

Shoe contact dermatitis from dimethyl fumarate: clinical manifestations, patch test results, chemical analysis, and source of exposure

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Background: The methyl ester form of fumaric acid named dimethyl fumarate (DMF) is an effective mould-growth inhibitor. Its irritating and sensitizing properties were demonstrated in animal models. Recently, DMF has been identified as responsible for furniture contact dermatitis in Europe.

Objective: To describe the clinical manifestations, patch test results, shoe chemical analysis, and source of exposure to DMF-induced shoe contact dermatitis.

Patients, Materials, and Methods: Patients with suspected shoe contact dermatitis were studied in compliance with the Declaration of Helsinki. Patch test results obtained with their own shoe and the European baseline series, acrylates and fumaric acid esters (FAE), were recorded according to international guidelines. The content of DMF in shoes was analysed with gas chromatography and mass spectrometry.

Results: Acute, immediate irritant contact dermatitis and non-immunological contact urticaria were observed in eight adults and two children, respectively. All the adult patients studied developed a delayed sensitization demonstrated by a positive patch testing to DMF $\leq 0.1\%$ in pet. Cross-reactivity with other FAEs and acrylates was observed. At least 12 different shoe brands were investigated. The chemical analysis from the available shoes showed the presence of DMF.

Conclusion: DMF in shoes was responsible for severe contact dermatitis. Global preventive measures for avoiding contact with DMF are necessary.

Key words: allergic contact dermatitis; allergy; contact dermatitis; contact urticaria; dimethyl fumarate; fumaric acid; irritant contact dermatitis; shoe; urticaria. © John Wiley & Sons A/S, 2009.

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Fumaric acid (FA) is a white crystalline compound, chemical formula $C_4H_4O_4$. It is one of the two isomeric unsaturated dicarboxylic acids, the other one being maleic acid wherein the carboxylic groups are *cis*. The salts and esters of FA are known as fumarates (1, 2). FA is found in fumitory (*Fumaria officinalis*), bolete mushrooms (specifically, *Boletus fomentarius* var. *pseudo-igniarius*), lichen, and Iceland moss. It is an intermediate

in the citric acid cycle used by cells to produce energy in the form of adenosine triphosphate from food. It is also a by-product of the urea cycle. Human skin naturally produces FA when exposed to sunlight. FA is used as food acidulants since 1946 as it is considered non-toxic. It is also used in the manufacture of polyester resins and polyhydric alcohols and as a mordant for dyes.

Dimethyl fumarate (DMF, dimethylfumarate) is the methyl ester form of FA, $C_6H_8O_4$. DMF has been demonstrated as an effective mould-growth inhibitor in bread, also showing an antibacterial activity against *Escherichia coli* (K-12) (3, 4). DMF is included in the polyurethane/sulfonated DMF complex and is successfully involved in the synthesis of solid polymer electrolytes (5).

The antipsoriatic effect of fumaric acid esters (FAEs) was first observed in 1959 by the German chemist Schweckendiek who suffered psoriasis (6). A deficiency of FA was suspected to be crucial in the pathogenesis of psoriasis. As orally administered FA caused gastrointestinal adverse reactions and flushing, it was not useful in treating psoriasis. However, with esters the adverse reactions were less pronounced. The essential component of Fumaderm[®] is DMF, which is more lipophilic than monomethyl fumarate and shows better penetration into cells. A defined mixture of FAEs has been available for the oral treatment of psoriasis vulgaris since 1994 in Germany and the Netherlands (7,8).

Topical application of monoethyl fumarate (MEF) at 3% gave disappointing results with regard to clearing of psoriatic lesions, and perilesional skin irritation was observed (9). Maculopapular reactions in healthy volunteers were reported after overnight application of 0.3%, 1%, and 3% DMF on the volar side of the forearm (9). DMF and MEF induced itchy maculopapular rashes on the unprotected face and arms of pharmacy technicians during or shortly after capsulating these substances (10). Workers in the polymer industry were sensitized by FA (11). At that time, Haan et al. showed the irritating and sensitizing properties of MEF and DMF in a pilot toxicity study (12).

