

Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive

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Summary

Background. Fragrance ingredients are a frequent cause of allergic contact dermatitis. The EU Cosmetics Directive states that 26 specific fragrance ingredients, known to cause allergic contact dermatitis, must be declared on the ingredient lists of cosmetic products.

Objectives. To investigate frequencies of sensitization to the 26 individual fragrances and evaluate their importance as screening markers of fragrance allergy.

Method. This was a retrospective study based on data from the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte. Eczema patients ($n = 1508$) were patch tested (January 2008 to July 2010) with the 26 fragrance ingredients.

Results. Sensitization to the 26 fragrances was identified in 115 (7.6%) subjects. The most frequent allergens were *Evernia furfuracea* ($n = 50$), *Evernia prunastri* ($n = 31$), and hydroxyisohexyl 3-cyclohexene carboxaldehyde ($n = 24$). Including fragrance mix I, fragrance mix II and *Myroxylon pereirae*, 196 (13.0%) had a fragrance allergy. Testing with the 26 fragrances additionally identified 23 subjects who would otherwise have gone undetected. The majority (75.7%) of positive reactions to the 26 fragrances were of clinical relevance.

Conclusions. Sensitization to the 26 individual fragrance ingredients was identified in 7.6% of the subjects patch tested. Most reactions were of clinical relevance. Fragrance-allergic subjects would be missed if testing with the individual fragrance ingredients was not performed.

Key words: allergic contact dermatitis; clinical relevance; cosmetics directive; *Evernia furfuracea*; fragrance mix I; fragrance mix II; fragrances.

Fragrance ingredients are the most frequent cause of allergic contact dermatitis (1, 2). More than 2500 different fragrance ingredients exist (3) and many are allergens (4). The EU regulations pertain to 26 fragrance ingredients in particular, known to be contact allergens in humans

(Table 1). The Cosmetics Directive states that cosmetic products sold on the European market containing any of these 26 fragrances must have the ingredient listed on the product's ingredient label if the concentrations exceed 10 ppm in leave-on products or 100 ppm in rinse-off products. The Cosmetics Directive also states that if a product contains other fragrances, this must appear on the label of the product as aroma, fragrance, or perfume (5).

This mandatory labelling of fragrance ingredients on cosmetic products helps the clinician to diagnose fragrance allergy and the patients to avoid the fragrance ingredients (6).

The first objective of this study was to report the frequencies of positive patch test reactions to the 26

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Table 1. Patch test reaction pattern of the 26 individual fragrance ingredients

