

Fragrance mix II in the baseline series contributes significantly to detection of fragrance allergy

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Background: Fragrance mix II (FM II) is a relatively new screening marker for fragrance contact allergy. It was introduced in the patch test baseline series in Denmark in 2005 and contains six different fragrance chemicals commonly present in cosmetic products and which are known allergens.

Aim: To investigate the diagnostic contribution of including FM II in the baseline series by comparing it with other screening markers of fragrance allergy: fragrance mix I (FM I), *Myroxylon pereirae* and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC).

Method: Retrospective study of 12 302 patients consecutively patch tested with FM II by members of the Danish Contact Dermatitis Group 2005–2008.

Results: FM II gave a positive patch test in 553 patients (4.5%), and in 72.2% of these patients the reaction was judged to be clinically relevant. FM II ranked second in detecting fragrance allergy, after FM I. If FM II had not been included as a screening marker in the baseline series, 15.6% ($n = 202$) of individuals with fragrance allergy would not have been identified by the other fragrance screening markers (FM I, *M. pereirae* or HICC).

Conclusion: FM II contributes substantially to detecting fragrance allergy. It ranked second among the fragrance screening markers tested in the baseline series and detects individuals with an allergy who otherwise would not have been identified.

Key words: allergic contact dermatitis; clinical relevance of a patch test; cosmetics; FM II; fragrance; fragrance mix II. © John Wiley & Sons A/S, 2010.

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Fragrance contact allergy is caused mainly by exposure to cosmetic products, but exposures to household and industrial products may contribute (1). The most common fragrance allergens are included in the European baseline series (2). However,

because the fragrance ingredients consumers are exposed to through cosmetic products are continually changing (3), a new screening marker of fragrance allergy, the fragrance mix II (FM II), was introduced (4). FM II consists of six

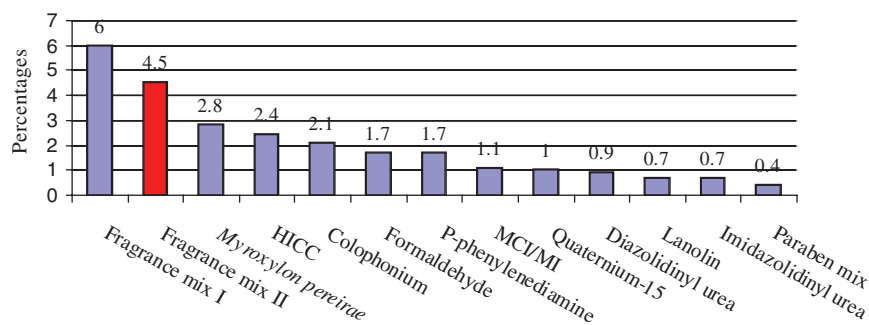


Fig. 1. Prevalences of positive patch test reactions to screening markers associated with cosmetic allergy among 12 302 subjects. HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.

different fragrance compounds [hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), citral, farnesol, coumarin, citronellol, and α -hexyl cinnamal], all known to have sensitization properties and which are used in cosmetics (5). In Denmark FM II was introduced in the European baseline series in 2005 together with HICC with the aim of detecting more fragrance allergic individuals.

The objective of this study was to evaluate the contribution of FM II as a screening marker of fragrance allergy in a large population in comparison with other markers in the baseline series.

Material

Data were retrieved from a clinical database where the Danish Contact Dermatitis Group (DCDG) contributes with information. At the time of study DCDG comprised three dermatology departments (University Hospitals in Gentofte, Odense and Århus), and seven dermatology practices (Rødovre, Aalborg, Herning, Vejle, Bagsværd, Hørsholm, and Kalundborg). We included subjects patch tested with FM II in the baseline series. Testing spanned 2005–2008 as the FM II was introduced in the patch test baseline series in 2005. We included 12 302 subjects: 8063 females and 4239 males, mean age 44.8 years (± 18.2 ; range 1–97 years). Table 1 shows the group's demographic characteristics.

