

Baseline series fragrance markers fail to predict contact allergy

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doi:10.1111/cod.12171

Summary

Background. Negative patch test results with fragrance allergy markers in the European baseline series do not always predict a negative reaction to individual fragrance substances.

Objectives. To determine the frequencies of positive test reactions to the 26 fragrance substances for which labelling is mandatory in the EU, and how effectively reactions to fragrance markers in the baseline series predict positive reactions to the fragrance substances that are labelled.

Methods. The records of 1951 eczema patients, routinely tested with the labelled fragrance substances and with an extended European baseline series in 2011 and 2012, were retrospectively reviewed.

Results. Two hundred and eighty-one (14.4%) (71.2% females) reacted to one or more allergens from the labelled-fragrance substance series and/or a fragrance marker from the European baseline series. The allergens that were positive with the greatest frequencies were cinnamyl alcohol (48; 2.46%), *Evernia furfuracea* (44; 2.26%), and isoeugenol (40; 2.05%). Of the 203 patients who reacted to any of the 26 fragrances in the labelled-fragrance substance series, only 117 (57.6%) also reacted to a fragrance marker in the baseline series. One hundred and seven (52.7%) reacted to either fragrance mix I or fragrance mix II, 28 (13.8%) reacted to *Myroxylon pereirae*, and 13 (6.4%) reacted to hydroxyisohexyl 3-cyclohexene carboxaldehyde.

Conclusions. These findings confirm that the standard fragrance markers fail to identify patients with contact allergies to the 26 fragrances.

Key words: 26 labelled fragrances; allergic contact dermatitis; cross-reactions; fragrance series; fragrances; markers; screens

Fragrance substances are considered to be the most frequent causes of contact allergy after metals (1, 2), and affect between 1.1% and 2.3% of the general population (3). In Europe (4), 26 fragrance substances are required to be labelled if present at a concentration of ≥ 10 ppm in leave-on cosmetic products and if present at

a concentration of ≥ 100 ppm in rinse-off cosmetics and household detergent products.

Fragrance mix I (FM I) and fragrance mix II (FM II), both of which are used as markers for fragrance contact allergy in the European baseline series, contain 12 of the 26 fragrance substances (5), but may give negative results in patients who react to a constituent (6–12). FM I, for example, may fail to identify 15% of patients reacting to any of its constituents (6), or 22.2% of those who react to an individual constituent (7).

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) is now included in the European baseline series of contact allergens, and is the only fragrance chemical

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Conflicts of interest: The authors have declared no conflicts of interest.

Accepted for publication 7 October 2013

included as a single substance. The other 25 may now be individually tested by specialized clinics, usually as part of a 'fragrance series' of patch tests. The indications for applying such a fragrance series vary between centres. Some will only do so if the clinical history suggests fragrance allergy, or if the patient reacts to a fragrance screening marker in the baseline series. However, a number of data series in the literature suggest that this method will not diagnose all cases of fragrance contact allergy (5–11, 13, 14).

At a tertiary referral centre, we undertook routine patch testing with the 26 labelled fragrance substances (fragrance series). This was to enable evaluation of the relative frequency of reactions to the individual substances, and improve the advice given to patients. In addition, trimethyl-benzenepropanol (Majantol®) was tested, owing to some interest in this substance as a relevant fragrance allergen (15, 16).

This study explored whether routine patch testing with all individual fragrance substances that are labelled above a threshold, together with trimethyl-benzenepropanol, identified cases of fragrance contact allergy that would have remained undetected were markers in the baseline series relied upon.

Methods

The patch test records of all eczema patients who underwent routine testing with the fragrance series and the European baseline series during 2011 and 2012 were retrieved from the database at St John's Institute of Dermatology at St Thomas' Hospital, London. The data recorded at the time of consultation included the age, sex and occupation of patients, the primary site affected by eczema, and the duration of eczema.