INCI name	%	Numbers tested		Positive reactions					Doubtful reactions			Irritant reactions		
		n _{tested}	n ₊	n ₊₊	n ₊₊₊	n _{pos}	% _{pos}	CI (%)	n ₊ ?	% ₊ ?	CI (%)	n _{IR}	% _{IR}	CI (%)
<i>Evernia furfuracea</i>	1	1503	23	27	0	50	3.3	2.5–4.3	38	2.5	1.8–3.4	2	0.1	0.0–0.4
<i>Evernia prunastri</i> ^a	1	1503	10	20	1	31	2.1	1.4–2.9	21	1.4	0.9–2.1	1	0.1	0.0–0.3
HICC ^{b,c}	5	1502	9	15	0	24	1.6	1.1–2.3	13	0.9	0.5–1.4	0	0	0.0–0.2
Cinnamal ^a	1	1503	13	7	0	20	1.3	0.8–2.0	14	0.9	0.5–1.5	2	0.1	0.0–0.4
Isoeugenol ^a	1	1502	5	9	0	14	0.9	0.5–1.5	14	0.9	0.5–1.5	2	0.1	0.0–0.4
Cinnamyl alcohol	1	1501	8	2	0	10	0.7	0.3–1.9	10	0.7	0.3–1.2	0	0	0.0–0.2
Hydroxycitronellal ^a	1	1498	5	4	0	9	0.6	0.3–1.1	10	0.7	0.3–1.2	0	0	0.0–0.2
Hexyl cinnamal ^b	10	1503	4	5	0	9	0.6	0.3–1.1	10	0.7	0.3–1.2	1	0.1	0.0–0.3
Farnesol ^b	5	1502	2	3	0	5	0.3	0.1–0.7	8	0.5	0.2–1.0	2	0.1	0.0–0.4
Butylphenyl methylpropional	10	1503	1	3	0	4	0.3	0.1–0.6	2	0.1	0.0–0.4	1	0.1	0.0–0.3
Citral ^b	2	1502	4	0	0	4	0.3	0.1–0.6	9	0.6	0.3–1.1	3	0.2	0.1–0.5
Eugenol ^a	1	1502	4	0	0	4	0.3	0.1–0.6	18	1.2	0.7–1.9	0	0	0.0–0.2
Amyl cinnamal ^a	1	1503	3	0	0	3	0.2	0.1–0.5	14	0.9	0.5–1.5	1	0.1	0.0–0.3
Coumarin ^b	5	1503	3	0	0	3	0.2	0.1–0.5	7	0.5	0.2–0.9	2	0.1	0.0–0.4
Benzyl salicylate	1	1503	3	0	0	3	0.2	0.1–0.5	5	0.3	0.1–0.7	2	0.1	0.0–0.4
Benzyl alcohol	1	1508	1	1	0	2	0.1	0.0–0.4	3	0.2	0.1–0.5	1	0.1	0.0–0.3
Anise alcohol	1	1503	0	1	0	1	0.1	0.0–0.3	3	0.2	0.1–0.5	0	0	0.0–0.2
Benzyl cinnamate	5	1503	1	0	0	1	0.1	0.0–0.3	4	0.3	0.1–0.6	0	0	0.0–0.2
Amylcinnamyl alcohol	1	1503	0	1	0	1	0.1	0.0–0.3	12	0.8	0.4–1.4	1	0.1	0.0–0.3
Citronellol ^b	1	1503	1	0	0	1	0.1	0.0–0.3	11	0.7	0.4–1.3	4	0.3	0.1–0.6
Linalool	10	1397	1	0	0	1	0.1	0.0–0.4	4	0.3	0.1–0.7	0	0	0.0–0.2
Limonene	2	1399	0	0	0	0	—	—	4	0.3	0.1–0.7	0	0	0.0–0.2
Geraniol ^a	1	1502	0	0	0	0	—	—	22	1.5	0.9–2.2	4	0.3	0.1–0.6
Alpha-isomethyl ionone	1	1503	0	0	0	0	—	—	6	0.4	0.2–0.8	1	0.1	0.0–0.3
Benzyl benzoate	1	1503	0	0	0	0	—	—	6	0.4	0.2–0.8	0	0	0.0–0.2
Methyl 2-octynoate ^d	1	211	0	0	0	0	1.0	—	1	0.5	0.0–2.3	1	0.5	0.0–2.3
Sorbitan sesquioleate ^e	20	1502	0	1	0	1	0.1	0.0–0.3	15	1.0	0.6–1.6	2	0.1	0.0–0.4

CI, confidence interval; IR, irritant reactions.

^aFragrance ingredients constituting fragrance mix I.

^bFragrance ingredients constituting fragrance mix II.

^cHydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC).

^dOnly 211 patients were tested with methyl 2-octynoate 1% in pet., as active sensitization was observed in two patients and we stopped testing with it.

^eSorbitan sesquioleate is not a fragrance marker but an emulsifier used in fragrance mix I.

fragrance ingredients and to determine clinical relevance. The other objective was to investigate whether patch testing with the individual fragrance ingredients would reveal fragrance allergic subjects who otherwise would go undetected by the standard fragrance screening markers [fragrance mix I (FM I), fragrance mix II (FM II), and *Myroxylon pereirae*].

Materials

Data were retrieved from the database at the Dermato-Allergy Department of Copenhagen University Hospital Gentofte (7). This contains structured information from the patient files, including patch test results, patient demographics, exposures, and clinical relevance of the patch test.

In January 2008, we began patch testing with the 26 fragrance ingredients on the EU Cosmetics Directive's

list of mandatory labelling (8). From January 2009 to July 2009 (6 months), only subjects suspected of having fragrance allergy were tested with the 26 individual ingredients; otherwise, all eczema patients suspected of having contact allergy were tested consecutively. We included all subjects (n = 1508) patch tested with at least one of the 26 fragrance ingredients in the period from January 2008 to July 2010. The majority were women [1056 women (70%) versus 452 men (30%)]. The mean age was 46 years (standard deviation, ±16.9). Table 2 shows the study participants' demographic characteristics.

