

Active sensitization and contact allergy to methyl 2-octynoate

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Background: Methyl 2-octynoate is a synthetic fragrance which was first described to have sensitizing properties in 1935. It is one of the 26 fragrances to be labelled on the ingredient list according to current European cosmetics regulation.

Objectives: To report the experience with patch testing with methyl 2-octynoate 1% and 2% in pet.

Methods: 230 eczema patients were consecutively patch tested with 1% methyl 2-octynoate at department of Dermato-allergology Gentofte Hospital, Denmark and 120 eczema patients were consecutively patch tested with 2% M2O in Finn Chambers® at the Département de Dermatologie, CHU Saint Jacques, France.

Results: Three cases of active sensitization were observed. 2 (0.87%) of the 230 Danish subjects tested with 1% in pet. and of the 120 French subjects patch tested with 2% in pet. 1 (0.83%). There was no statistical difference in active sensitization between the two groups ($P = 0.72$). Allergic contact dermatitis was observed in two patients (1.67%) in the French group and none in the Danish group.

Conclusion: Contact allergy to methyl 2-octynoate was frequently seen when patch testing with 2% in pet. However, active sensitization was also observed, when patch testing with concentrations of 1% and 2% methyl 2-octynoate. The patch test concentration should be below 1% in pet., but a safe concentration remains to be defined.

Key words: active sensitization; allergenic degradation product; methyl heptene carbonate; fragrance; methyl 2-octynoate. © John Wiley & Sons A/S, 2010.

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Introduction

Methyl 2-octynoate (CAS 111-12-6) is a fragrance chemical with strong allergenic properties (1), which has been known for decades (2, 3). It is also known as methyl heptene carbonate. It is one of the 26 fragrance chemicals to be specifically declared by name on the ingredient label of cosmetic products according to Article 6 of the Cosmetic Directive when concentrations exceeds 0.001% in leave on cosmetic products, and 0.01% in rinse-off cosmetic products (4). A maximum authorized concentration in the finished cosmetic product is set at 0.01%. If the fragrance is applied in combination with methyl octine carbonate,

which is a related fragrance compound, the level of maximum authorized concentration in the finished product should not be more than 0.002% of methyl 2-octynoate and their combined concentration should not exceed 0.01% (4). In their recent guidelines, the International Fragrance Association (IFRA) have set lower acceptable limits of methyl 2-octynoate in some types of cosmetic products (5). The restrictions on the use of methyl 2-octynoate are based on its sensitizing effect and indicate the awareness of its strong allergenic potential. Methyl octine carbonate has a synergistic effect with methyl 2-octynoate, which is why when used in combination the restricted concentrations are even more limited (6).

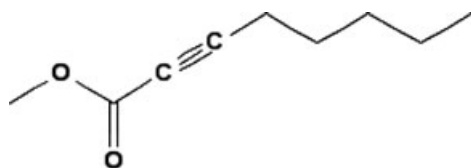


Fig. 1. Methyl 2-octynoate.

In this study, we report our experience with patch testing with methyl 2-octynoate in Danish and French eczema population.

Material & Method

A total of 350 eczema patients were consecutively patch tested with methyl 2-octynoate; 120 subjects were tested at the department of Dermatologie at CHU Saint Jacques, France (French group), and 230 at the department of Dermato-allergology at Gentofte Hospital, Denmark (Danish group) as part of routine investigation.

The Danish subjects were tested in the period August 2007 to June 2008, the female/male ratio was 2.3 and the average age was 45.5 (SD 16.8) ranging from 16–93 years). Demographic characteristics of all subjects patch tested in the Danish group are shown according to the MOAHLFA index (Table 1). The French MOAHLFA index was not available.

The patch tests were performed according to international guidelines (7) using Finn Chambers® (8 mm; Epitest Ltd Oy, Tuusula, Finland) applied on the back with Scanpor tape® (Norgesplaster A/S, Amphora As, Norway). The Danish department tested with methyl 2-octynoate 1% supplied by Trolab® (Hermal, Reinbek, Germany). The French department tested with methyl 2-octynoate 2% and also tested with methyl octine carbonate (CAS 111-80-8) at 2% in pet. The supplier of both substances was Dior, and the substances were diluted by a

chemist connected to the department. Readings were done on D2, D3 or D4 and D7 according to the recommendations of the International Contact Dermatitis Research group (8).

Statistics

Crude percentages of positive reactions, active sensitization and concomitant reactions between methyl 2-octynoate and methyl octine carbonate were performed. Fisher's exact test was done in www.openepi.com. *P* values below 0.05 were considered significant.