Positive reactions, on or after day 4 of testing, to fragrance markers in the European baseline series (FM I, FM II, *Myroxylon pereirae*, and HICC) or allergens from the fragrance series (the 26 labelled fragrances and trimethyl-benzenepropanol, but excluding HICC) were tabulated with spss™ version 12. Data were also collected for patients who reacted to colophonium and epoxy resin. The concentrations and constituents of the fragrance markers are shown in Table 1, and those of the allergens used in the fragrance series are shown in Table 2. Limonene and linalool were used in their *unoxidized* forms throughout the study. Patch testing was performed with aluminium Finn Chambers® provided by Bio-Diagnostics® (Upton-Upon-Severn, United Kingdom) and allergens provided by Bio-Diagnostics®, Trolab® (Hermal Almirall, Reinbeck, Germany) and Chemotechnique® (Vellinge, Sweden). Allergens were in petrolatum. Reactions were read on

days 2 and 4, according to the recommendations of the International Contact Dermatitis Research Group. Reactions documented as questionable or irritant were considered to be negative.

Results

There were 1951 records of eczema patients tested with the European baseline series and the fragrance series between January 2011 and December 2012. Of these, 281 (14.4%) reacted either to a fragrance marker from the European baseline series or to at least one of the allergens in the fragrance series. Among these, 71.2% were female, and the most common primary sites affected were the face or neck (36.2%), 'generalised' (25.2%), and the hands (18.3%).

In a minority of patients, patch testing with the fragrance series was felt to be inappropriate. These included most children, and those patients for whom other tests were of greater importance and available skin for patch testing was limited. There were 353 such patients, and they are not included in the 1951 analysed.

Frequencies of reactions to fragrance series allergens

The allergens that were positive with the greatest frequencies (Table 1; Fig. 1) were cinnamyl alcohol (48; 2.46%), *Evernia furfuracea* (44; 2.26%), isoeugenol (40; 2.05%), *Evernia prunastri* (34; 1.74%), cinnamal (27; 1.38%), HICC (25; 1.28%), citral (20; 1.03%), and hydroxycitronellal (20; 1.03%). Limonene gave negative results in all but 1 patient (who had reacted to all fragrance substances except for benzyl benzoate), and benzyl benzoate and α -isomethyl ionone caused positive reactions in only 2 patients.

'Fragrance marker-positive' subgroup

Of the 197 (10.1%) patients who reacted to at least one fragrance marker (Table 2), 117 (59.4%) also reacted to at least one chemical in the fragrance series (Fig. 2). Of the 156 who reacted to either FM I or FM II, 107 (68.6%) reacted to an allergen in the fragrance series. Of the 68 who reacted to *M. pereirae*, 28 (41.2%) also reacted to the fragrance series, and 13 (52%) of the 25 who reacted to HICC, 27 (51.9%) of the 52 who reacted to colophonium and 1 of the 18 (5.6%) who reacted to epoxy resin also reacted to at least one allergen in the fragrance series.

'Fragrance series-positive' subgroup

There were 203 (10.4%) patients who reacted to the fragrance series (Fig. 2). Of these, 117 (57.6%) reacted to both the fragrance series and a fragrance marker, 107

Table 1. Patch test reactions to the fragrance series. Includes concentrations of allergens in the fragrance series and fragrance mixes, and data on co-reactions between fragrance series allergens and fragrance markers, fragrance mix I (FM I), or fragrance mix II (FM II). Fragrance markers include FM I, FM II, *Myroxylon pereirae*, and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)