The 26 fragrance ingredients are listed in Table 1 with their patch test concentrations. The patch test material was obtained from Hermal (Reinbek, Germany). The subjects were also patch tested with the European baseline series, which, in that period, included

Table 2. MOAHLFA index of patch-tested eczema patients (n = 1508); patients with a positive patch test reaction to any of the 26 specific fragrances (n = 115)

Index	Tested subjects		Positive patch reaction to the 26 fragrances	
	No.	%	No.	%
M	452	30.0	25 ^a	21.7
O	358	23.7	20	17.4
A	279	18.5	27	23.5
H	634	42.0	48	41.7
L	30	2.0	4	3.5
F	406	26.9	43 ^a	37.4
AA	970	64.3	80	69.6
Total	1508	100	115	100

MOAHLFA index: A, atopy; AA, age 40 years or above; F, facial dermatitis; H, hand dermatitis; L, leg dermatitis; M, male; O, occupational cause of dermatitis.

^a χ^2 -test, $p < 0.05$.

four fragrance screening markers: fragrance mix I (FM I), fragrance mix II (FM II), *M. pereirae* (balsam of Peru), and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). HICC is also one of the 26 fragrances requiring mandatory labelling. The two fragrance mixes consist, respectively, of eight different fragrance ingredients (FM I) and six different fragrance ingredients (FM II); all 14 of these fragrance ingredients are included among the 26 fragrances requiring mandatory labelling (Table 3). FM I also contains the emulsifier sorbitan sesquioleate.

The clinical relevance of a positive patch test reaction is evaluated routinely, and registered according to standardized guidelines, which are based on: (i) medical history; (ii) results of patch test and/or use test; (iii) ingredient labelling; or (iv) chemical analysis (Table 4).

Relevant exposure sources causing allergic contact dermatitis are registered in the database. The exposure sources are categorized into specific cosmetic product groups (Table 5). One subject could have more than one exposure listed as the cause of allergic contact dermatitis.

Methods

The patch tests were performed according to international guidelines (9), with Finn Chambers® applied on the back with Scanpor® tape (Vitalfo Scandinavia, AB, Allerød, Denmark) for a period of 2 days. Readings were performed on days 2, 3 or 4, and 7, according to the recommendations of the International Contact Dermatitis Research Group (10).

Not all subjects were patch tested with limonene and linalool, as the patch test material during the

study period changed from being the pure compounds (Hermal) to oxidized materials (Göteborg), because several studies have shown that it is the oxidized products that cause allergy (11–17). In this study, we report the results of patch testing with the pure compounds. Methyl 2-octyonate 1% was not patch tested in all of the subjects routinely patch tested, because active sensitization was observed in two patients, and we then stopped patch testing with it; thus only 211 patients were tested (18).

Data management and statistical analysis were performed using SPSS™ version 15. Percentages of positive patch test reactions and confidence intervals were calculated with www.openepi.com. Chi-square tests and Fisher's exact tests for characteristic differences were performed, and $p < 0.05$ was considered to be significant.

Results

Prevalence of positive patch test reactions

A positive patch test reaction to at least one of the 26 fragrance ingredients was identified in 115 (7.6%) of the subjects patch tested. Most had one single positive patch test reaction (60.9%), and 39.1% reacted to more than one of the 26 fragrance markers.

The total number of subjects identified with sensitization to a fragrance ingredient was 196 (13.0%), when all of the fragrance screening markers (FM I, FM II, and *M. pereirae*) were included.

Rates of positive patch test reactions for each of the 26 fragrances are shown in Fig. 1. Among the 26 individual fragrance ingredients, *Evernia furfuracea* (tree moss) was positive in the highest number of subjects (n = 50); next came *Evernia prunastri* (oak moss) (n = 31), HICC (n = 24), and cinnamal (n = 20). Four of the 26 fragrance ingredients did not give any positive patch test reactions: geraniol, alpha-isomethyl ionone, limonene, and benzyl benzoate. Methyl 2-octynoate produced active sensitization in two subjects.

Irritant reactions were most common for limonene, linalool, citronellol, geraniol, and methyl 2-octyonate, but all at 0.5% or less. Doubtful reactions were quite frequent for *E. furfuracea* (2.5%) as compared with the other fragrance markers (Table 2).

The participants had not all been patch tested consecutively, as only subjects suspected of having fragrance allergy were tested during a period of 6 months (n = 87), but no statistically significant difference was observed in the prevalence of positive patch test reactions ($p > 0.05$). In the group tested only on suspicion of fragrance allergy, only 10 had positive reactions.