Results and Case Reports

Among the 120 French subjects tested with 2% methyl 2-octynoate, two (1.67%) reacted positive and none of the Danish subjects tested with methyl 2-octynoate 1% had positive reactions. There was no statistical difference between the two groups (*P* = 0.12 Fisher exact) (Table 2).

Subjects with a positive patch test reaction were found positive at D4 (2+) and at D2/D4 (2+/1+), respectively. They also reacted towards many other fragrance markers including mixes of allergens such as lavender oil, narcissus absolute, and ylang ylang, and one also reacted towards methyl octine carbonate.

One irritant reaction and one doubtful reaction were observed in the Danish group.

Three incidences of active sensitization from patch testing with methyl 2-octynoate were observed and are described below. The frequency of active sensitization was 0.83% in the French group and 0.87% in the Danish group; there was no significant difference between the frequencies of active sensitization (*P* = 0.72 Fisher exact) (Table 2).

Case 1

A 42-year-old woman was investigated for post-surgical allergic contact dermatitis at the department of Dermatologie at CHU Saint Jacques, France. She previously had a reaction towards deodorants and was also tested with a fragrance series. Readings at D2 and D4 showed reactions towards nickel sulphate (++). At D16 she experienced pruritus around two erythematous, oedematous round marks on her back and a blister developed. On D37 she was seen again at the dermatology department as part of a systematic review and there were two dry, erythematous round marks concurrence to the areas where methyl 2-octynoate 2% pet. and methyl octine carbonate 2% pet. had been tested. She was not repeat patch tested.

Table 1. MOAHLFA index of the subjects tested with methyl 2-octynoate at the Department of Dermato-allergology at Gentofte Hospital, Denmark

	Subjects tested to methyl 2-octynoate	
	n	%
M	69	30.0
O	54	23.5
A	57	24.8
H	95	41.3
L	9	3.9
F	32	27.0
A	150	65.2
Total	230	100

M, male; O, occupational causation of dermatitis; A, atopy; H, hand dermatitis; L, leg dermatitis; F, face affected by dermatitis; A, age above or equal to 40 years.

Table 2. Patch reactions to methyl 2-octynoate and concomitant reactions to methyl octine carbonate

Centre	Methyl 2-octynoate	Numbers tested	Positives (+, + +, + + +)			Patch test reactions to methyl octine carbonate 2%			Concomitant reactions to methyl octine carbonate 2%			Active sensitization		
			n	%	Fisher's test	n	%		n	%		n	%	Fisher's test
French group	2% pet.	120	2	1.67	$P = 0.12$	1	0.83		1	0.83		1	0.83	$P = 0.72$
Danish group	1% pet.	230	0	0		0	–		2	0.87				

Case 2

A 28-year-old woman with facial eczema not responding to treatments was referred to the Department of Dermato-allergology at Gentofte Hospital, Denmark. She had a history of eczema in the flexural aspects of the lower and upper extremities but had never received the diagnosis of atopic eczema. She was patch tested with the European baseline series, extended series, and fragrance series. Reactions were observed to nickel sulphate 5% in pet. and to methylchloroisothiazolone/methylisothiazolinone (3:1) 0.01% in aqua. At D20 she was seen again at the dermatology department because of a late reaction to one of the fragrance substances. Repeat patch testing a week later with the fragrance series revealed a 1+ towards methyl 2-octynoate 1% pet. at D2.

Case 3

A 21-year-old woman suspected of occupational hand eczema was referred to the department of Dermato-allergology at Gentofte Hospital, Denmark. She was working at a café as a waitress with frequent hand washing and handling of food. She had no prior skin diseases. She was patch tested with the European baseline series, extended series, fragrance series, and prick tested with a standard series and food series. All tests were negative and the hand eczema cleared after being treated with steroid cream (mometasone furoate 0.1%). It was not considered to be occupationally related. Four weeks later she reconsulted with a pruritic area on her back; a well-demarcated extremely infiltrated erythematous plaque was observed at the area where one of the fragrances had been tested. She was retested with the fragrance series a week later. At D2 a 2+ reaction towards methyl 2-octynoate 1% in pet. was observed.

Discussion

We report three cases of late patch test reactions (2–4 weeks) towards methyl 2-octynoate. Two were retested and both were positive, which indicates that sensitization was induced by the patch testing procedure. Case 1 was not retested but the late reaction was most likely due to active sensitization based on the case history. The definition of

active sensitization is 'a negative patch test with a flare up after 10–20 days, and a positive reaction within a few days after retesting with the suspected substance' (9). In addition, it is necessary to determine if there had been any previous contact with the allergen, and if so the patch test reaction could be attributed to a booster effect and not a sign of active sensitization. This may be difficult in the case of reactions to fragrance ingredients as everybody is exposed, however, the clinical aspects observed in the three cases are typical of the active sensitization (10).

