

Fragrance contact dermatitis: a worldwide multicenter investigation (Part II)

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The purpose of this study was to determine the frequency of responses to selected fragrance materials in patients who were fragrance sensitive. 178 patients were evaluated in 8 centers worldwide with a fragrance mix (FM) and 20 other fragrance materials. Reaction to the fragrance mixture (FM) occurred in 78.7% of the subjects. Substances reacting at a rate of 2% or higher included jasmine absolute, geranium oil bourbon, l-citronellol, spearmint oil, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta- γ -2-benzopyran, omega-6-hexadecenlactone, dimethyltetrahydrobenzaldehyde (isomer mixture), and α -amylcinnamaldehyde. These chemicals should be further evaluated to corroborate their allergenicity. We are constantly looking for new fragrance allergens to extend the diagnostic capability of the fragrance mix (FM).

Key words: allergic contact dermatitis; fragrance; jasmine absolute; geranium oil bourbon; 1-citronellol; spearmint oil; 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta- γ -2-benzopyran; omega-6-hexadecenlactone; dimethyltetrahydrobenzaldehyde; α -amylcinnamaldehyde. © Munksgaard, 2001.

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Fragrance sensitization remains a significant clinical problem. Contact allergy to fragrance materials is the most common cause of contact dermatitis due to cosmetics (1). Though the fragrance mixture (FM) has been used for over 20 years, it may not be the optimal combination of allergens to test for the presence of allergy to fragrance materials (2). We are constantly trying to improve our ability to screen for fragrance materials.

This report is the 2nd part of a 3-year investigation into fragrance material allergy by the investigators (3). The 20 fragrance chemicals tested were of interest to the fragrance industry and were selected by the fragrance industry and dermatologists. Our interest is in testing select fragrance materials in an effort to discover new fragrance allergens and also to define fragrance materials safe for use in cosmetics. By specifically testing fragrance-sensitive patients, we can achieve this goal using a smaller patient pool.

Materials and Methods

Study population

178 volunteers were patch tested over a 3-month period in 8 centers in Japan, Northern Ireland, United States, England, Switzerland and Sweden. All of the volunteers had proven sensitization to fragrance materials established by previous patch tests to fragrance allergens. The majority were drawn from the clinical practices of the participating investigators.

Test substances

All test materials (Table 1) used in the investigation were prepared in batches in Japan by 3 major perfume companies and distributed to all the test centers. All were formulated in petrolatum. The challenge concentrations for the 20 new fragrance ingredients used for this study were established by

Table 1. Results from 8 centers

Fragrance materials Total number of patients tested	England 25	Ireland 24	Japan 19	Sweden 28	Switzer- land 26	USA Oregon 24	USA Penn. 7	USA Virginia 25	# positive	% positive 178
1 fragrance mix 8% pet.	24	19	11	20	23	17	6	20	140	78.7
2 jasmine absolute 10% pet.	3	2	3	6	5	6	0	5	30	16.9
3 geranium oil bourbon 10% pet.	0	2	1	1	5	1	2	3	15	8.4
4 l-citronellol 5% pet.	0	1	0	4	2	0	0	3	10	5.6
5 spearmint oil 5% pet.	1	0	1	0	2	3	2	0	9	5.0
6 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran 7% pet.	0	0	1	2	0	0	0	3	6	3.4
7 omega-6-hexadecenolactone 5% pet.	0	0	1	1	1	1	0	2	6	3.4
8 dimethyltetrahydrobenzaldehyde (isomer mixture) 5% pet.	0	0	0	1	1	0	0	2	4	2.3
9 α -amylcinnamaldehyde 5% pet.	0	0	1	0	1	1	0	1	4	2.3
10 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone 5% pet.	1	0	0	0	1	0	0	1	3	1.7
11 cyclopentadecanone 5% pet.	0	0	1	0	1	1	0	0	3	1.7
12 2-methyl-5-(2,3-dimethyl tricyclo[2.2.1.0(2,6)]hept-3-yl-2-pentenol(α -form) and 2-methyl-5-(2-methyl-3-methylenebicyclo[2.2.1]hept-3-yl-2-penten-1-ol(β -form) 5% pet.	0	0	0	1	1	0	0	0	2	1.1
13 isolongifolene ketone 5% pet.	0	0	0	0	0	0	1	0	1	0.6
14 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol 5% pet.	0	0	0	1	0	0	0	0	1	0.6
15 hexadecanolide 5% pet.	0	0	0	0	0	0	0	1	1	0.6
16 1-(2,2,6-trimethylcyclohexyl)-3-hexanol 5% pet.	0	0	0	0	0	0	0	0	0	0.0
17 2-pentylcyclopentan-1-one 5% pet.	0	0	0	0	0	0	0	0	0	0.0
18 6-ethylideneoctahydro-5,8-methano-2H-benzo-1-pyran 5% pet.	0	0	0	0	0	0	0	0	0	0.0
19 10-oxahexadecanolide 5% pet.	0	0	0	0	0	0	0	0	0	0.0
20 12-oxahexadecanolide 5% pet.	0	0	0	0	0	0	0	0	0	0.0
21 artificial jasmine 10% pet.	0	0	0	0	0	0	0	0	0	0.0

testing 20 control subjects without clinical evidence of fragrance allergy, to prove that the challenge concentrations for each individual ingredient were subirritant, using serial dilution challenge tests. Each participating center procured its own supply of the fragrance mix (FM).

