

Sensitization to dimethyl fumarate with multiple concurrent patch test reactions

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Background: Chairs and sofas imported from China to Europe were shown to contain dimethyl fumarate (DMF), a sensitizing, volatile chemical. Many of the sensitized patients also had positive patch test reactions to acrylates.

Objectives: To analyse the occurrence and strength of DMF sensitization and the appearance of concomitant reactions.

Methods: Patch testing with DMF in concentrations of 0.1–0.00001% was carried out in 37 patients. Diethyl fumarate (DEF), diethyl maleate (DEM), dimethyl maleate (DMM), ethyl acrylate (EA), methyl acrylate (MA), and methyl methacrylate (MMA) were also tested with a dilution series at equimolar concentrations.

Results: The lowest concentration of DMF eliciting a reaction varied between 0.0001% and 0.1% and all but four patients reacted concurrently to DEF. DEM elicited positive patch test reactions in 21/37 patients and DMM reactions were seen in all 9 patients tested. EA elicited positive reactions in 13/37 patients and a positive MA reaction was seen in 7/37 patients, 2 of whom also reacted to MMA.

Conclusions: The strength of the sensitization to DMF showed variation and concurrent reactions were common. Concurrent reactions to (meth)acrylates were seen in patients, who reacted to lower (0.001% or less) DMF concentration probably elicited by cross-reactivity.

Key words: concurrent reactions; contact sensitization; cross-reactions; dimethyl fumarate; patch test.
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Since the autumn 2006 cases of allergic contact dermatitis caused by Chinese sofas and chairs were diagnosed and reported in the United Kingdom, in Finland (1–4), and in France (5). Sensitization to (meth)acrylates was seen in many of the first patients before dimethyl fumarate (DMF) was proven a strong sensitizer in those pieces of furniture (6, 7). The thin layer chromatogram (TLC) strips allow skin testing with separated chemicals extracted from the material (8). DMF was analysed from the skin test positive spot of the TLC strips

prepared from the chair textile extracts (3, 6) and the patients with a furniture-related dermatitis had patch test reactions to DMF. With one exception, the patients had no reactions to other chemicals analysed in the same TLC spot. DMF was also analysed in the sachets inside chairs and sofas (3, 6). In primary skin tests, multiple reactions to (meth)acrylates had been detected (6) and cross-reactivity was suspected. The purpose of this study was to analyse the pattern of sensitization to DMF in patients sensitized from Chinese furniture paying particular attention to

potential cross-reactions to chemicals with structural similarities.

Materials and Methods

Patients

In the United Kingdom and in Finland, 37 patients (13 males and 24 females) were studied. Eight patients had a proven and 29 had suspected furniture-related dermatitis. The patients with a suspected furniture-related dermatitis were also tested with the textile and/or with the content of the sachets and positive reactions were seen in all of them. Nine patients were studied in Finland and 28 patients in the United Kingdom. In each case, the dermatitis had started behind the thighs, on the buttocks, and/or on the back, but the degree of the dermatitis varied from redness and itching to oedematous oozing and painful dermatitis. The extent of the dermatitis also showed remarkable variation from hand-sized patches to extensive skin areas depending on the style and habits of the patients when sitting on sofas and on arm chairs and the positioning of the sachets containing DMF within the furniture (6). The period between the purchase of the new piece of furniture and the appearance of the skin symptoms ranged from few weeks to several months, probably depending on the time spent sitting on the chair or sofa and on the number and location of the DMF sachets in the furniture (6).

Patch test substances

On the basis of the above-mentioned data, a patch test series for the furniture-related dermatitis patients was developed (Table 1). A dilution series of multiple equimolar concentrations of DMF (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), diethyl fumarate (DEF; Sigma-Aldrich Chemie GmbH), diethyl maleate (DEM; Fluka AG, Buchs, Switzerland), dimethyl maleate (DMM; Alfa Aesar GmbH & Co KG, Karlsruhe, Germany), ethyl acrylate (EA; Acros Organics, Geel, Belgium), methyl acrylate (MA; Sigma-Aldrich Chemie GmbH), and methyl methacrylate (MMA; Chemotechnique Diagnostics, Vellinge, Sweden) was tested in patients with suspected or verified furniture dermatitis. The concentrations chosen were equimolar to the concentrations used for the serial dilution of DMF, which consisted of 5–10-fold dilutions from 0.10% w/w in petrolatum (pet.) down to a final concentration of 0.000010%. However, for MMA, the starting and the end points of the dilution series were 10 times higher, on an equimolar basis, than for the other compounds. Patch test preparations were prepared in the laboratory of the Department of

Occupational and Environmental Dermatology in Malmö.