Recently, the strong sensitizing capacity of DMF has been demonstrated in humans. DMF was responsible for a, 'epidemic' of severe contact dermatitis cases related to furniture such as sofas and chairs (13–15); one case concerning shoes has been already reported (16).

The aim of this study is to report a cluster of shoe contact dermatitis from DMF observed in Spain, and to discuss its peculiar characteristics concerning the clinical manifestations, patch test results, shoe chemical analyses, and sources of exposure.

Patients and Methods

Patients

Seventeen patients suffering from a shoe contact dermatitis from DMF were studied. Four departments of dermatology from the East of Spain, Hospital del Mar Universitario from Barcelona, Hospital

General Universitario Morales Meseguer from Murcia, Hospital General Universitario from Alicante, and Hospital General Universitario from Valencia had the opportunity to evaluate an outbreak of shoe contact dermatitis induced by DMF. Fifteen adult women (aged 33–74) and two children (9-month-old girl and 17-month-old boy) were involved. Two patients had a familial (case 12) or personal background of atopy (case 8). At least two patients showed previous well-demonstrated contact allergy (cases 4 and 11). Thirty adult healthy controls were also studied with the same DMF patch test preparations. After full explanation, each patient and control provided written, informed consent to participate in the study protocol. The diagnostic study was conducted in compliance with the Declaration of Helsinki and applicable local and European laws and regulations.

Patch Testing

Patch testing results were collected along with basic demographic and clinical data. The European baseline series (ESS) and other selected allergens included in the Spanish baseline series were applied using 8 mm aluminium Finn Chambers[®] on Scanpor[®] tape and fixed to the back with an adhesive tape such as Fixomull[®] stretch or Micropore[®] paper (3M). The allergen in petrolatum (pet.) filled slightly more than half the chamber volume, and for aqueous allergens, a filter paper disc (Whatman 3M) was placed into the chamber. Routine patch test exposure time was 2 days. The results were recorded according to the international guidelines (17). The standard 'positive outcome' (allergic reaction) of the patch test was defined as a morphological + to +++ reaction between day 2 (D2) and day 4 (D4) after the application of the patch test which was not, upon final evaluation, considered irritant.

Chemicals

The following chemicals were used for patch testing preparation: ethyl acetate in high performance liquid chromatography (HPLC) gradient grade (Mallinckrodt Baker B.V., Deventer, Holland); DMF 97%, diethyl fumarate 98%, and methyl acrylate 99% (Sigma Aldrich, St Louis, MO, USA); ethyl acrylate 99.5% (Acros Organics, Geel, Belgium); dimethyl maleate 96% (Alfa Aesar GmbH & Co KG, Karlsruhe, Germany); methyl methacrylate (Chemotechnique Diagnostics, Vellinge, Sweden); diethyl maleate 90% (Fluka AG, Fuchs, Schweiz); pet. snow white quality E (Apoteket, Göteborg, Sweden).

Patch Test Preparations

ESS and Spanish adaptation of the ESS suppliers were Hermal Trolab-Almirall® and Allergeaze Marti-Tor®. Special series tested were: shoe contact allergens series from Hermal Trolab-Almirall®, acrylates included in the dental series from Allergeaze Marti-Tor®, and methacrylate series from Chemotechnique Diagnostics®.

A special patch test series for patients with suspected shoe dermatitis from DMF was prepared by the Department of Occupational and Environmental Dermatology, Malmö University Hospital, Sweden. The series consisted of DMF, diethyl fumarate, diethyl maleate, dimethyl maleate, methyl acrylate, ethyl acrylate, and methyl methacrylate, with each substance in five 10-fold serial dilution steps in pet. The dilution series of DMF started at 0.10% w/w and the dilution series of the other test substances were equimolar to the concentrations of DMF in the DMF serial dilution (Table 1).

DMF for patch testing was also provided by the Pharmacy Departments in Murcia and Alicante. Increasing aqueous dilutions of DMF provided by Across Organics® (Geel, Belgium) were also tested. Four patients registered in this study were patch tested with this series. Just one case in Valencia was patch tested with DMF 0.01% pet. provided by Allergeaze Marti-Tor®.