The patch test results of subjects tested with FM II were compared with patch test results of other fragrance screening markers and also to other markers associated with cosmetic ingredient allergy (Fig. 1). The fragrance screening markers were fragrance mix I (FM I) 8% petrolatum (pet.), HICC 5% pet., *Myroxylon pereirae* 25% pet., and colophonium 20% pet. Colophonium is considered a fragrance marker as it is used in cosmetics and may cross-react with *M. pereirae* and FM I (6). However, allergy to colophonium from adhesives (colophonium or its derivatives) used in footwear (7), paper, diapers, and sanitary wear is also common (8). This may make colophonium a less specific marker of

Table 1. MOAHLFA index of consecutively patch-tested eczema patients and patients with a positive patch test reactions to fragrance mix II (FM II)

Index	Tested subjects		FM II positive	
	Numbers	%	Numbers	%
M	4239	34.5	136*	24.6
O	1468	11.9	71	12.8
A	2109	17.1	103	18.6
H	4619	37.5	220	39.8
L	625	5.1	24	4.3
F	2287	18.6	129*	23.3
AA	7389	60.1	329	59.5
Total	12 302	100	553	100

MOAHLFA index is an initialization: M: male; O: occupational causation of dermatitis; A: atopy; H: hand dermatitis; L: leg dermatitis; F: face affected by dermatitis; and AA: Age ≥ 40 years. * χ^2 -test, $P < 0.05$.

fragrance allergy; consequently, comparisons of fragrance allergy in this study were done both with and without colophonium.

The other cosmetic-related screening markers were formaldehyde 1% aq., quaternium-15 1% pet., diazolidinyl urea 2% pet., imidazolidinyl urea 2% pet., *p*-phenylenediamine 1% pet., methylchloroisothiazolinone (and) methylisothiazolinone (MCI/MI) 0.01% aq., paraben mix 16% pet., and lanolin 30% pet.

FM II 14% consists of six different fragrances: 2.5% HICC, 1% citral, 2.5% farnesol, 2.5% coumarin, 0.5% citronellol, and 5% α -hexyl cinnamal in pet.

Clinical relevance was evaluated and registered according to standardized guidelines set by DCDG. In this study, clinical relevance covers current and/or past relevance based on (i) medical history, (ii) results of patch and/or use tests, (iii) ingredient labelling, or (iv) chemical analysis.

Methods

DCDG members used three different suppliers of the compounds tested: (i) TRUE Test® (MEKOS

Laboratories AS, Denmark), (ii) Trolab® (Hermal, Reinbeck, Germany), and (iii) Chemotechnique® (Chemotechnique Diagnostics, Vellinge, Sweden). The concordance rate between test material from different suppliers is generally high (9, 10), and in this study all materials were viewed as equal. No comparison of allergy rates was conducted between the different suppliers in this study.

The patch tests were done according to international guidelines (11) using Finn Chambers® (8 mm; Epitest Ltd Oy, Tuusula, Finland) applied on the back with Scanpor® tape (Norgesplaster A/S, Alfarma, As, Norway) and occluded for two days. Readings were done on D3 or D4 according to the recommendation of the International Contact Dermatitis Research group (12). Positive patch test reactions of +, ++, and +++ were defined as a contact allergy. An irritant reaction, a doubtful reaction (+?), or a negative reading was interpreted as a negative response.

Statistics

Data administration and statistical analysis were done in SPSS® version 15. Demographic characteristics of subjects tested with FM II were registered according to the MOAHLFA index (Table 1). FM II was compared with 12 other screening markers associated with cosmetics shown as crude percentages of positive patch test reactions and clinically relevant reactions. The prevalence of cumulative fragrance allergy frequency was determined and expresses the number of patients with a positive patch test to one or more fragrances among all the subjects tested. Likewise, a prevalence of 'preservative allergy' was determined. Concomitant reactions were determined between FM II and other fragrance markers and also their association, which are expressed by odds ratios (ORs) with 95% confidence intervals (CIs). The OR expresses the odds of having a positive patch test to FM II and a positive patch test to the investigated marker. χ^2 tests were performed. *P* values below 0.05 were considered significant.

Results

A positive reaction to FM II among 12 302 consecutively patch-tested individuals was observed in 4.5% (*n* = 553). The sex distribution was uneven: 417 females and 136 males, which is a significant overrepresentation of females (*P* < 0.001), OR = 1.6 (CI 1.4–2.0) expressing the OR of females having a positive patch test compared to males. There was a significant association between FM II allergy and facial dermatitis (Table 1). A positive patch test reaction to one or more of the fragrance markers (FM I, FM II, *M. pereirae* and HICC) was detected in 1298 (10.6%) of the participants. If colophonium was included as a fragrance screening marker, 1484 (12.1%) subjects had a positive patch test reaction. Allergy to fragrances had a higher prevalence than did allergy to other potential cosmetic ingredients: preservatives 4.0% (*n* = 491), *p*-phenylenediamine 1.7% (*n* = 196), or lanolin 0.7% (*n* = 90) (Table 2).