Skin testing

The patch test chemicals were applied to the upper back in Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Venesla, Norway). The test chambers were removed 2 days after the application (D2) and test reactions were read and interpreted 1–3 days after the removal (D3, D4, or D5), according to the International Contact Dermatitis Research Group (ICDRG) criteria.

In Finland, 8 of these patients (patients 1, 2, 4–7, 36 and 37 in Table 2) had been tested with the baseline standard series (Chemotechnique, Vellinge, Sweden), with a modified series of glues and plastics comprising selected (meth)acrylates (EA, 2-hydroxyethyl methacrylate, MMA, ethyleneglycol methacrylate, ethyleneglycol dimethacrylate) (Chemotechnique) and with their own chair or sofa textile or with a corresponding textile 5–10 months earlier. Patients 8–35 (Table 2) were skin tested in the United Kingdom with the patch test series for patients with suspected or confirmed furniture dermatitis. Thus, the UK patients and patient 3 (Table 2) had never been tested with the (meth)acrylates earlier.

Statistical calculations

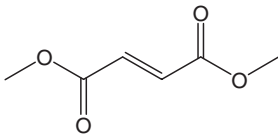
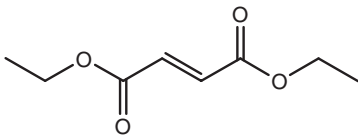
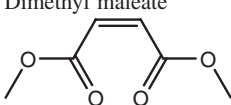
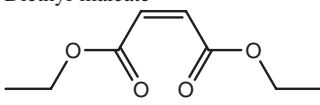
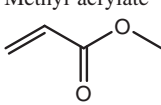
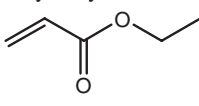
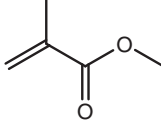
The association between the degree of reactivity judged as the lowest concentration giving at least a positive + reaction to DMF and simultaneous contact allergy to EA and MA, respectively, was calculated with Cochran-Armitage trend test. The association between pairs of the fumarates and maleates, DMF, DMM, DEF, and DEM was investigated with sign test, two-sided. A *P*-value below 0.05 was considered statistically significant.

Results

Patch test reactions to dimethyl fumarate, diethyl fumarate, and to corresponding maleates

Table 2 presents the patch test reactions to the chemicals in the series for suspected or verified furniture-related dermatitis. Patch test reactions to 0.01% DMF were ++ or more in a majority of the patients (22/37) and to 0.1% DMF in 21/23, correspondingly. DMF 0.1% was not tested in 14 patients, since too strong reactions were expected. Two patients had a positive patch test reaction down to 0.0001% DMF concentration and +? was seen in one. A positive patch test reaction to 0.12% DEF was seen in 33/37 patients, who also had positive

Table 1. Patch test series for the furniture-related dermatitis patients

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
			
Dimethyl maleate	624-48-6	144	0.10 0.010 0.0010 0.00010 0.000010
			
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
			

MW, molecular weight; pet., petrolatum.

reactions to DMF and an uncertain +? reaction to DEF was seen in 2 patients. DEM elicited positive patch test reactions in 21/37 patients and positive reactions to DMM were seen in all 9 patients tested.

When statistically calculated, the degree of the reactivity to DMF was significantly higher as compared with the reactivity to DMM, DEF, or DEM (Table 3). The same was true for DEF when

compared with DEM (Table 3), but not for DMM when compared with DEF and DEM (Table 3).

Reactions to (meth)acrylates

EA elicited a positive reaction in 13/37 patients and 1 patient had an uncertain +? reaction. Four patients had a ++ reaction to 0.069% EA (Table 2). A positive MA reaction was seen in 7/37 patients

and 1 patient had a +? reaction. Two patients had a positive reaction to MMA and those patients also had reactions to EA and MA. The concurrent positive reactions to EA, MA, and MMA were most common in patients with a high degree of patch test reactivity to DMF (Table 4 and Fig. 1). The patients with the highest degree of DMF reactivity most often had concurrent positive reactions to EA and MA, respectively ($P = 0.001$ and 0.01). Figure 2 presents concomitant reactions to DMF, DEF, DEM, MA, and EA in patient 3 (Table 2).