Active sensitization occurs when the patch test concentration of the allergen is too high in relation to its allergenic potency (11). It is a rare complication (12, 13) and consequences have been little investigated, some studies indicate that it has little to no clinical relevance (12, 13). However, it is an unwanted and potential serious adverse effect as sensitized subjects acquire a lifelong allergy.

Methyl 2-octynoate is available from both Trolab® (Almirall-Hermal, Reinbeck, Germany) and Chemotechnique Diagnostics® (Vellinge, Sweden) at a patch test concentration of 1%. This choice of patch test concentration is probably based on data from the Information Network of Departments of Dermatology (IVDK) in Germany, where 1% methyl 2-octynoate was consecutively patch tested in 2401 subjects without recording of any cases of active sensitization (14), however, no late readings (beyond D7) were included in the study.

A review from 2006 (1) refers to a study being conducted of induction with 5% methyl 2-octynoate on 45 healthy subjects, and when retested with 1% methyl 2-octynoate a sensitization rate of 13.3% ($n = 6$) was found. The knowledge of this substance's ability to cause active sensitization in patch test concentrations as low as 1% is new and shows that patch testing with methyl 2-octynoate at 1% in pet. is too high a concentration.

Allergic contact dermatitis towards methyl 2-octynoate was first described in 1935 (2,3) and as several reports have followed (3,6,15,16), most are more than 20 years old. One study among patients suspected of a cosmetic allergy revealed a prevalence of positive patch tests of 1.1% towards methyl 2-octynoate 0.5% in pet. among 182 subjects (17). This study also investigated cosmetic products ($n =$

79) brought in by the subjects for the presence of M2O as an ingredient and found three to contain methyl 2-octynoate (17). An American study (18) among subjects consecutively patch tested with 1% methyl 2-octynoate found one positive reaction in 278 tested (0.4%). The largest study was the IVDK study testing with methyl 2-octynoate 1% mentioned above which found 6 (0.2%) allergic reactions, 12 doubtful or irritant reactions.

A recent study of fragrance labelling did not find methyl 2-octynoate to be labelled on any of the 300 fragrance products investigated (19). This could be because methyl 2-octynoate is not used very often in cosmetic products or it is used in concentrations lower than requires labelling (0.01%).

Animal and human studies have been conducted to describe the allergenic profile of methyl 2-octynoate mainly by the Research Institute for Fragrance Materials (RIFM), which are unpublished. Apparently a Local Lymph Node Assay (LLNA) study showed methyl 2-octynoate to be a strong sensitizer (5). Opdyke likewise described studies which indicated methyl 2-octynoate as having strong sensitizing properties, but not when freshly distilled preparations were tested. Only when a time-lapse had occurred did the test material appear to have a very powerful sensitizing capacity (21). The accumulating component could not be explained by auto oxidation or peroxidation (20). It is further argued that a degradation product not yet identified is the allergen and it might be the same degradation product for methyl 2-octynoate and methyl octine carbonate (6). However, no data has been published to support this.

De Groot suggested a patch test concentration of methyl 2-octynoate at 0.5% in pet. and a non-irritating patch test conducted at 2% in pet. based on the literature (21).

The restriction concentration of methyl 2-octynoate in cosmetic products is currently set at 0.01% which is 100–200 times lower than the doses our subjects were exposed to at respectively 1% and 2%. It is common that the patch test concentrations of fragrances are higher than the doses actually applied in the cosmetic products because it enables detection of allergic reactions when tests are conducted in a short period and on a small surface area. Nonetheless, this discrepancy in the concentration used in patch testing and the concentration allowed in cosmetic products is large, and suggest that adverse reactions might have been anticipated, as we have observed.

A study concerning the optimal patch test concentration of methyl 2-octynoate and other of the labelled fragrance allergens is currently being conducted by a group under the European Society of Contact Dermatitis. The recommended patch test

concentration of methyl 2-octynoate will be 0.2% w/w% in pet., when 20 mg is applied in ordinary (8 mm) Finn chambers® (Personal communication M. Bruze).

Conclusion

Contact allergy to methyl 2-octynoate was frequently detected when testing with 2% in pet., however, this patch test concentration is too high as methyl 2-octynoate has a strong sensitization potential.

A patch test concentration of methyl 2-octynoate at 1% in pet. or above is too high and may lead to active sensitization as observed in this study.

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