Patch testing with the suspected shoe responsible for the contact dermatitis was also performed in nine cases. Solid material was tested 'as is', placing cut pieces in the test chamber or applied on acrylic tape avoiding pressure effects. Shoe textile extracts 10% in water and also in ethanol were also patch tested in two patients (Fig. 3).

Shoe Providers

The shoes involved in skin reactions belonged to at least 12 different brands (Table 2). These shoes were bought from street markets and conventional shoe stores. Most of the shoes were sold in boxes where anti-mould sachets were present. But it was not always the case, and the shoes were also sold without boxes and/or the anti-mould sachets.

Chemical Analysis

Samples (0.5–1 g) from the shoes were extracted with ethyl acetate (around 5 ml) in an ultrasonic bath for 5 min. The volume of the extracts was reduced to 0.5 ml in a rotary evaporator prior to analysis with gas chromatography–mass spectrometry (GCMS). When possible, the samples were taken from an area corresponding to the localization of the patients' eczema.

Separation of components in the samples was performed with an Agilent 6890N gas chromatograph (Agilent Technologies, Palo Alto, CA, USA) equipped with an HP-MSI™ capillary column (Agilent Technologies) of length 30 m, an internal diameter of 0.250 mm, and a film thickness of 0.25 µm. Helium of alphagaz 2 quality (Air Liquide, Malmö, Sweden) was used as the carrier gas with a flow rate of 1.0 ml/min. The injection was splitless and the inlet was heated to 250°C. The injection volume was 1.0 µl. The temperature programme was isothermal at 70°C for 3 min, then rose at 8°C per min to a final temperature of 300°C, and isothermal at this temperature for 10 min.

Electron ionization (EI) mass spectra were recorded from components in the analysed samples with a Jeol GCmate II mass spectrometer (Jeol Datum Ltd., Tokyo, Japan) in scan mode, recording ions with m/z from 50 to 600 u, with a scan duration of 0.3 s and an inter-scan delay of 0.2 s. The temperature of the ion source was 250°C and the GCMS interface temperature was 250°C. The electron energy was 70 eV. The National Institute of Standards and Technology (NIST) library of mass spectra was used for identification. The substance was considered identified in the sample when the match factor between the recorded mass spectrum at the expected retention time for DMF and the mass spectrum stored in the NIST library was at least 90.

Results

Clinical Manifestations

Seventeen patients suffering from a shoe-induced contact dermatitis caused by DMF were studied (Table 3). At least 10 patients, 8 adults and 2 children, showed an immediate shoe contact reaction after wearing the shoes for the first time. The lesions involved the feet and/or the legs. Acute irritant contact dermatitis was found with an immediate itchy erythema developing vesicles and bulla, followed by skin desquamation (eight adults). Contact urticaria/angioedema appeared immediately after the first exposure to the shoe in two cases (two children) (Fig. 1). This itchy local erythematous foot oedema lasted for at most 3 days. Acute irritant contact dermatitis and acute non-immunological contact urticaria healed without skin sequela, although the skin remained very sensitive for several months.

Seven adult patients developed allergic contact dermatitis without a previous irritant episode. These cases showed vesicular eczematous reaction of the feet and toes after a repeated use of the shoes. Skin biopsy always showed a florid dermal lymphocytic inflammatory infiltrate with spongiosis and exocytosis characteristic of acute

Table 1. Fumaric acid ester and acrylate series proposed to be tested in patients suspected of DMF shoe contact allergy

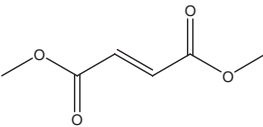
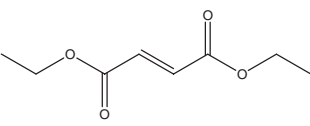
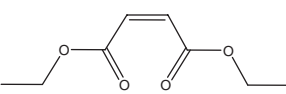
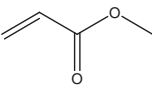
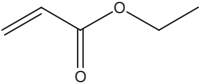
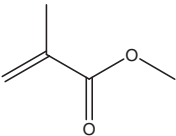
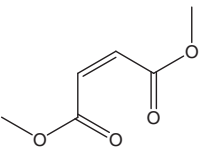
Substance	CAS	MW	Concentration (% w/w in pet)
Dimethyl fumarate	624–49-7	144	0.10 0.010 0.0010 0.00010 0.000010
			