Clinical relevance of a positive patch test to FM I, FM II, and HICC were all above 70%, whereas *M. pereirae* and colophonium had approximately 50% of the reactions judged to be clinically relevant. None of the other screening markers had the same high prevalences of clinical relevance as FM I, FM II, and HICC (Table 3).

Concomitant reactions between FM II and each of the other fragrance markers are illustrated for each marker in Fig. 2a–d. There was a significant association between a positive reaction to each of the fragrance markers and FM II allergic subjects. In particular, HICC and FM II had a strong association with 243 (40.4%) concomitant reactions and an OR of 187.2. HICC alone identified 292 patients with fragrance allergy. If HICC had not been included as a screening marker, 49 subjects (16.8%) would not have been detected by only testing with FM II (Fig. 2c). The FM I identified 737 subjects with fragrance allergy, which is 56.3% of all patients (1298) with a positive patch test to one or more of the fragrance allergy markers (FM I, FM II, HICC, and *M. pereirae*). When comparing FM II allergic patients with the cumulative number of subjects with an allergy to FM I, *M. pereirae*, and

Table 2. Prevalences of allergy to 'fragrances', 'preservatives', hair dye, and other markers related to cosmetics

Screening markers related to cosmetics		Number of positive patch tests (%)	
Fragrance	Fragrance mix I, fragrance mix II, <i>Myroxylon pereirae</i> , and hydroxyisohexyl 3-cyclohexene carboxaldehyde	1298	(10.6)
	Fragrance mix I, fragrance mix II, <i>Myroxylon pereirae</i> , hydroxyisohexyl 3-cyclohexene carboxaldehyde, and colophonium	1484	(12.1)
Preservative	Formaldehyde, quaternium-15, diazolidinyl urea, imidazolidinyl urea, methylchloroisothiazolinone/methylisothiazolinone, paraben mix	491	(4.0)
Hair dye	<i>p</i> -phenylenediamine	209	(1.7)
Other marker	Lanolin	90	(0.7)

Numbers patch-tested: 12 302.

Table 3. Prevalence of clinically relevant patch test reactions

Screening markers	Numbers positive	Numbers relevant in regard of eczema (%)
A: Fragrance mix I	737	523 (71.0)
A: Fragrance mix II	553	399 (72.2)
A: <i>Myroxylon pereirae</i>	347	175 (50.4)
A: Hydroxyisohexyl 3-cyclohexene carboxaldehyde	292	224 (76.7)
B: Colophonium	262	124 (47.3)
C: <i>p</i> -phenylenediamine	209	108 (51.7)
D: Formaldehyde	204	105 (51.5)
D: MCI/MI	134	66 (49.3)
D: Quaternium-15	126	62 (62.2)
D: Diazolidinyl urea	111	47 (42.3)
E: Lanolin	90	44 (48.9)
D: Imidazolidinyl urea	78	27 (34.6)
D: Paraben mix	49	25 (51.0)
Cosmetic allergy	2034	1286 (63.2)

Markers of: A: fragrance allergy; B: Colophonium associated with fragrances; C: Hair colouring agent; D: Preservatives; and E: Lanolin. MCI/MI = methylchlorisothiazolinone/methylisothiazolinone.

HICC, concomitant reactions were observed in 351 individuals. As FM II alone identified 553 allergic subjects, 15.6% of the FM II allergic subjects ($n = 202$) would not be detected by the other standard fragrance screening markers FM I, *M. pereirae*, and HICC (Fig. 3). A similar comparison was conducted between the group of subjects with an allergy to FM II and/or HICC and the group of subjects allergic to one or more of the other fragrance markers FM I, *M. pereirae*, and/or colophonium (Table 4). The comparison shows that FM II and HICC would

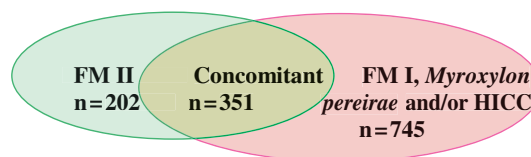


Fig. 3. Illustration of concomitant reactions to fragrance mix II (FM II) and subjects allergic to fragrance mix I (FM I), *Myroxylon pereirae*, and/or hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). Subjects with fragrance allergy identified with FM II, FM I, *Myroxylon pereirae* and HICC ($n = 1298$). FM II additionally identified 202 (15.6%) allergic subjects.

identify additionally 338 (26.0%) fragrance allergic individuals as opposed to only testing with FM I and *M. pereirae*. When including colophonium as a fragrance screening marker, 322 fragrance allergic subjects would still be missed, if not testing with FM II and HICC, which is only 16 more subjects being identified when including colophonium (Table 4).