Patient 2 (Table 2) had + reactions to EA and MA, although he had no reaction to EA (0.1% pet.; Chemotechnique) when tested 7 months earlier and he had not had (meth)acrylate exposure afterwards. Patient 5 had developed occupational allergic contact dermatitis from artificial nails after primary skin testing with negative EA patch test correspondingly. Now, after sensitization from artificial nails, patient 5 also reacted to 2-hydroxyethyl methacrylate, ethylene glycol dimethacrylate, and to 2-hydroxypropyl methacrylate.

Discussion

There were several positive reactions in many of the patients, who all showed contact sensitization to DMF. Thus, a contamination of the primary sensitizer in other test substances (9, 10) has to be considered. The patch testing with a dilution series of DMF and with possible cross-reacting substances at equimolar concentrations was performed to analyse the primary sensitizer and to define the degree of DMF contamination. The chemical analyses, however, did not show any DMF contamination that could explain the simultaneous reactions to the fumarates, maleates, and acrylates. Concomitant sensitization to these chemicals was excluded, because the TLC strip band, which elicited positive patch test reactions in the patients sensitized from chair materials (6), did not contain DEF, DMM, DEM, or (meth)acrylates, although multiple chemicals were analysed from it (6).

Although structural similarities between DMF and other alkyl esters of fumaric and maleic acids as well as low molecular weight acrylates, such as EA, MA, and MMA, causes expectation of cross-reactivity (see Table 1), alteration of chemical structures in the skin is a noteworthy explanation for

Table 2. Patch test reactions to the chemicals in the series for patients with suspected or confirmed furniture-related dermatitis (spread across the facing page). Read according to international guidelines

[illegible]

the simultaneous positive reactions. In the skin, the isomeric forms of DMF and DMM, on the one hand, and of DEF and DEM, on the other hand, can be expected to form the same complete antigen after having reacted with nucleophilic proteins (11). If the same complete antigens are formed, the patch test reactivity towards the respective alkyl fumarate/maleate (DMF/DMM and DEF/DEM) is expected to be the same. Although only nine patients were tested with both DMF and DMM, there was a statistically significantly higher test reactivity towards DMF than to DMM (Table 3). The same pattern of reactivity is seen when comparing the reactivity to DEF and to DEM, but with a higher degree of statistical significance, because more patients were concomitantly tested with both DEF and DEM (Table 3). The patch test reactivity to DMF is also statistically significantly higher when compared with the ethyl esters of fumaric acid and maleic acid. Again, there is a slight trend towards a larger difference in reactivity between DMF and DEM than between DMF and DEF.

The patch test reactivity to DMF and to DMM, on the one hand, and to DEF and to DEM, on the other hand, was not the same, suggesting different mechanisms leading to positive reactions. However, 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 the degree of the reactivity with proteins in the skin may explain the higher patch test reactivity to DMF and DEF when compared to DMM and DEM, respectively.

DMM is extensively used in different industries. It is used as an additive and intermediate for plastics, pigments, pharmaceuticals, and agricultural products and it is an intermediate for the production of paints, adhesives, and copolymers. DMM has been used to improve the anti-blocking properties of copolymers of vinyl acetate. It is also used as an internal modifier to increase the glass transition temperature of styrene or vinyl chloride polymers. In furniture materials, however, no DMM, DEM, or DEF was detected and the sensitization to DMF, analysed from the materials, is apparent. Since a cutaneous metabolism between fumarates and maleates cannot be excluded multiple mechanisms may be contributing, occasionally leading to extensive reactivity to (meth)acrylates as described earlier (6).