Diethyl fumarate	623–91-6	172	0.12 0.012 0.0012 0.00012 0.000012
			
Diethyl maleate	141–05-9	172	0.12 0.012 0.0012 0.00012 0.000012
			
Methyl acrylate	96-33-3	86	0.060 0.0060 0.00060 0.000060 0.0000060
			
Ethyl acrylate	140–88-5	100	0.069 0.0069 0.00069 0.000069 0.0000069
			
Methyl methacrylate	80–62-6	100	0.69 0.069 0.0069 0.00069 0.000069
			
Dimethyl maleate	624–48-6	144	0.10 0.010 0.0010 0.00010 0.000010
			

Table 2. Shoe brands involved

	Type of shoe	Case
<i>Adults' shoe brands</i>		
Gracia from Lian Chang	Shoe	1
Unknown ^a	Shoe	2
Amelia Zaragoza	Boots	3
Amelia Zaragoza	Boots	4
Charo Fernandez	Boots	4
Ito 3	Boots	5
Gios Eppo	Boots	6
Merkel Calzados	Boots	7
Amelia Zaragoza	Shoe	8
Unknown ^a	Shoe	9
Farashion	Shoes, Boots	10
Rabal	Shoes	11
Be Sweet	Shoes	12
Dulce Rubio	Shoes	13
Arian	Shoes	14
Arian	Shoes	15
<i>Children's shoe brands</i>		
Pasite	Boots	1
Pasite	Boots	2

^aThe patient has lost or disposed of the responsible shoe.

eczema. At least three of these patients (cases 2, 6, and 13) had recurrent episodes of shoe contact dermatitis during several summers. One of them was previously studied with the baseline and shoe allergen series with negative results. These episodes were induced by different types of shoes suggesting a previous unknown exposure to DMF in these patients (Table 3 and Figs 2 and 3).

Treatment was always for acute episodes of dermatitis and consisted of wet dressings, (very) potent topical corticosteroid application and a topical antimicrobial. In addition, all adult cases required systemic corticosteroids.

Patch Test Results

The 15 adult patients who suffered from a shoe contact dermatitis developed a delayed sensitization that was demonstrated by a positive patch test. DMF 0.1% in pet. or 0.01% in water or in pet. were capable of inducing a positive delayed reaction with erythema, cutaneous infiltration, and vesicles (+++ D4). At least 5 out of 10 patients tested showed a clearly positive reaction with DMF at 0.001% in petrolatum. These five strongly sensitized patients initially showed an acute irritant contact dermatitis after the first exposure to the new shoe. A concomitant positive patch test to other contact allergens was demonstrated in 10 patients (Table 3). Four of these patients showed delayed hypersensitivity to different acrylates, and in one of them there was a history with a past occupational relevance related to sculptured nails (Fig. 3). The testing in adult healthy controls gave negative patch test results ($n = 30$).

Eleven DMF sensitized patients were also studied with other acid fumaric esters such as diethyl fumarate, dimethyl maleate, and diethyl maleate. Ten of these patients showed a positive patch test reaction to different concentrations of acid fumaric isomers and esters (Table 4 and Fig. 3).

The two children showed an immediate contact urticaria/angioedema lasting for three days after the first exposure to new boots contaminated with DMF from the anti-mould sachets that were present in the box. The negative open and occluded patch test reaction in both children supported the diagnosis of non-immunological contact urticaria. The immature immune system in children could explain the negative DMF patch test response after a single exposure.

Chemical Analysis

We could demonstrate the presence of DMF in all the shoes studied that were directly involved in the skin contact reactions ($n = 7$). GCMS analysis allowed us to demonstrate DMF in amounts ranging from 3 to 95 ppm (detection limit 0.1) (Table 5). The brown shoe brand 'Gracia from Lian Chang', bought in a Chinese store in Barcelona, showed large variations in concentrations of DMF in the two parts of the shoe, the plastic component (90 ppm) and the fabric (8.4 ppm). DMF was present in the plastic constituent of the shoe.