Fragrance allergen and concentration in fragrance series	Concentration in series (%)	Presence and concentration in fragrance mix (%)	No. of positive reactions/1951 (%; 95% confidence interval)	Co-reactions with		
				any fragrance marker (% of reactions to fragrance series substance)	Co-reactions with FM I (% of reactions to ingredient)	Co-reactions with FM II (% of positive reactions to ingredient)
Cinnamyl alcohol	2	FM I, 1	48 (2.5, 1.8–3.1)	26 (54)	25 (52)	5 (10)
<i>Evernia furfuracea</i>	1	–	44 (2.3, 1.6–3.0)	27 (61)	24 (55)	9 (20)
Isoeugenol	2	FM I, 1	40 (2.1, 1.5–2.7)	28 (70)	25 (63)	8 (20)
<i>Evernia prunastri</i>	2	FM I, 1	34 (1.7, 1.1–2.3)	27 (79)	26 (76)	10 (29)
Cinnamal	1	FM I, 1	27 (1.4, 0.9–1.9)	22 (81)	22 (81)	4 (15)
HICC	5	FM II, 2.5	25 (1.3, 0.8–1.8)	25 (100)*	9 (36)	20 (80)
Hydroxycitronellal	2	FM I, 1	20 (1.0, 0.6–1.4)	18 (90)	15 (75)	9 (45)
Citral	2	FM II, 1	20 (1.0, 0.6–1.4)	16 (80)	13 (65)	11 (55)
Trimethyl-benzenepropanol	5	–	15 (0.77, 0.4–1.2)	8 (53)	7 (47)	4 (27)
Eugenol	2	FM I, 1	12 (0.62, 0.3–1.0)	11 (92)	9 (75)	2 (17)
Geraniol	2	FM I, 1	9 (0.46, 0.2–0.8)	5 (56)	5 (56)	2 (22)
Hexyl cinnamal	10	FM II, 5	9 (0.46, 0.2–0.8)	6 (67)	5 (56)	4 (44)
Butylphenyl methylpropional	10	–	9 (0.46, 0.2–0.8)	5 (56)	4 (44)	4 (44)
Coumarin	5	FM II, 2.5	8 (0.41, 0.1–0.7)	7 (88)	5 (63)	5 (63)
Farnesol	5	FM II, 2.5	8 (0.41, 0.1–0.7)	5 (63)	2 (25)	5 (63)
Citronellol	1	FM II, 0.5	6 (0.31, 0.1–0.6)	3 (50)	2 (33)	3 (50)
Amylcinnamyl alcohol	1	–	6 (0.31, 0.1–0.6)	2 (33)	2 (33)	2 (33)
Linalool†	10	–	6 (0.31, 0.1–0.6)	4 (67)	3 (50)	3 (50)
Benzyl salicylate	1	–	5 (0.26, 0.0–0.5)	3 (60)	3 (60)	1 (20)
Anise alcohol	1	–	4 (0.21, 0.0–0.4)	2 (50)	1 (25)	1 (25)
Benzyl alcohol	10	–	4 (0.21, 0.0–0.4)	3 (75)	1 (25)	2 (50)
Amyl cinnamal	2	FM I, 1	3 (0.15, 0.0–0.3)	2 (67)	2 (67)	1 (33)
Benzyl cinnamate	5	–	3 (0.15, 0.0–0.3)	1 (33)	1 (33)	1 (33)
Methyl 2-octynoate	1	–	3 (0.15, 0.0–0.3)	3 (100)	2 (67)	2 (67)
α -Isomethyl ionone	1	–	2 (0.10, 0.0–0.2)	1 (50)	1 (50)	1 (50)
Benzyl benzoate	1	–	2 (0.10, 0.0–0.2)	1 (50)	0 (0)	0 (0)
Limonene†	2	–	1 (0.05, 0.0–0.1)	1 (100)	1 (100)	1 (100)

*HICC is one of the fragrance markers. Of the 25 patients that reacted to it, only 13 also reacted to our fragrance series (in which HICC was replaced by trimethyl-benzenepropanol).

†Unoxidized forms of limonene and linalool were used.

(52.7%) reacted to FM I or FM II, 28 (13.8%) reacted to *M. pereirae*, and 13 (6.4%) reacted to HICC.

Reactions to FM I and FM II and their constituents

There were 124 patients who reacted to FM I and 64 who reacted to FM II. Of the 115 who reacted to the constituents of FM I (Fig. 3a), only 67 (58.3%) also reacted to FM I itself, and, of the 42 patients who reacted to a constituent of FM II, only 22 (52.4%) also reacted to FM II itself (see Fig. 3b).

Comparisons with previously reported associations

Of those who reacted to *E. furfuracea*, 40.9% also reacted to colophonium. Of those who reacted to *E. prunastri*,

8.82% also reacted to colophonium. Of all 1951 patients, 2.87% reacted to either *E. prunastri* or *E. furfuracea*, and 1.13% reacted to both.

In this series, only 1 of the 18 patients who reacted to epoxy resin also reacted to any allergen in the fragrance series (butylphenyl methylpropional and hydroxycitronellal).