Fragrance mix (FM) used consisted of 8 fragrance ingredients at 1% each (cinnamic alcohol, cinnamic aldehyde (cinnamal), α -amyl cinnamaldehyde, eugenol, isoeugenol, hydroxycitronellal, geraniol and oak moss absolute). The FM contained 5% sorbitan sesquioleate as an emulsifier.

Patch test method

Patch test methods and reading were according to internationally accepted criteria (4, 5). The patch test sites were evaluated initially at 2 or 3 days (D). The sites were re-examined in the majority of cases, usually between 2 and 5 D after the 1st reading.

Results

178 fragrance-sensitive patients were entered into the study. The results are tabulated in Table 1. Table 2 lists the fragrance materials according to the Principal Name adopted by the Research Institute of Fragrance Materials (RIFM), followed by the CAS number and abbreviations.

Discussion

78.7% of the participants reacted to the fragrance mix (FM). This is not surprising, since most patients were selected by a positive FM reaction or a reaction to some fragrance material. A reactivity rate above 2% included jasmine absolute, geranium oil bourbon, l-citronellol, spearmint oil, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran, omega-6-hexadecanolide, dimethyltetrahydrobenzaldehyde (isomer mixture), and α -amylcinnamaldehyde. These substances should be further evaluated to corroborate

Table 2. RIFM names, CAS numbers and abbreviations

1.	fragrance mixture
2.	jasmine absolute CAS 84776-64-7
3.	geranium oil, bourbon CAS 8000-46-2
4.	l-citronellol CAS 7540-51-4
5.	spearmint oil CAS 8008-79-5
6.	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopentagamma-2-benzopyran CAS 1222-05-5 (HHCB)
7.	omega-6-hexadecenolactone CAS 7779-50-2 (HDL)
8.	dimethyltetrahydrobenzaldehyde (isomer mixture) CAS 68737-61-1 (DTB)
9.	α -amylcinnamaldehyde CAS 122-40-7
10.	1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone CAS 54464-57-2 (OTNE)
11.	cyclopentadecanone CAS 502-72-7
12.	mixture of 2-methyl-5-(2,3-dimethyltricyclo[2.2.1.0(2,6)]hept-3-yl-2-penten-ol(α -form) and 2-methyl-5-(2-methyl-3-methylenebicyclo[2.2.1]hept-3-yl-2-penten-1-ol(β -form) (MMCP)
13.	isolongifolene ketone CAS 33407-62-4
14.	3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol CAS 67801-20-1 (MTCP)
15.	hexadecanolide CAS 109-29-5
16.	1-(2,2,6-trimethylcyclohexyl)-3-hexanol CAS 70788-30-6 (TMCH)
17.	2-pentylcyclopentan-1-one CAS 4819-67-4
18.	6-ethylideneoctahydro-5,8-methano-2H-benzo-1-pyran CAS 93939-86-7
19.	10-oxahexadecanolide CAS 1725-01-5
20.	12-oxahexadecanolide CAS 6707-60-4

their allergenicity. The following 5 fragrance materials have not previously been reported as contact allergens: (i) omega-6-hexadecenolactone; (ii) dimethyltetrahydrobenzaldehyde (isomer mixture); (iii) cyclopentadecanone; (iv) isolongifolene ketone; (v) 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol.

De Groot et al. (6) tested 9 fragrance materials (benzyl salicylate, citral, coumarin, hydroabietyl alcohol, jasmine synthetic, lilial, linalool, methyl salicylate, and ylang-ylang oil) in consecutive patients (1825) being routinely patch tested in The Netherlands. The frequency of positive reactions to the individual fragrance materials tested was only 1% or less. Since 2/3 of these reactions were in patients positive to the FM, most reactions had no added diagnostic value. They have therefore stopped testing with these chemicals; in contrast, our earlier studies (7) showed that testing with ylang-ylang oil, narcissus oil and sandalwood oil did extend the diagnostic capability of the FM.

Recently Frosch et al. (8) in Europe studied 11

fragrance materials in 1855 consecutive patients attending contact dermatitis clinics. They discovered that the widely used lylal (4-(4-hydroxy-4-methylpentyl)-3-cyclohexane carboxaldehyde) was an important sensitizer. Lylal sensitivity was found in many patients missed by the FM.

Thus, they recommend that Lylal be used in addition to the FM in patients suspected of contact dermatitis. Continuing studies such as these will be helpful in developing better screening chemicals and also mixes for the detection of fragrance sensitivity.

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