Discussion

The irritating and sensitizing properties of DMF was reported by Haan et al. in a pilot toxicity study with three healthy volunteers (12). Following the application of FA (100 mM), MEF (10 mM), and DMF (2 mM) in alcohol (70%) only DMF caused an early (10 min) itching skin reaction in all the three individuals, followed by a bullous reaction at the site of DMF application after 10 days in one subject. Retesting with open application of 2 mM DMF in alcohol (70%) in this volunteer resulted in a vesicular reaction within 48 hours. To determine *in vitro* and *in vivo* the non-immunological contact urticaria (NICU) and irritating and sensitizing properties of FA derivatives, ear NICU swelling test, flank irritation test, cytotoxicity, and guinea pig maximization tests were performed. The cytotoxicity test demonstrated DMF as the most toxic FA derivative. DMF also induced contact urticaria reaction in contrast to MEF. Challenge experiments with FA, MEF, and DMF in MEF and DMF sensitized guinea pigs demonstrated that both MEF and DMF are moderate contact sensitizers. In DMF sensitized animals cross-reactions with MEF were found. Because DMF and MEF have cytotoxic,

Table 3. Clinical manifestations and patch test results from the adult and children patients studied with shoe contact dermatitis by dimethyl fumarate

Clinical pattern				Body location	Baseline and other series patch tested	Own shoe patch test	DMF patch test	
Adult cases								
1 B	Female	62	None	ACD	Dorsum of 10 toes	Nickel sulfate (+++D4)	'as is' (+++D4) aq. (+++D4) eth. (+++D4)	0.1% pet. (+++D4) 0.01% pet. (+++D4)
2 B	Female	66	None	ACD	Entire feet	Negative	'as is' (+++D4) aq. (+++D4) eth. (+++D4)	0.1% pet. (+++D4) 0.01% pet. (+++D4)
3 B	Female	37	None	ICD	Entire feet and legs	Negative	Not tested	0.1% pet. (+++D4) 0.01% pet. (+++D4) 0.001% pet. (+++D4)
4 B	Female	33	Hairdresser allergic to <i>p</i> -phenylenediamine; nickel sulfate	ICD	Entire feet and leg	Nickel sulfate (+++D4)	Not tested	0.1% pet. (+++D4)
5 B	Female	33	None	ACD	Entire feet and ankles	<i>Myroxylon perirae</i> (+++D4)		0.01% pet. (+++D4)
6 B	Female	47	None	ICD	Entire feet and legs	Formaldehyde (+++D4)	Not tested	0.001% pet. (+++D4)
7 B	Female	37	None	ACD	Dorsum feet, 10 toes, hands and neck	Negative	Not tested	0.1% pet. (+++D4)
8 Mu	Female	33	Atopy, allergic rhinitis	ACD	Dorsum of 10 toes	Potassium dichromate (++) D4)	'as is' (- D4)	0.1% pet. (+++D4)
9 Mu	Female	50	Metal-induced dermatitis	ACD	Dorsum of 10 toes	Methylchloroisothiazolinone/ Methylisothiazolinone (++)D4)	aq. (+++D4) eth. (+D4)	0.01% pet. (+++D4)
10 Mu	Female	48	Metal-induced dermatitis	ICD	Dorsum feet and legs	Negative	'as is' (+++D4)	0.01% aq. (+++D4)
11 A	Female	37	Finger dermatitis by sculptured nails	ICD	Dorsum and plantar of toes	Nickel sulfate (+D4)	Not tested	0.1% pet.
			Acrylate positive reaction was demonstrated	ACD	2-Hydroxypropyl-metacrylate (+D4) Thiomersal (++)D4)	Nickel sulfate (+D4)	'as is' shoe (++)D4) 'as is' boot (++)D4) 'as is' (++)D4)	0.01% pet. (+++D4) 0.01% aq. (+D4)
					Disperse Blue 106 (++)D4)			0.1% pet. (+++D4)
					Butyl acrylate (++) D4) Ethyl methacrylate (++)D4) 2-Hydroxyethyl methacrylate (++) D4) 2-Hydroxypropylmethacrylate (+ D4) Ethylene glycol dimethacrylate (++) D4) Ethyl acrylate (++) D4) 2-Hydroxyethyl acrylate (++) D4)			0.001% pet. (+++D4)