Discussion

Our data show that > 40% of those reacting to a substance in the fragrance series would have been missed had we sought for evidence of fragrance allergy with the European baseline series alone, and that a similar proportion of those reacting to FM I or FM II constituents did not react to the mixes themselves. This is despite our use

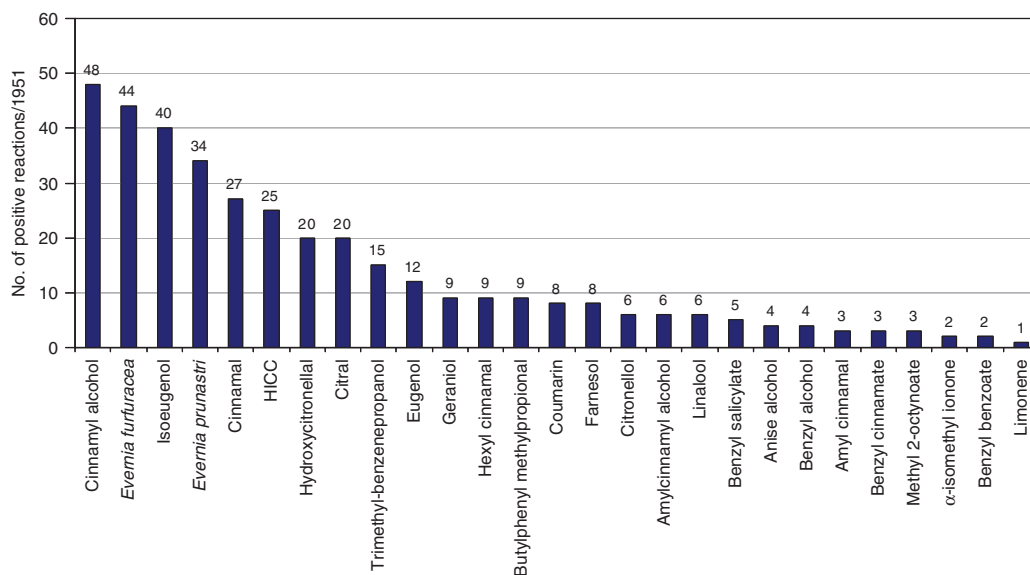


Fig. 1. Frequency of reactions to allergens in the fragrances series, including hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). Limonene and linalool were used in their unoxidized forms.

Table 2. Fragrance markers in the European baseline series, and their concentrations and association with reactions in the fragrance series

Fragrance marker	Concentration in European baseline series (%)	No. of positive reactions (% of 1951)	Co-reactions with any fragrance series substance (% of reactions to fragrance marker)
FM I	8	124 (6.4)	93 (46)
FM II	14	64 (3.3)	38 (19)
<i>Myroxylon pereirae</i>	25	68 (3.5)	28 (14)
HICC	5	25 (1.3)	13 (6.4)
Colophonium*	20	52 (2.7)	27 (13)

FM I, fragrance mix I; FM II, fragrance mix II; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

*Colophonium was not considered as a baseline series fragrance marker in this study.



Fig. 2. Reactions to fragrance markers (cyan) and to the fragrance series (orange). Venn diagram. Fragrance markers include fragrance mix I, fragrance mix II, *Myroxylon pereirae*, and hydroxyisohexyl 3-cyclohexene carboxaldehyde.

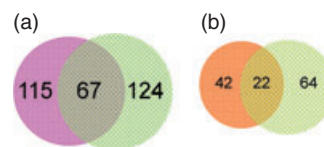


Fig. 3. Reactions to fragrance mixes and their constituents. (a) Venn diagram of the number of patients who reacted to fragrance mix I (FM I) constituents (pink) and the number of those who also reacted to FM I (green). (b) Venn diagram of the number of patients who reacted to fragrance mix II (FM II) constituents (orange) and the number of those who also reacted to FM II (pale green).

of the pure compounds of linalool and limonene, rather than their oxidized forms, which are considered to be more allergenic (17–23). Previous studies have not reported such large discrepancies (6, 7, 10, 11, 13). However, this is the first in which all patients reported were routinely tested with the 26 labelled fragrances,

regardless of clinical history or previous patch test results.

We did not follow up the patients after patch testing, so we do not know whether avoidance led to an improvement of their eczema. We have also not reported the clinical relevance of our positive test results. However,

with fragrance allergy, the history is not as indicative as it is with other common allergens such as nickel, *p*-phenylenediamine, and colophonium.

