

## Persistent Shoe Dermatitis Caused by Dimethyl Fumarate

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A widespread epidemic of severe sofa/chair dermatitis, caused by an anti-mould agent, dimethyl fumarate (DMF), appeared in several European countries in 2006 to 2008 (1–3). Thereafter, two reports of DMF-induced foot dermatitis (4, 5) have been published. In addition, on the internet pages of the European Union (rapid alert system for dangerous consumer products) several types of shoes marketed in Central and Southern Europe have been reported to contain DMF (6). To the best of our knowledge, shoe-induced allergy to DMF has not yet been reported in Scandinavia.

### CASE REPORT

A 30-year-old, healthy woman with no history of atopy or long-lasting dermatitis was referred to our department in May 2009 with severe foot dermatitis. Twenty-three days previously she had worn some new moccasin-type shoes (manufactured in China) for approximately 8 hours. Prior to that, she had used the shoes only once for about 10 min one month previously. The morning after wearing the shoes for 8 h, her feet had become so red, painful and swollen that she contacted the emergency unit. She was treated with potent topical steroids and oral prednisolone (maximally 40 mg/day), resulting in only slight amelioration of her condition. During the first visit to our department, strong redness and dry eczema, corresponding exactly to the shoe contact area, was still visible (Fig. 1). Topical treatment with potent steroids was continued, in addition to wet dressings, and the dermatitis faded slowly. During the entire course of the dermatitis, the prevailing symptoms were burning and stinging without any itching.



Fig. 1. Strong foot dermatitis 23 days after wearing the shoes containing dimethyl fumarate.

In August 2009, the patient was patch-tested according to the International Contact Dermatitis Research Group criteria with the Finnish baseline, cosmetic and shoe series, with 0.01%, 0.001% and 0.0001% DMF and with the shoe materials. The reactions were as follows: both outside and inside material of the shoe caused +++, 0.01% DMF ++ (negative to 0.001% and 0.0001% DMF), 5% nickel sulphate + (only past relevance) and 0.5% potassium chromate an irritant reaction.

### Chemical analysis

The patient's shoes and 9 different types of silica gel sachets used in shoe boxes were analysed for the presence of DMF. The sachets were provided by the importer of the patients' shoes. An absorbing material (0.5 g, Biobeads XAD2, SKC Inc., Eighty Four, PA, USA) was placed inside the shoe, which was then wrapped in aluminium foil and placed in a plastic bag, which was sealed air-tight. After 24 h the absorbent was removed and extracted with 1 ml ethyl acetate (Mallinkrodt Baker, Deventer, The Netherlands). This solution was analysed by gas chromatography-mass spectrometry (GCMS) (Jeol GCmateII, Jeol, Tokyo, Japan). A 1.0 g amount of the contents of the sachets was extracted with 2.0 ml ethyl acetate and analysed in the same way. A standard curve was obtained by analysing solutions with known concentrations of DMF (Sigma-Aldrich, St Louis, MO, USA). The concentrations in the samples were determined by comparing them with the standard curve. DMF was detected both in shoes and in sachets (Table I).

### DISCUSSION

The beginning of the dermatitis, as an acute, sharply demarcated eczema corresponding exactly to the contact area of the shoe exposure, refers to irritant rather than allergic contact dermatitis. The irritant nature of DMF (5, 7), the insufficient response to the treatment and the relatively high concentration of DMF in the shoes further support the initial irritant nature of the dermatitis. The shoes probably contained a higher concentration of DMF while being used by the patient compared with the time of analysis 5 months later. However, the convincing results of positive patch-testing to the shoe material and DMF itself, led us to conclude that the primary irritant state facilitated the induction of sensitization to DMF and a subsequent transformation

Table I. Total amount of dimethyl fumarate (DMF) in the analysed samples and the calculated corresponding concentration in the analysed items

Item	Total amount in the analysed extract ( $\mu\text{g}$ )	Corresponding concentration in the item (ppm = mg/kg)
Shoe A <sup>a</sup>	431	2.2 <sup>b</sup>
Shoe B <sup>a</sup>	553	2.8 <sup>b</sup>
Shoe A/2 <sup>c</sup>	34	0.22 <sup>b</sup>
Silica gel 1	5.1	8.5
Silica gel 2	2.8	4.7
Silica gel 3	588	390
Silica gel 4	683	460
Silica gel 5	4.9	2.5
Silica gel 6	48	19
Silica gel 7	19	7.6
Silica gel 8	5.3	2.1

<sup>a</sup>The same pair of shoes.

<sup>b</sup>These are only minimal values because only a part of the DMF in the shoe was absorbed by the absorbing material. The shoes might therefore contain 10–100 times higher concentrations of DMF and, as the substance is probably not evenly distributed in the shoe, local areas might have even higher concentrations.

<sup>c</sup>Shoe A exposed to air for 2 weeks and re-analysed.

into an allergic contact dermatitis. This sequence of events also occurred in several Spanish patients with DMF-induced shoe contact dermatitis (5).

The shoes in this case had probably absorbed DMF from a sachet. The concentration of DMF decreased by a factor close to 10 after 2 weeks of storing at room temperature without any wrapping at the laboratory in Malmö (Table I). This indicates that DMF-contaminated shoes must be left for several months in the open air before the DMF level can be regarded as harmless. It appears that some shoes contain DMF because the substance has been deliberately incorporated into the structure of the shoe in a white stiff structural layer placed between layers of fabric or leather. In such shoes the evaporation of DMF is slow and the time of airing required to reach safe levels of DMF is considerably longer, possibly years instead of months. At least two of the analysed silica gel sachets had concentrations of DMF so high that it is likely that they contained both

silica gel and DMF, but were labelled only as silica gel sachets. Regarding the other six sachets with lower DMF levels, we cannot exclude that they had absorbed DMF from sachets, shoes or boxes containing it.

DMF has been used to protect items from moulding in a moist climate during storing and importation from the Far East. Due to the large epidemic of chair/sofa-induced DMF allergy, the European Union banned DMF-containing items in the member countries from May 1, 2009. This is the first reported case of shoe-induced allergy to DMF in Scandinavia, and it shows that DMF-containing shoes have also been on the market in Northern Europe, at least prior to this new DMF regulation. Since only spot checks of imported items are possible at the customs laboratory in Finland it is not known how well this new regulation is being adhered to.

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