Table 3. Concomitant positive patch test reactions for each of the 26 individual fragrances and the fragrance screening markers: fragrance mix I (FM I) and fragrance mix II (FM II)

	Positive patch test reactions	Concomitant reactions to FM I				Concomitant reactions to FM II			
		Numbers of positive co-reactions with FM I	Percentages of positive co-reactions with FM I of n_{pos}	Percentages of positive co-reactions to the 26 fragrance ingredients	Numbers of positive co-reactions with FM II	Percentages of positive co-reactions with FM II of n_{pos}	Percentages of positive co-reactions to the 26 fragrance ingredients		
	n_{pos}	n_{co-FMI}	$\% (n_{co-FMI} / n_{pos})$	$\% (n_{co-FMI} / 110)$	$n_{co-FMII}$	$\% (n_{co-FMII} / n_{pos})$	$\% (n_{co-FMII} / 60)$		
<i>Evernia prunastri</i> ^a	31	29	93.5	26.4	7	23.3	11.7		
Cinnamal ^a	20	18	94.7	16.4	6	30.0	10.0		
Cinnamyl alcohol ^a	10	10	100.0	9.1	3	30.0	5.0		
Eugenol ^a	4	3	100.0	2.7	2	50.0	3.3		
Isoeugenol ^a	14	11	84.6	10.0	2	15.4	3.3		
Hydroxycitronellal ^a	9	9	100.0	8.2	8	88.9	13.6		
Amyl cinnamal ^a	3	3	100.0	2.7	2	66.7	3.3		
Geraniol ^a	0	—	—	—	—	—	—		
HICC ^{b,c}	24	13	56.5	11.8	23	95.8	38.3		
Hexyl cinnamal ^b	9	3	33.3	2.7	7	77.8	11.7		
Farnesol ^b	5	3	60.0	2.7	4	80.0	6.7		
Citral ^b	4	4	100.0	3.6	4	100.0	6.7		
Citronellol ^b	1	1	100.0	0.9	1	100.0	1.7		
Coumarin ^b	3	0	—	—	0	—	—		
<i>Evernia furfuracea</i>	50	31	63.3	28.2	10	20.4	16.7		
Linalool	1	1	100.0	0.9	0	—	—		
Butylphenyl methylpropional	4	4	100.0	3.6	3	75.0	5.0		
Benzyl salicylate	3	3	100.0	2.7	3	100.0	5.0		
Benzyl alcohol	2	1	1	50.0	0.9	50.0	1.7		
Anise alcohol	1	1	100.0	0.9	0	—	—		
Benzyl cinnamate	1	1	100.0	0.9	1	100.0	0.9		
Amylcinnamyl alcohol	1	1	100.0	0.9	1	100.0	1.7		
All 26 individual fragrances	115	70	62.5	63.6	40	35.1	66.7		
Sorbitan sesquileate ^d	1	1	100.0	0.9	1	100	1.7		

n_{pos} : number of positive patch test reactions; n_{co-FMI} : number of concomitant positive patch test reactions between FM I and at least one of the 26 fragrance ingredients; $\% (n_{co-FMI} / n_{pos})$, percentages of concomitant reactions between FM I and the 26 fragrance ingredients of the number of positive reactions to the respective fragrance ingredient; $\% (n_{co-FMI} / 110)$, percentages of concomitant reactions between FM I and the 26 fragrance ingredients of the number of positive reactions to FM I ($n = 110$); $n_{co-FMII}$, concomitant positive patch test reactions between FM II and at least one of the 26 fragrance ingredients; $\% (n_{co-FMII} / n_{pos})$, percentages of concomitant reactions between FM II and the 26 fragrance ingredients of the number of positive reactions to the respective fragrance ingredient; $\% (n_{co-FMII} / 60)$, percentages of concomitant reactions between FM II and the 26 fragrance ingredients of the number of positive reactions to FM II ($n = 60$).

^aFragrance ingredients constituting fragrance mix I.

^bFragrance ingredients constituting fragrance mix II.

^cHydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC).

^dSorbitan sesquileate is not a fragrance marker but an emulsifier used in fragrance mix I.