Table 3. Continued

12 A	Female	33	None	ICD	Entire feet	Ethyl acrylate (++) D4) Methyl acrylate (++) D4)	'as is' (+++D4)	0.1% pet. (+++D4) 0.01% pet. (+++D4) 0.001% pet. (+++D4) 0.1% pet. (+++D4) 0.01% pet. (+++D4)
13 A	Female	74	None	ACD	Entire feet	Colophonium (++) D4) Nickel sulfate (++)D4) Ethyl acrylate (++)D4) Methyl acrylate (++)D4) Nickel sulfate (++) D4) Cobalt chloride (++) D4) Palladium chloride (++) D4) Nickel sulfate (++) D4)	'as is' (++)D4) aq. (++)D4)	0.1% pet. (+++D4) 0.01% pet. (+++D4) 0.001% pet. (+++D4) 0.1% pet. (+++D4) 0.01% pet. (+++D4)
14 A	Female	34	None	ICD	Entire feet		'as is', negative	0.1% pet. (+++D4) 0.01% pet. (+++D4) 0.001% pet. (+++D4) 0.01% pet. (+++D4)
15 V	Female	42	Metal-induced dermatitis	ACD	Dorsum feet		'as is' (++)D4)	0.01% pet. (+++D4)
<i>Children</i>								
1 Mu	Female	9 M	None	NICU	Entire feet	Not tested	Negative occluded and open	0.01% pet. (neg D4)
2 A	Male	17 M	None	NICU	Entire feet	Negative	Negative	0.001% pet. (neg D4) 0.01% aq. (neg D4) 0.001% aq. (neg D4)

NICU, non-immunological contact urticaria; ICD, irritant contact dermatitis; ACD, allergic contact dermatitis; DMF, dimethylfumarate; pet., petrolatum; M, month-old; B, Barcelona; Mu, Murcia; A, Alicante; V, Valencia.



Fig. 1. Itchy feet eruption, immediate erythema, and oedema. Local contact urticaria that appeared few hours after the first use of a new pair of leather boots branded 'Pasite®' (Wenzhou Pasite Shoes, Ltd).

contact urticaria, and/or sensitizing properties, Haan et al concluded at that time that topical application should be avoided (12).

Starting in 2006–2007, an epidemic of severe contact dermatitis cases related to newly acquired sofas and chairs manufactured in China acquired a lot of attention in the media in Finland (13) and the UK (14). Buttocks, back, thighs, or arms were the initial locations of the severe dermatitis. The cause of the contact dermatitis was independently revealed by three groups in 2008 as DMF (18, 19). Up to 470 µg/kg of DMF was found in chairs. Patients showed strong positive patch test reactions to fabric samples and to DMF at 0.01% and 0.001% in aqueous dilutions. Recently, a case of foot dermatitis was reported (16).

The discussion of the present study will be addressed to the clinical manifestations, patch test results, shoe chemical analysis, and source of exposure.

All the adult patients studied had DMF contact allergy. The DMF exposure elicited a clinically acute reaction with vesicles. Even after several months, the skin remained very sensitive and slight friction induced pain. Delayed sensitization to DMF was demonstrated by positive patch test reactions to DMF 0.1% in pet. (11 cases) or 0.01% aq. (2 cases) or pet. (2 cases).

Two children developed a non-immunological immediate contact reaction after the first wearing of new boots. This short DMF exposure was capable of inducing these skin reactions but was not enough to induce immediate or delayed sensitization. The early identification of the responsible shoe and avoidance of further exposure most likely protected the children from developing contact allergy to DMF. The immature immunological system of children was probably another reason.

In order to avoid active sensitization, we recommend patch testing with FAEs only for diagnostic purposes when suggestive clinical features are present.