Discussion

Fragrance contact allergy is common among eczema patients in Denmark. In this study, 10.6% (1298) of patch-tested eczema patients ($n = 12302$) were fragrance allergic. This makes fragrance allergy the second most common cause of contact allergy after nickel, in accordance with other studies (13–15).

FM II identified 553 (4.5%) patients with a fragrance allergy and thus ranked second in the detection of fragrance allergy and in detecting allergy to cosmetic ingredients. There were significantly

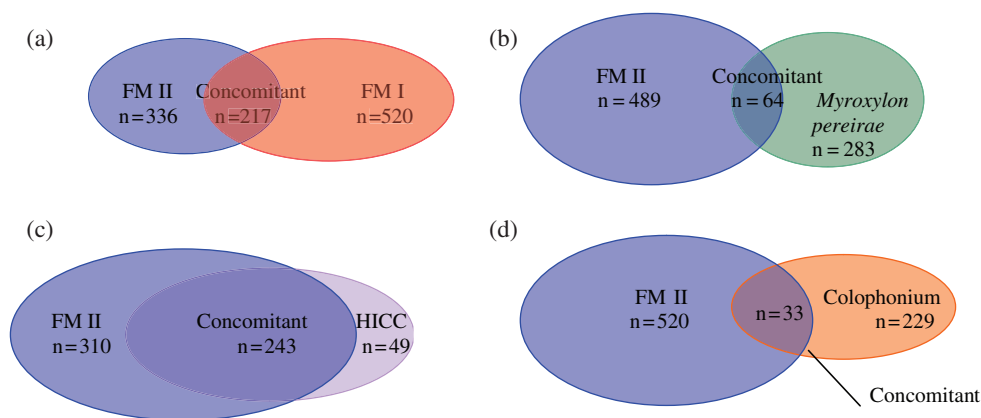


Fig. 2. (a) Illustration of concomitant reactions to fragrance mix II (FM II) and fragrance mix I (FM I). Subjects with fragrance allergy identified by FM II and FM I = 1073. A significant statistical association was observed between the two groups, χ^2 , $P < 0.0000001$. OR = 14.0 (CI 11.5–16.9). (b) Illustration of concomitant reactions to fragrance mix II (FM II) and *Myroxylon pereirae*. Subjects with fragrance allergy identified by FM II and *Myroxylon pereirae* = 836. A significant statistical association between the two groups was observed, χ^2 , $P < 0.0000001$. OR = 5.3 (CI 4.0–7.1). (c) Illustration of concomitant reactions to fragrance mix II (FM II) and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). Subjects with fragrance allergy identified by FM II and HICC = 602. A significant statistical association was observed between the two groups, χ^2 , $P < 0.000001$. OR = 187.2 (CI 135.3–259.6). (d) Illustration of concomitant reactions to fragrance mix II (FM II) and colophonium. Subjects with fragrance allergy identified by FM II and colophonium = 782. A significant statistical association was observed among the two groups, χ^2 , $P < 0.0000001$. OR = 3.2 (CI 2.2–4.7).

Table 4. Comparison of patch test reactions to fragrance mix II (FM II) and/or hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) with other markers of fragrance allergy: fragrance mix I (FMI) and *Myroxylon pereirae* (Group 1) and FM I, *Myroxylon pereirae* and colophonium (Group 2)

		Other fragrance screening markers (FM I, <i>Myroxylon pereirae</i> , and/or colophonium)				
		Positive		Negative		Total
		Group 1	Group 2	Group 1	Group 2	
FM II	Positive	264	280	338	322	602
and/or	Negative	696	882	11 004	10 818	11 700
HICC	Total	960	1162	11 342	11 140	12 302

A significant positive association was found between positive reactions to FM II and/or HICC and to one or more positive reactions to the other screening markers (χ^2 test, $P < 0.001$).

more females than males with allergy to FM II, OR = 1.6. This sex difference has been reported in other studies on fragrance allergy (13, 15–17), only one recent publication (18) reports the opposite, where FM II was significantly more frequent among males. The discrepancy compared to our study may be because of different age distribution among males and females or because of exposure differences.

Facial dermatitis was significantly more common among patients with a positive patch test to FM II and is viewed as a classical manifestation of fragrance allergy (6, 19, 20).