Table 4. Clinical relevance in eczema patients with a positive patch test reaction

INCI name	Clinical relevance						
	Present		Past		Present and past		
	$n_{\text{rel}}/n_{\text{pos}}$	(%)	$n_{\text{rel}}/n_{\text{pos}}$	%	$n_{\text{rel}}/n_{\text{pos}}$	%	CI (95 %) ^a
<i>Evernia furfuracea</i>	37/50	74.0	12/50	24.0	39/50	78.0	65.0–87.9
<i>Evernia prunastri</i> ^b	23/31	74.2	10/31	32.3	26/31	83.9	67.8–93.8
HICC ^{c,d}	21/24	87.5	6/24	25.0	22/24	91.7	75.1–98.6
Cinnamal ^b	8/20	40.0	2/20	10.0	9/20	45.0	24.6–66.7
Isoeugenol ^b	8/14	57.1	4/14	28.6	10/14	71.4	44.6–90.2
Cinnamyl alcohol	7/10	70.0	2/10	20.0	8/10	80.0	48.1–96.5
Hydroxycitronellal ^b	6/9	66.7	0/9	0.0	6/9	66.7	33.2–90.7
Hexyl cinnamal ^c	5/9	55.6	2/9	22.2	6/9	66.7	33.2–90.7
Farnesol ^c	3/5	60.0	0/5	0.0	3/5	60.0	18.2–92.7
Butylphenyl methylpropional	1/4	25.0	0/4	0.0	1/4	25.0	1.3–75.8
Citral ^c	2/4	50.0	0/4	0.0	2/4	50.0	9.4–90.6
Eugenol ^a	2/4	50.0	1/4	25.0	2/4	75.0	24.2–98.8
Amyl cinnamal ^b	1/3	33.3	0/3	0.0	1/3	33.3	1.7–86.8
Coumarin ^c	1/3	33.3	1/3	33.3	2/3	66.7	13.2–98.3
Benzyl salicylate	1/3	33.3	0/3	0.0	1/3	33.3	1.7–86.8
Benzyl alcohol	0/2	0.0	0/2	0.0	0/2	0.0	—
Anise alcohol	1/1	100.0	0/1	0.0	1/1	100.0	5–100
Benzyl cinnamate	0/1	0.0	0/1	0.0	0/1	0.0	—
Amylcinnamyl alcohol	1/1	100.0	0/1	0.0	1/1	100.0	5–100
Citronellol ^c	1/1	100.0	0/1	0.0	1/1	100.0	5–100
Linalool	1/1	100.0	0/1	0.0	1/1	100.0	5–100
All 26 fragrances	79/115	68.7	27/115	23.5	87/115	75.7	67.2–82.8
Fragrance mix I	84/110	76.4	35/110	31.8	90/110	81.8	73.8–88.2
Fragrance mix II	50/60	83.3	15/60	25.0	54/60	90.0	80.3–95.9
<i>Myroxylon pereirae</i>	31/53	58.5	9/53	17.0	35/53	66.0	52.6–77.8
All fragrance markers	149/196	76.0	55/196	28.1	161/196	82.1	76.3–87.0
Sorbitan sesquioleate ^e	1/1	100.0	0/1	0.0	1/1	100.0	5–100

n_{rel} , number of subjects with clinically relevant positive patch test reactions with regard to eczema; n_{pos} , number of subjects with a positive patch test reaction.

^aCI, 95% confidence interval (lower and upper).

^bFragrance ingredients constituting fragrance mix I.

^cFragrance ingredients constituting fragrance mix II.

^dHydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC).

^eSorbitan sesquioleate is not a fragrance marker but an emulsifier used in fragrance mix I.

In the subjects patch tested with the standard fragrance screening markers, the prevalences of positive reactions were 7.5% for FM I, for 4.0% for FM II, and 3.6% for *M. pereirae*.

Patient characteristics

Women (78.3%) and patients with facial eczema (37.4%) were more likely to have a positive patch test reaction to one of the 26 fragrance ingredients (Table 2).

Concomitant reactions

Concomitant positive patch test reactions between the 26 fragrance ingredients and FM I and FM II were often observed (Table 3). On comparison of positive reactions to

at least one of the 26 fragrance ingredients with positive reactions to at least one of the standard fragrance screening markers (*M. pereirae*, FM I, and/or FM II), concomitant reactions were seen in 92 fragrance-allergic subjects. This left 23 subjects who were identified only by the individual fragrance ingredients, and thus patch testing with the individual fragrance ingredients additionally identified 14.0% with a fragrance allergy.