DEF has been described as causing non-immunologic contact urticaria (12) and some patients had a history of swollen skin symptoms conceivably suggesting of immediate contact urticaria. However, primary contact urticaria was not seen in our patients, when tested. Respiratory symptoms were

Table 2. Continued

SW	SW	SW	SW	SW	SW	SW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW
13	14	15	16	17	18	19	20	21	22	23	24	25
f/70	m/62	f/41	f/34	f/62	f/60	f/62	m/41	f/55	f/53	f/50	f/38	m/51
+++	++	++	++	+	++	++	nt	+	++	nt	nt	++
++	+	++	+	–	+	+	++	+	–	++	++	+
+	–	–	–	–	–	–	+	–	–	++	+	–
–	–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–	–
++	+	+	++	+	+	+	nt	+	+	++	nt	+
+	+	+	+	–	–	–	++	–	–	+	–	–
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Continued

experienced by some of our patients and these symptoms have also been reported to be experienced by occasional patients (13). No immunologic mechanism, however, has been shown leading to dyspnea or other respiratory symptoms. One of our patients (patient 2 in Table 2) had been hospitalized in the neurology department, due to neurological symptoms affecting the upper extremities. He had extensive dermatitis of the back and of the upper extremities. Both symptoms then slowly resolved, but minor neurological symptoms in his upper extremities still persisted 2 years later. Besides DMF, multiple chemicals were analysed in the chair textile (6) and it remained unanswered whether some of those chemicals were contributing to the neurological and or to respiratory symptoms.

Fumaric acid esters with DMF have been used as a systemic antipsoriatic medicine (14) and in the treatment of necrobiosis lipoidica (15). Because of moderate efficacy and adverse effects, such as flushing, gastrointestinal upset, and a relative lymphocytopenia, fumaric acid esters have not been an attractive treatment of choice in dermatology. Oral fumarate has been reported useful in the treatment of relapsing multiple sclerosis (16, 17). Among

patients with severe, poorly controlled immunological disease, side-effects may be of less importance, if reasonable efficacy is achieved. In systemic use, DMF apparently modifies immunological responses. In experimental studies, DMF has been shown to have influence on T-cell responses, on interferon- γ (IFN- γ) production, and on expression of immunological markers (18). Inhibition of dendritic cell differentiation by fumaric acid esters has also been documented (19). Immunological effects after percutaneous absorption through inflamed, oozing skin probably are different as compared with those after systemic exposure and they may be unpredictable.

For all patients, the degree of the reactivity was equal or higher for DMF compared with DEF, with maleates, and with acrylates when tested at equimolar concentrations; this favours DMF as the primary sensitizer. Several patients had been exposed to the sensitizer in patch-like areas (diameter was a couple of centimetres), where DMF gradually evaporated from sachets (3, 6). The induction dose of the sensitizer per unit area was high, increasing opportunities for contact sensitization (20). Reactions to (meth)acrylates were most often seen in patients

Table 2. Continued

	Doctor	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	MB/JW	PS	PS
Substance	Patient Sex/age Concentration (% w/w in pet.)	26 f/49	27 f/43	28 m/54	29 f/41	30 m/43	31 f/51	32 f/42	33 f/64	34 m/56	35 m/67	36 m/45	37 f/37
Dimethyl fumarate	0.10	nt	nt	nt	++	++	++	++	nt	++	+++	nt	nt
	0.010	++	++	++	+	++	+	+	++	++	–	++	+
	0.0010	–	++	+	–	–	–	–	++	–	–	+	+
	0.00010	–	–	–	–	–	–	–	+	–	–	–	–
	0.000010	–	–	–	–	–	–	–	–	–	–	nt	nt
Diethyl fumarate	0.12	++	nt	nt	+	++	+	++	++	++	++	nt	nt
	0.012	+	++	++	–	+	+	–	–	+	–	++	+
	0.0012	–	–	+	–	–	–	–	–	–	–	+	+
	0.00012	–	–	–	–	–	–	–	–	–	–	–	–
Diethyl maleate	0.12	+	nt	nt	–	++	+	+	++	++	+	nt	nt
	0.012	–	+	++	–	–	–	–	–	++	–	+	–
	0.0012	–	–	–	–	–	–	–	–	–	–	–	–
	0.00012	–	–	–	–	–	–	–	–	–	–	–	–
Dimethyl maleate	0.1	nt	nt	++	+	nt	++	++	++	nt	++	nt	nt
	0.01	nt	nt	++	–	nt	–	–	–	++	–	nt	nt
	0.001	nt	nt	–	–	nt	–	–	–	–	–	–	–
	0.0001	nt	nt	–	–	nt	–	–	–	–	–	–	–
Methyl acrylate	0.06	–	–	–	–	–	–	–	–	–	–	+	–
	0.006	–	–	–	–	–	–	–	–	–	–	–	–
	0.0006	–	–	–	–	–	–	–	–	–	–	nt	nt
Ethyl acrylate	0.069	–	+	–	–	–	–	–	+	–	–	+	+
	0.069	–	–	–	–	–	–	–	–	–	–	nt	nt
	0.00069	–	–	–	–	–	–	–	–	–	–	nt	nt
Methyl meth acrylate	0.69	–	–	–	–	–	–	–	–	–	–	nt	nt
	0.069	–	–	–	–	–	–	–	–	–	–	nt	nt
	0.0069	–	–	–	–	–	–	–	–	–	–	nt	nt