DMF (13) and diethyl fumarate (20) have been described as a cause of allergic contact dermatitis in humans. FA and maleic acid (carboxylic groups are *cis*) are isomeric unsaturated dicarboxylic acids. In industry, FA is produced from maleic acid. Cross-reaction between diethyl fumarate and diethyl maleate has been described (17). In the skin, the isomeric forms, DMF and dimethyl maleate on the one hand, and diethyl maleate and diethyl fumarate on the other, can be expected to form the same complete antigen after having reacted with nucleophilic proteins (18). If the same complete antigens are generated, the patch test reactivity towards the respective alkyl fumarate/maleate is expected to be the same. For DMF and dimethyl maleate, the patch test reactivity is similar but the corresponding comparison for diethyl fumarate and diethyl maleate demonstrated a higher reactivity towards diethyl fumarate (Table 4; $P = 0.002$, sign test, two sided) in all patients with contact allergy to at least one of them (diethyl fumarate or diethyl maleate). This discrepancy in patch test reactivity does not necessarily contradict the hypothesis of formation of the same complete antigen in the skin from skin exposure to the isomeric fumarate and maleate esters. Differences in skin penetration and degree of reactivity with proteins in the skin may explain the higher patch test reactivity to diethyl fumarate as compared with diethyl maleate.

Eleven DMF sensitized adults were also patch tested with diethyl fumarate, dimethyl maleate, and diethyl maleate in this study. Nine of them showed positive reactions to both esters from the two isomers (Fig. 3). As maleic acid is an industrial raw material for the production of glyoxylic acid and ozonolysis, this information may have clinical impact. Maleic acid is mainly used for making maleate salts of bulk drugs such as common antihistamines like pheneramine maleate, chlorpheniramine maleate, and others. Also, it is employed in the manufacture of phthalic-type alkyd and polyester resins, surface coatings, copolymers, plasticizers, lubricant additives, and agricultural chemicals, in adhesives and sealants, as a preservative to prevent rancidity in oils and fats, in organic synthesis, and in dyeing and finishing wool, cotton, and silk. As individuals with contact allergy to fumaric acid esters may have cross sensitivity to maleic acid esters (21–23), when such cross sensitivity occurs advice on sources of exposure to these esters should be given.



Fig. 2. Case 12 A in Table 3. Severe acute contact dermatitis characterized by haemorrhagic blisters on the feet, affecting the entire surface of the skin in contact with a new pair of red shoes branded 'Be Sweet'.

Table 4. Cross-reactions in patients sensitized to dimethyl fumarate

Substance	Concentration (% w/w)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Dimethyl fumarate	0.10	+++	+++	+++	+++	++	++	+++	+++ ^a	+++	nt	+++	+++	+++	+++	nt
	0.010	+++	+++	+++	+++	–	–	+++	+++ ^a	+++	+ ^a	+++	+++	+++	+++	+++
	0.0010	–	nt	+++	+++	–	–	–	nt	–	nt	+++	+++	–	+++	nt
	0.00010	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Diethyl fumarate	0.12	+++	nt	+++	+++	–	+	+++	nt	+++	nt	++	++	++	++	nt
	0.012	–	nt	+++	+++	–	–	+	nt	++	nt	++	++	++	++	nt
	0.0012	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Dimethyl maleate	0.10	+++	nt	+++	+++	–	–	+++	nt	+++	nt	+++	+++	++	+++	nt
	0.010	+++	nt	+++	+++	–	–	+++	nt	+++	nt	+++	+++	++	+++	nt
	0.0010	–	nt	–	+++	–	–	–	nt	–	nt	+++	+++	–	+++	nt
	0.00010	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Diethyl maleate	0.12	–	nt	–	–	–	–	+	nt	–	nt	–	–	–	–	nt
	0.012	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Methyl acrylate	0.060	–	nt	–	–	–	–	–	nt	–	nt	–	++	++	–	nt
	0.0060	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Ethyl acrylate	0.069	–	nt	–	–	–	–	–	nt	–	nt	++	++	++	–	nt
	0.0069	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt
Methyl methacrylate	0.69	–	nt	–	–	–	–	–	nt	–	nt	–	–	–	–	nt

nt, not tested.

^aTested with dimethyl fumarate in water.



Fig. 3. Case 11 A in Table 3. **a.** Severe acute contact dermatitis characterized by blisters on the feet affecting the entire surface of the skin in contact with a new pair of white shoes branded 'Rabal'. **b.** Patch test results showing positive reaction to different pieces of the own shoe as is; **c.** to dimethyl fumarate 0.1–0.001% in pet., and cross-sensitization with diethyl fumarate 0.12–0.012% in pet., dimethyl maleate 0.12–0.012% in pet., diethyl maleate 0.01% in pet., all esters and isomers of fumaric acid and also with **d.** ethyl acrylate and other acrylates (Table 3).