Concomitant positive patch test reactions between the 26 fragrances and FM I and/or FM II were observed in 75.7% ($n = 87$) of the subjects identified by the 26 fragrance ingredients. The individual fragrances that had the lowest concordance with both mixes were *E. furfuracea* [64.0% confidence interval (CI) 50.1–76.0] and benzyl alcohol (50.0% CI 2.5–97.5).

Table 5. Cosmetic exposures causing allergic contact dermatitis resulting from the 26 individual fragrance ingredients (n = 183)

	Cream	Shampoo	Fine fragrance	Sun lotion	Hairstyling products	Shaving foam	Deodorant	Liquid soap	Toothpaste	Lipstick	Make-up cream	Mascara	Unspecified products	All cosmetic products
<i>Evernia furfuracea</i>	5	3	2	1	0	0	1	1	0	0	0	1	31	45
<i>Evernia prunastri</i>	5	2	2	1	0	0	0	0	0	0	0	0	21	31
HICC	2	3	2	3	2	0	1	1	0	0	1	0	13	28
Cinnamal	4	2	0	0	1	0	0	0	1	0	0	0	11	19
Isoeugenol	2	0	1	1	1	1	0	0	0	1	0	0	6	13
Cinnamyl alcohol	1	1	0	0	0	0	0	0	1	0	0	0	6	9
Hydroxycitronellal	1	2	1	1	0	0	0	0	0	0	0	0	4	9
Hexyl cinnamal	2	0	1	1	0	1	0	0	0	0	0	0	4	9
Eugenol	1	0	1	1	0	0	0	0	0	0	0	0	2	5
Farnesol	1	1	0	0	1	0	0	0	0	0	0	0	2	5
Citral	1	0	1	1	0	0	0	0	0	0	0	0	1	4
Amyl cinnamal	1	0	1	1	0	0	0	0	0	0	0	0	0	3
Anise alcohol	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Coumarin	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Linalool	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Total	27	14	12	11	5	2	2	2	2	1	1	1	103	183
Percentages of the specific cosmetic products having caused ACD resulting from at least one of the 26 fragrance ingredients (n = 80)	33.8	17.5	15.0	13.8	6.3	2.5	2.5	2.5	2.5	1.25	1.3	1.3		

ACD, allergic contact dermatitis; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

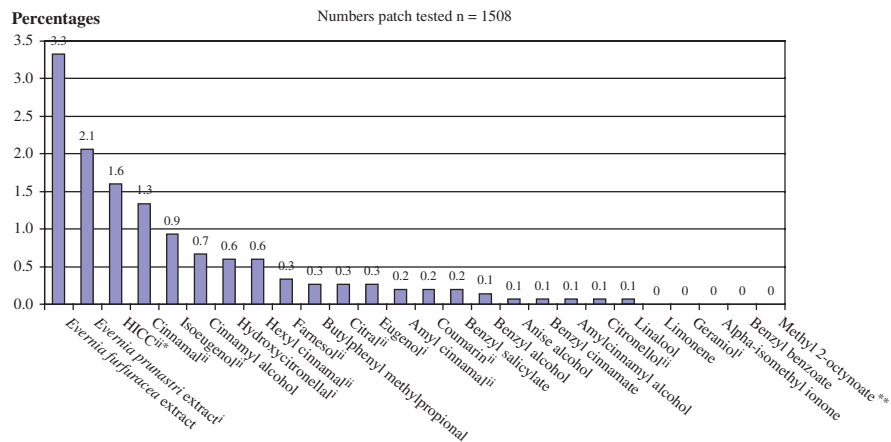


Fig. 1. Rates of positive patch test reactions to each of the 26 individual fragrance ingredients to be declared on cosmetic products in the EU.

* Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)

** Methyl 2-octynoate had 2 late reactions, previously described (18).

ⁱ Fragrance ingredients constituting fragrance mix I

ⁱⁱ Fragrance ingredients constituting fragrance mix II

Prevalence of clinical relevance of positive patch test reactions

The majority of positive patch test reactions to the 26 fragrance ingredients were of clinical relevance, as shown in Fig. 2. Of the 115 positive patch test reactions to the 26 fragrance ingredients, 87 (75.7%) were of clinical relevance. The reactions were mainly of present clinical relevance (79/87) rather than past clinical relevance (Table 4). HICC had the highest prevalence (91.7%) of clinical relevance of the positive patch test reactions. FM I and FM II also had high rates of clinical relevance, 84.9% and 90.0%, respectively, whereas subjects with a positive patch test reaction to *M. pereirae* differed in having a lower prevalence (66%) of clinically relevant

reactions. Taken together, all the fragrance screening markers (FMI, FM II, and *M. pereirae*) and the 26 fragrance ingredients had a prevalence of clinical relevance of 82.1%.