nt, not tested; pet., petrolatum.

*Tested with 0.1% w/v (Chemotechnique) only.

Table 3. Comparison of individual degrees of patch test reactivity judged as the lowest concentration giving a positive reaction in pairs of dimethyl fumarate, dimethyl maleate, diethyl fumarate, and diethyl maleate using sign test, two-sided

		Dimethyl maleate*	Diethyl fumarate	Diethyl maleate
Dimethyl fumarate	<	0	0	0
	=	3	18	6
	>	6	19	31
	<i>n</i>	9	37	37
	<i>P</i> -value	0.03	<0.001	<0.001
Dimethyl maleate*	<		0	0
	=		7	6
	>		2	3
	<i>n</i>		9	9
	<i>P</i> -value		>0.3	0.25
Diethyl fumarate	<			0
	=			22
	>			13
	<i>n</i>			35**
	<i>P</i> -value			<0.001

<, lower reactivity for the substance to the left of the arrow; =, equal reactivity; >, higher reactivity for the substance to the left of the arrow; *n*, the number of patients tested with pairs of substances.

*Only nine patients were patch tested with dimethyl maleate.

**Two patients, numbers 5 and 24 in Table 2, were not shown to be hypersensitive to diethyl fumarate and diethyl maleate, but not tested with the highest concentration why conclusions on degree of reactivity cannot be drawn.

with high degree of sensitization to DMF. Sensitization to EA or MA was seen in slightly more than one third of the patients. In all but two cases, the patients had + or ++ reactions to 0.001% DMF concurrently and they also had reactions to DEF, DEM, or DMM. Patient 5, however, was an exception. She

Table 4. The distribution of positive patch test reactions to ethyl acrylate, methyl acrylate, and methyl methacrylate, respectively, in 37 to dimethyl fumarate reacting patients, with regard to the degree of reactivity to dimethyl fumarate judged as the lowest concentration eliciting at least a + reaction

	Patch test reactivity to dimethyl fumarate in % w/v			
	0.1	0.01	0.001	0.0001
<i>n</i>	5	18	12	2
Ethyl acrylate	0	4 (22%)	7 (58%)	2 (100%)
Methyl acrylate	0	2 (11%)	3 (25%)	2 (100%)
Methyl methacrylate	0	0	1	1

developed an occupational hand dermatitis caused by acrylate nails after the episode of 'chair dermatitis'. This patient reacted to the chair textile without reactions to acrylates before she started as a nail stylist. In that profession she developed occupational allergic dermatitis within 4–6 months. Sensitization to acrylates is common among people who make artificial nails (21, 22). This patient had a positive patch test reaction to 0.01% DMF without reactions to DEF and to maleates tested. Acrylate sensitization seemed to be a separate phenomenon in this particular patient. Patient 2, instead, had no (meth)acrylate exposure. He developed positive patch test reactions to EA, and to MA having been EA negative 7 months earlier. In that patient active sensitization via primary testing cannot be excluded, since (meth)acrylates have been considered as potential sensitizers, when repeatedly tested (23). However, an equally likely explanation is variation in patch test reactivity between the two occasions as the patient only tested positively to the highest concentrations with weak positive reactions to EA and to MA. Cross-reactivity probably played