DMF is not only chemically closely related to alkyl esters of maleic acid, but also related to low molecular weight acrylates such as methyl acrylate, ethyl acrylate, and methyl methacrylate. When tested at equimolar concentrations to DMF, 3 out of 11 patients allergic to DMF also reacted positively to at least one of the three acrylates (Table 4). It should be pointed out that the acrylates were tested at lower concentrations than recommended (2% for methacrylates and 0.1% for acrylates), as the testing was not primarily performed to trace contact allergy to acrylates but to investigate cross-reactivity between DMF and acrylates in a way that could help draw conclusion on primary sensitization.

DMF was present in all the shoes that were worn in the contact reactions ($n = 9$) and allowed us to demonstrate the responsible agent of the shoe contact allergy. Gas chromatography combined with

mass spectrometry allowed us to demonstrate DMF in amounts ranging from 3 to 95 ppm (detection limit 0.1 ppm). It must be realized that some of the shoe analyses were performed months after the shoe was worn for the first time and far from the original place of manufacture. DMF is a volatile substance. Although the lowest amount of DMF was detected in three summer shoes that had been worn many times, a severe contact dermatitis was elicited and a strong positive patch test was observed when the shoe material was patch tested 'as is'. The amount of DMF found in one of the new baby leather boots was higher than the other shoes, and in this case, the anti-mould sachets were still present inside the shoe box. After contact sensitization, even low concentrations of DMF elicited severe delayed hypersensitivity reactions.

Table 5. Dimethyl fumarate chemical analysis from the shoes analyzed responsible of contact dermatitis.^a

Shoe	Dimethylfumarate		
	µg/g	ppm	% w/w
Case 1			
from fabric and plastic	90 plastic	90 plastic	0.0090
Gracia Lian Chang®	8.4 fabric	8.4 fabric	0.0008
Case 8			
Amelia Zaragoza®	5.0	5.0	0.00050
Case 11			
Rabal®	3.0	3.0	0.00030
Case 12			
Be Sweet®	23	23	0.0023
Case 2			
Leather, unknown brand	36	36	0.0036
Case 15			
Arian®	95	95	0.0095
	850 ^b	850 ^b	0.085 ^b
Case 1 children			
Pasite®	24	24	0.0024
Case 2 children			
Pasite®	43	43	0.0043
Case 2 children			
Pasite®	16	16	0.0016

Comparison of surface concentrations in shoes and in patch testing:

0.1% dimethyl fumarate on a Finn Chamber® ($d = 8$ mm) with 20 mg patch test preparation will give a surface concentration of 40 µg/cm (2).

The surface concentrations calculated from the red/white shoe samples, leather and non-woven, are 10 and 46 µg/cm (2), respectively.

^aDetection limit for most samples was 0.1 ppm.

^bValue from a sample of the resin reinforced non-woven material in the heel region of the shoe.

Although most of the cases presented in this study probably were due to the FAE included in the anti-mould sachets impregnating the shoe, at least in one of the cases we could demonstrate DMF integrated into a structural component of the shoe. The brown shoe brand 'Gracia from Lian Chang' bought in a Chinese store in Barcelona showed hugely different concentrations of DMF in the two former parts of the shoe, the plastic component (90 ppm) and the fabric (8.4 ppm). This significant difference suggests that DMF was itself a component of the plastic shoe material.

We can conclude that besides sofas and chairs, shoes have been a common source of DMF inducing sensitization and subsequent elicitation of allergic contact dermatitis. Different brands bought from street markets and shoe stores were considered.

In the eastern part of Spain, we have had the opportunity to demonstrate how DMF included in different shoe brands was responsible for customer health impairment. We should consider DMF as a possible allergen in any case of shoe contact dermatitis. DMF is currently employed as an anti-mould in more than one type of manufactured product. In order to avoid the increase in the number of cases, European preventive measures

have been recently developed (24) and should be applied. Global preventive measures for avoiding DMF exposure are required.

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