Exposures causing allergic contact dermatitis to fragrance ingredients

The exposure sources causing allergic contact dermatitis to one or more of the 26 fragrance ingredients were registered in 78 (67.8%) subjects. Some had more than one product listed as an exposure source, and, on average, 2.4 products were listed for each subject. A total of 191 exposure products were listed, and most were cosmetic products (95.8%).

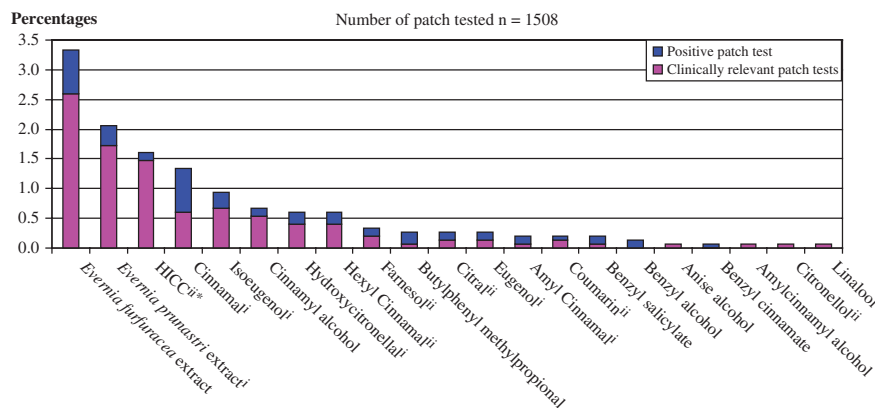


Fig. 2. Rates of positive patch test reactions and clinically relevant patch test reactions to the 26 individual fragrance ingredients.

* Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)

ⁱ Fragrance ingredients constituting fragrance mix I

ⁱⁱ Fragrance ingredients constituting fragrance mix II

For the most part (56.3%), the cosmetic products listed were in the category 'unspecified cosmetic products'. Among the specified cosmetic products, the most frequently listed groups were: cream (33.8%), shampoo (17.5%), fine fragrance (15.0%), and sun lotion (13.8%). The fragrances most frequently involved, accounting for 67.2% of the cosmetic exposure sources having caused allergic contact dermatitis, were *E. furfuracea* (25.6%), *E. prunastri* (16.9%), HICC (15.3%), and cinnamal (10.4%). The non-cosmetic exposures were medicine ($n = 4$) and cleansing agents ($n = 4$).

Discussion

In this retrospective study, we determined the frequencies of contact allergy to the 26 individual fragrance ingredients patch tested in 1508 subjects and evaluated their contribution in identifying subjects with a fragrance allergy. The prevalence of fragrance allergy to at least one of the fragrance ingredients was 7.6%. A previous study investigating a selected group of subjects suspected of having fragrance allergy reported a higher contact allergy rate of 10.3% (19).

We suspect that the number of subjects with a fragrance allergy in our population is actually higher, as patients were not tested with oxidized limonene and oxidized linalool, which would identify further subjects with an allergic contact dermatitis (11–17). Additionally, for 6 months patients were patch tested only if there was a suspicion of fragrance allergy ($n = 87$) and were not investigated consecutively, like the rest of the study population ($n = 1419$). Consequently, subjects with a fragrance allergy could have gone undetected in this period (20). No statistical difference between the two groups in identification of fragrance allergy was seen, as our study population was too small. However, we found that 11.7% would be undetected with a fragrance allergy if they had not been patch tested with the fragrance series, and this underlines the value of patch testing all subjects with a fragrance series.