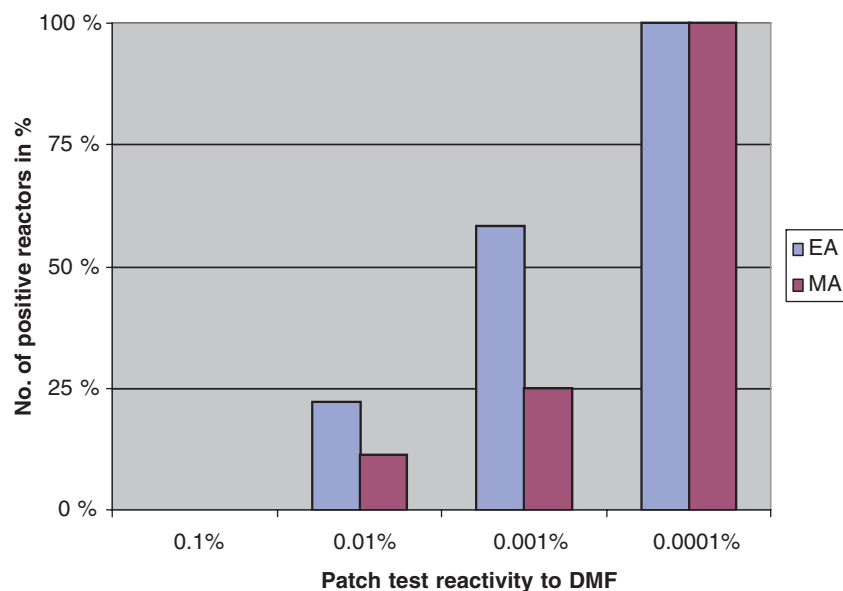


Fig. 1. Patch test reactivity to dimethyl fumarate (DMF) judged as the lowest concentration giving at least a + reaction and the occurrence (*n* as seen in Table 4) of positive reactions to ethyl acrylate (EA) and to methyl acrylate (MA).

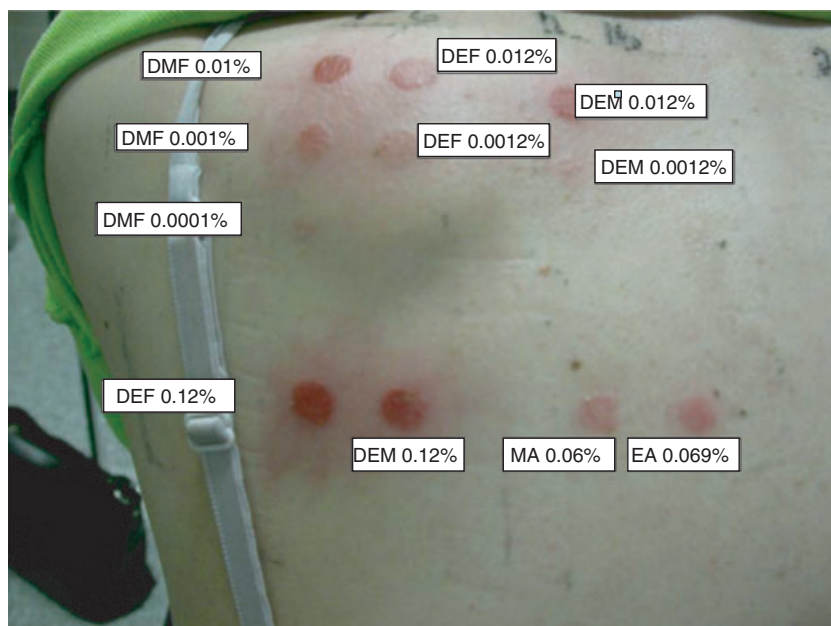


Fig. 2. Concurrent patch test reactions to different concentrations of dimethyl fumarate (DMF), diethyl fumarate (DEF), diethyl maleate (DEM), ethyl acrylate (EA), and to methyl acrylate (MA) in patient 3 (Table 2).

a role even in that patient, as he had extensive reactions to DEF and to DEM, too. MA had not been tested in initial testing. On the basis of lymph node assay analysis, EA has been regarded as a weak sensitizer (24) and it is not one of the most common sensitizers, in dentistry (25, 26), in glues (27), and in artificial nails (21, 22). At the same time the patient had negative tests to the other chemicals analysed in the skin test positive TLC spot and non-specific reactivity was not suspected.

In conclusion, the patients with strong sensitization to low concentrations of DMF had multiple concurrent reactions to DEF, DEM, and DMM. Reactions to (meth)acrylates were seen in patients with multiple reactions to fumarates and maleates.

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