Most of the positive patch test reactions (>70%) to FM II were of clinical relevance as were the reactions to HICC and FM I (Table 3). These relatively high frequencies of clinical relevance imply that the tests have a high diagnostic value. *M. pereirae*, however, differed from the other three markers of fragrance allergy in having a much lower frequency of clinical relevance at 50.4%. This could imply that *M. pereirae* is not as specific a marker of fragrance allergy as the other fragrance markers, or it could reflect the difficulty in establishing *M. pereirae* exposure sources. The use of *M. pereirae* in cosmetics as a fragrance is banned in the EU but extracts of *M. pereirae* are allowed up to a maximum of 0.4% concentration and is not required to be labelled as a fragrance ingredient. *M. pereirae* may also be used in other products than cosmetics where labelling is not required. Likewise, colophonium had a clinical relevance of less than 50% because of the same reasons as for *M. pereirae*.

A decrease in prevalence of positive patch test reactions to FM I have been reported in recent studies (15, 17, 21); nevertheless, it is the screening marker of fragrance allergy with the highest prevalence of positive reactions, 6.0% in our study. If, however, FM I had been used as the sole screening marker in our study, only 56.8% of the patients

with fragrance allergy would have been identified. This is a lower figure than described by Larsen in 1998 (22), who estimated that FM I would identify 67% of all fragrance allergic patients. The declining prevalence of allergy measured with FM I is not an indication of a decline in fragrance allergy in general, but rather a likely result of a change in fragrances' composition and exposure (3).

HICC is one of the six fragrance compounds constituting the FM II and is also tested as a single compound with twice the concentration (HICC 5%). Concomitant reactions were anticipated between HICC and FM II and occurred in 40.4% of subjects positive to HICC and/or FM II. If HICC had not been tested as a single compound but only as a constituent of FM II, 16.8% of the HICC allergic patients would have been missed, confirming HICC as an important individual screening marker for fragrance allergy (17, 23–25). HICC and FM II have a complementary effect as some are detected by the individual fragrance and even more by FM II. We did not investigate the complementary effect of testing with the other individual fragrances constituting FM II, but a similar effect would be anticipated, as observed when testing with FM I and its individual fragrances. A previous study, where 1701 subjects were tested with FM II and its individual fragrances (24), reports of 50 subjects with a positive patch test reaction to FM II (14%), and of these 48% would have been detected by the individual fragrances. Further studies with larger study populations are needed on this subject to draw any conclusion.

The relatively high prevalences of allergy to HICC reported in this study (2.4%) and also in other studies (17, 24, 26, 27) might be the result of its frequent use in cosmetic products (28) and the use of high concentrations compared to the safe use dose (29–31). A study from the UK showed that almost 30% of 300 cosmetic and household products contained HICC (32), and in a Danish study, 72% of 25 cosmetic products contained HICC (28). According to the EU Cosmetic Directive HICC is one of the 26 fragrances to be declared specifically on the ingredient label of cosmetic products, when present at doses of 0.001% in leave-on products and 0.01% in rinse-off products (33). The European Commission's Scientific Committee on Consumer Products (SCCP) recommended 200 ppm as maximum amount of HICC in cosmetic products (34) and International Fragrance Association (IFRA) has recently further limited their recommended HICC concentrations (35). Despite these attempts to diminish the high exposure to HICC, no decrease in allergy has yet been observed (23).

It is not known if other fragrance ingredients with a similar scent and allergenic potential are used to

substitute HICC or other of the FM II ingredients, as observed for isoeugenol in FM I (36). Another issue of relevance for prevention is auto-oxidation of FM II ingredients and formation of more allergenic oxidation products. Geranial, which is a component of citral, one of the ingredients in FM II, can oxidize to epoxygeranial, which increases the sensitization potential (37). Other candidates for investigation could be farnesol and citronellol, but no studies are available yet.

In our study an association between positive patch tests to FM II and each of the other fragrance markers (FM I, *M. pereirae*, HICC, and colophonium) were all significant. In a previous study, positive patch tests to FM I and HICC were independently also associated with a reaction to FM II, but no association was found between FM II and colophonium or *M. pereirae* (24). This divergence may be because of a smaller sample size ($n = 1701$) compared with our study.

In conclusion, FM II contributed significantly to the identification of fragrance allergic patients, and 26.0% of fragrance allergic patients would have been missed if FM II and HICC had not been included as markers of fragrance allergy in the baseline series. If only FM II had been excluded, 15.6% would not have been identified with a fragrance allergy. In a high proportion of cases with a positive patch test to FM II and/or HICC, the reactions were clinically relevant. This further emphasizes their importance as screening markers for diagnosing fragrance allergy.

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