The prevalences of positive patch test reactions to each of the 26 individual fragrance ingredients vary greatly. It is striking that the most frequent fragrance ingredient causing allergy was *E. furfuracea* ($n = 50$), with positive patch test reactions in 3.3% of the tested subjects. This has also been reported in two German studies. The first reported positive patch test reactions to *E. furfuracea* in 2.7% of 1658 consecutively patch tested subjects (21), and, in the most recent study, positive reactions were seen in 6.0% (standardized for age and sex) of 1947 patch tested subjects (22). In contrast, a small study ($n = 86$) from Spain (23) reported geraniol

as the most important allergen of the 26 specific fragrance ingredients. In Spain, geraniol is used in a medical treatment for eczema, which might be the explanation. Some previous studies have reported the most frequent allergen to be *E. prunastri* (22, 24, 25), while others report hexyl cinnamal and HICC (19). These differences in the prevalence of allergy to the fragrances reflect the diverse exposure pattern in time and place (26, 27). Nevertheless, our findings add weight to the most important fragrance allergens being *E. furfuracea*, *E. prunastri*, HICC, cinnamal, isoeugenol, cinnamyl alcohol, hydroxycitronellal and α -hexyl cinnamal.

Four fragrance ingredients did not cause any positive patch test reactions: limonene, geraniol, alpha-isomethyl ionone, and benzyl benzoate. Limonene and linalool were not patch tested in the oxidized form, which would have revealed more fragrance-allergic subjects (11–16). This may also be the case for geraniol, as one study has shown that it may auto oxidize and subsequently form sensitizing oxidation products (28). Benzyl benzoate and alpha-isomethyl ionone have, in previous studies, been reported to be fragrances of low importance (21, 22), which is in agreement with our results, as none of these gave positive reactions. Methyl 2-octynoate gave late reactions (active sensitization), and not patch tested in all participants, as described previously (18).

The majority of positive patch test reactions (75.7%) to the 26 fragrance ingredients had concomitant reactions with FM I and/or FM II, albeit some more than others. FM I had concomitant reactions to the 26 individual fragrance ingredients in 62.5% of cases, whereas FM II had them in only 35.1%. This can largely be explained by the similarly high number of positive patch test reactions detected by FM I, and by the higher rate of concomitant reactions between FM I and its constituents than for FM II (20, 22). It is noteworthy that *E. furfuracea* had concomitant reactions with FM I and/or FM II in only 64.0% of the 50 subjects with an allergy to *E. furfuracea*, so it is of great importance to include this fragrance ingredient when screening for fragrance allergy.

Most of the positive patch test reactions were of clinically relevant (75.7%), and this emphasizes the role of fragrance ingredients as causes of allergic contact dermatitis. Doubtful and irritant patch test reactions were also observed, and especially doubtful reactions occurred when patch testing with *E. furfuracea*, *E. prunastri*, eugenol and geraniol was performed, but no association between fragrances with low sensitization frequencies and doubtful/irritant reactions was observed, as suggested in a former study (21).

The majority of exposure sources (95.8%) registered as the cause of fragrance allergic contact dermatitis

were cosmetic products, which has also been shown in numerous other studies (29–32). The top four most frequent cosmetic product groups were creams, shampoos, fine fragrances, and sun lotions, which is in contrast to our previous study (33), where we reported deodorants as the leading cause of allergic contact dermatitis to fragrance ingredients. This inconsistency can be explained by differences in the study population, as the participants in this study were investigated at the hospital department, and the previous study included participants from dermatology clinics. Patients seen at dermatology clinics are usually seen at an earlier stage of their disease, which fits well with deodorants as the exposure causing symptoms for the first time (34).

Unsurprisingly, female sex and facial eczema were statistically significantly associated with fragrance allergy (1, 35–37), as both are known to be associated with cosmetic allergy (38, 39). This could indicate relevance of the reactions at an epidemiological level, corroborating the relevance found at an individual level (40).

The mandatory labelling of the 26 individual fragrance ingredients on cosmetic products is of great value to the doctor when determining the clinical relevance of a positive patch test reaction. If all fragrance ingredients were declared on cosmetic products, it would make it easier to establish 'new' allergies to other than the 26 fragrance ingredients, and thereby optimize the diagnosis of contact allergy to fragrance ingredients. The mandatory labelling also makes it possible for a patient with a diagnosed allergy to one of the specific 26 fragrances to avoid the allergenic fragrance and thereby not develop disease (41).

In conclusion, patch testing with the 26 fragrances requiring mandatory labelling is of great value, as it helps to identify fragrance-allergic subjects who would otherwise have gone undetected (11.7%). Most of the positive patch test reactions were of clinical relevance (75.7%), and in this group of eczema patients the main exposures causing the fragrance allergic contact dermatitis were cosmetics (95.8%), in particular creams, shampoos, and fine fragrances.

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