Other notable findings from our study include a very high rate of fragrance allergy. Over 14% of our patients reacted to either a fragrance marker or a substance in the fragrance series, suggesting that fragrance allergy may be more prevalent than allergy to metals. This finding supports those of Heisterberg et al. (7), who detected contact allergy to fragrance markers and individual substances in 13.6% of their routine patients (24).

Among our patients, reactions to colophonium were associated with reactions to *E. furfuracea* and *E. prunastri*, as reported elsewhere (25, 26). This may reflect contamination of both *E. furfuracea* and *E. prunastri* patch test materials with resin acids from the barks from which they are harvested (27). Our results do not, however, support an association between epoxy resin and reactions to isoeugenol and amylcinnamyl alcohol (28). Interestingly, 15 patients (0.77%) reacted to trimethyl-benzenepropanol (Majantol®). This result is comparable to those reported elsewhere (15, 16). However, some experts have suggested that reactions to trimethyl-benzenepropanol may, in fact, be related to an impurity in the preparation, rather than to the chemical itself (29).

It is difficult to find comparable studies in the literature. Most authors report testing patients with the 26 labelled fragrances only in the context of clinical suspicion or positive reactions to a fragrance marker in the baseline series (13, 30, 31). However, in a recent Danish study by Heisterberg et al. (7), all patients were routinely tested with a fragrance series composed of the 26 labelled fragrances (trimethyl-benzenepropanol was not included). Only for one-fifth of the study period, and for 87 of their 1508 patients, was use of the fragrance series limited to patients with a positive clinical history of fragrance allergy. Statistical analysis showed that there was no significant difference in the prevalence of positive reactions between these groups. Communication with the authors confirmed that only 15.6% of their patients who reacted to allergens in the fragrance series did not react to the European baseline series fragrance markers – far less than the 40.6% that we report here. Also, of their patients who reacted to a mix constituent, a far higher proportion also reacted to the relevant mix. Re-analysis of our data to imitate their methods (inclusion of HICC and removal of trimethyl-benzenepropanol from the fragrance series) made little difference to our results; the number who reacted to the fragrance series increased by 6, to 209, and the number who also reacted to a fragrance marker rose by 10, to 127 (60.8%).

There are a number of possible reasons why our results were different to those reported by Heisterberg et al. (7). Some of our individual fragrance substances were prepared at higher concentrations for patch testing. In particular, we tested all of the constituents of FM I (besides cinnamal) at double the concentrations used in the Danish study (7). Another factor that might have contributed was the timing of the readings, as they took a 7-day reading as well. Their study had fewer data on reactions to linalool and limonene, as reactions to the oxidized forms (which replaced the pure compounds during the study period) were not included. It also appears that these studies concerned two different populations with different distributions of sensitization; they reported *E. furfuracea* as the most frequent cause of a positive reaction, whereas cinnamyl alcohol held this position among our patients.

Despite this, it is reasonable to conclude that the sensitivity of the fragrance markers is limited. Our findings suggest that higher concentrations, and routine use of the fragrance series, will not only detect additional cases of fragrance contact allergy, but will enable clinicians to give useful advice on which substances patients should avoid. A recent study by Bruze et al. (5) concluded that higher concentrations of the fragrance series allergens not included in the fragrance mixes would improve our diagnostic ability. Another route to consider would be to expand the use of fragrance markers in the baseline series. Some authors consider colophonium to be a fragrance marker (6, 32). Re-analysis of our data showed that 66.5%, rather than 57.6%, of our patients who reacted to a substance in the fragrance series would have been anticipated from the European baseline series if colophonium had been included as a fragrance marker. However, although this is an improvement, missing 30% of cases is still far from ideal.

In summary, a large proportion of our patients (14.4%) reacted to either a fragrance marker or a substance in our fragrance series, and this figure might have been higher had we used oxidized forms of linalool and limonene. Importantly, our findings suggest that a considerably higher percentage of patients allergic to fragrances could be missed by screening with only FM I, FM II, *M. pereirae* and HICC than previous reports have suggested. To improve our ability to diagnose such patients, and so that we can provide them with useful advice about how to avoid the allergens relevant to them, we recommend routine testing with the 26 labelled fragrances, and giving consideration to use of the higher concentrations of these individual fragrance allergens.

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