.

### Discussion

The predominantly negative results of patch tests with the crude extracts among groups 2 and 3, combined with the positive test results among patients in group 1 point towards a high test specificity, and a moderate sensitivity. As no patients in group 1 were atopics, the risk of non-specific reactivity was limited.

As can be seen in Fig. 1, the patch test results with the black leather fractions form a bell-shaped figure, skewed towards the left with the top at fraction 11. The green leather fractions, however, also form a bell-shaped figure, but are skewed towards the right with the top at fraction 14. The (few) patch test positive fractions of undyed leather are more or less evenly distributed over fractions 13–16.

Knowing that the green and black leather are equal to the undyed leather, except for the addition of dye in the first 2, we conclude that there are a few positive patch test reactions to the leather itself (e.g. the process of tanning). These can be found by patch testing fractions 13–16, for which positive reactions were found among all types of leather. Furthermore, we assume that 1 or more dyes can be found in fractions 8–16 (black leather) and 9–16 (green leather).

In this study we chose hypoallergenic leather, with a very low chromate content, because we rec-

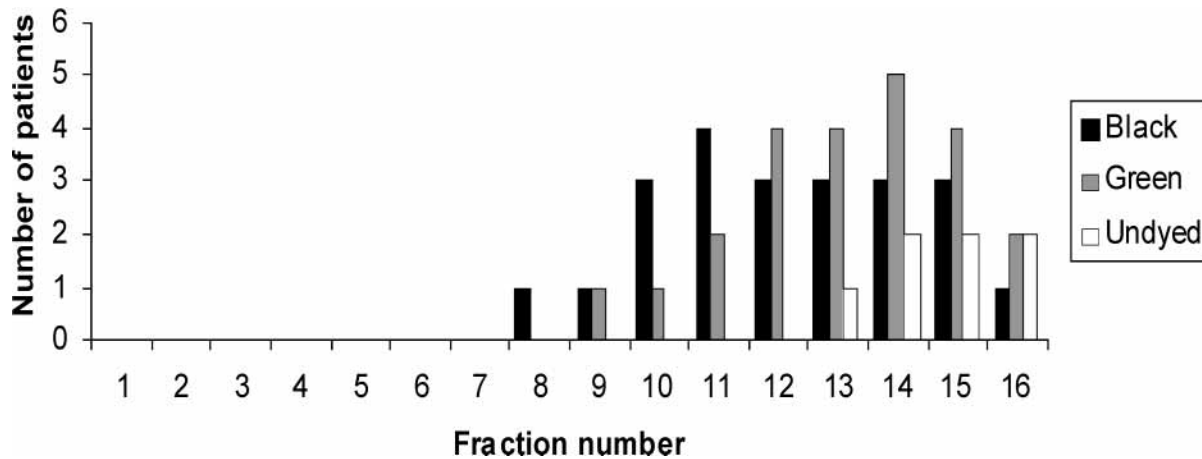


Fig. 1. Number of patients in group 1 with a positive patch test reaction to a paper chromatography fraction.

commend its use to patients with shoe leather allergy, such as the patients in group 1. We have demonstrated that there are allergens present in this widely used Dutch hypoallergenic shoe leather, such as 1 or more dyes and an allergen closely related to shoe leather itself; the latter might be a tanning agent. Potassium dichromate is known to be a frequently sensitizing tanning agent (approximately 1/4 of patients with shoe allergy) (2, 3) and its alternatives, which are frequently used in hypoallergenic shoe leather, may also cause contact allergies (4). The main alternative is vegetable tannin, e.g. quebracho. The use of other tanning agents, such as glutaraldehyde and formaldehyde (5), is determined by the manufacturer based upon the required properties of the shoe leather, rather than their sensitizing potential. The allergen could also be an unusual chemical added to the leather such as a biocide (6, 7).

Although tanning agents and dyes are the most likely sources of shoe leather allergy, allergies to dyes are far less common than allergies to tanning agents, probably, but not absolutely (8), with the exception of redyed leather (6, 9). The most commonly used dyes are azo-aniline group dyes, e.g. paraphenylenediamine and para-aminoazobenzene.

As mentioned in the introduction, there is a subgroup of patients with suspected shoe leather dermatitis who have negative patch tests to standard series and shoe wear screening trays. This is not an uncommon problem since negative patch tests have been reported in 35–79% of patients (1, 10, 11). This finding could be attributed to the fact that little is known about the tanning agents and dyes used. Much information is unknown or kept secret by the shoe manufacturers (12).

Patients with allergic contact eczema to shoe components are usually advised to use shoes made

of hypoallergenic material, which has proven to be effective (13). Some scepticism about the value of hypoallergenic shoe leather is justified (14). In this study we demonstrated that hypoallergenic shoe leather can indeed cause allergic contact eczema. In these cases, the following recommendations can be made: wearing wooden or plastic shoes (15), wearing good quality, new, leather shoes and discarding them after a few months (thus preventing the allergens from leaching out), and wearing extra pairs of socks in shoes that are too large (thus preventing contact with the allergens). These simple measures can result in clearance of half the cases of allergic shoe eczema due to an unknown allergen (3).

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- Address:  
A.M. van Coevorden  
Department of Dermatology  
Groningen University Hospital  
PO Box 30001  
9700 RB Groningen  
the Netherlands  
Tel: + 31 50 3612520  
Fax: + 31 50 3612624  
e-mail: a.m.van.coevorden@derm.azg.nl