

Fragrance contact dermatitis – a worldwide multicenter investigation (Part III)

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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. 218 fragrance sensitive subjects were evaluated in eight centres worldwide with a fragrance mixture (FM) and 17 less well-studied fragrance materials. Reaction to the fragrance mixture (FM) occurred in 76% of the subjects. The (FM) detected all reactions to nerol and hydroxycitronellol and 93% of the reactions to clove bud oil. Ten fragrance materials were not detected by the FM and deserve further study: benzenepropanol, beta, beta, 3-trimethyl, hexyl-salicylate, DL-citronellol, synthetic ylang ylang oil, benzyl mixture, cyclohexyl-acetate, eugenyl methyl ether, isoeugenyl methyl ether, 3-phenyl-1-propanol, and 3, 7-dimethyl-7-methoxyoctan-2-ol.

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Allergy to fragrance ingredients in cosmetics and toiletries accounts for many instances of sensitization associated with the use of such products (1–3). While positive responses to the fragrance mixture have identified many patients with allergy to such chemicals since FM was introduced as a patch test mixture over 20 years ago, other scented materials found in such products account for many reactions (4–10). Several were identified in the first and second phase of this study (17, 18).

This report is the 3rd part of a 3-year investigation into fragrance material allergy by the investigators. The present study was undertaken to explore the possibilities of using further fragrance materials to screen patients with suspect fragrance allergy and to further explore the effects of possible substitute fragrance ingredients on patients known to be fragrance sensitive.

Materials and Methods

Study population

A total of 218 fragrance-sensitive volunteers were patch tested in 7 centres in industrial countries around the world (Japan, Northern Ireland, United States, England, Germany, Switzerland and Sweden). Volunteers had proven sensitization to fragrance materials established by previous patch tests to fragrance allergens. All of the volunteers had at least 1 positive reaction to a fragrance material. These patients were free of eczema and were called in to participate in this fragrance study.

Test substances

Test materials (Table 2) used in the investigation were prepared in batches in Japan by 3 major perfume companies and 7 cosmetic companies and were formulated in petrolatum. The challenge concentrations for the 17 fragrance ingredients used for this study were established by testing 20 control subjects without clinical evidence of fragrance al-

*Deceased.

lergy to establish that the challenge concentrations for each individual ingredient were subirritant using serial dilution challenge tests.

The FM consisted of cinnamic alcohol, cinnamic aldehyde, amyl-cinnamaldehyde, eugenol, isoeugenol, hydroxycitronellal, geraniol and oak moss absolute, all at 1% concentration. It also contained sorbitan sesquioleate as an emulsifier at 5% concentration.

Table 1. Demographics

Characteristic	
Age (n = 218)	46.3 ± 14.7
Sex (% Female, n = 217)	85.3
Location of Rash (% , n = 218)	
Generalized	3.7
Hand	26.1
Foot	0.9
Face	28.0
Lips	3.2
Eyes	0.5
Eyelids	1.4
Scalp	0.9
Neck	10.6
Arm	7.3
Leg	6.0
Trunk	1.8
Anal/genital	0.9
Most exposed areas	2.8
Only under clothing	0
Other sites	2.3
Past history (% reporting)	
Hay fever (n = 196)	24.0
Eczema (n = 191)	26.7
Asthma (n = 198)	13.6

Table 2. Results of patch

Test substance	n	% Positive
1. fragrance mix 8%	204	75.5
2. clove bud oil 10%	218	19.3
3. DL-citronellol 5%	218	8.7
4. isoeugenyl methyl ether 5%	218	7.3
5. synthetic ylang ylang oil 10%	218	6.4
6. hydroxycitronellol 7%	216	6.0
7. nerol 5%	218	6.0
8. benzenepropanol, beta, beta, 3-trimethyl*	217	3.2
9. benzyl mixture 5%	218	3.2
10. lavender oil 10%	218	2.8
11. eucalyptus oil 10%	218	1.8
12. eugenyl methyl ether 5%*	218	1.8
13. 3, 7-dimethyl-7-methoxyoctan-2-ol*	218	0.9
14. ethylene dodecanedioate 5%*	218	0.9
15. 3-phenyl-1-propanol 5%*	218	0.9
16. cyclohexylacetate 5%*	218	0.5
17. hexyl salicylate 5%	218	0
18. linalool 5%	218	0

*Not previously reported as allergen.

Patch test method

Patch test methods and reading were according to internationally accepted criteria (7, 12). The patch test sites were evaluated initially at 2–3 days. The sites were reexamined in the majority of cases, usually between 2 and 5 days after the 1st reading.

Data collection

Data were collected for each patient using a consistent data collection form. The following information was tabulated:

- Demographic information including age, sex, occupation, race, and past family history of asthma, eczema, and allergic rhinoconjunctivitis (hay fever).
- Specific information including dermatitis site and type.

Results

A total of 218 patients with proven contact dermatitis due to fragrance materials were entered into the study. Age was tabulated for all study participants and was 46.3 ± 14.7 years (mean $\pm$ standard deviation [SD]). Women predominated, and the majority of subjects were Caucasian (Table 1). Many patients reported a personal history of hay fever, asthma or atopic dermatitis as reported previously. Facial eruptions (28%) and hand involvement (26%) were the most common location for eczematous dermatitis.

All but 6 test substances produced a response in more than 1% of the 218 patients. Many substances yielded a high proportion of true positive responses that were deemed to be relevant (Table 2). 6 fragrance materials were associated with more than a 5% positive rate. Table 3 lists the fragrance materials according to the principal name adopted by the Research Institute of Fragrance Materials (RIFM) followed by the CAS number and common names.

Discussion

The age and female preponderance in this population of patients evaluated for fragrance allergy is similar to our previous study (17, 18) and that of others (11–13). The proportion giving a personal history of asthma and atopic dermatitis is once again higher than what is considered the norm for the general population (13.6% vs 4% (27) and 27% vs 3% (15). Diepgen & Fartasch reported a prevalence of 17.9%, 4.8% and 4.7%, respectively, for allergic rhinitis, asthma and atopic dermatitis in a group of 659 normal Germans reported in 1992

Table 3. RIFM names, CAS numbers and other common names

Test substance
1. fragrance mix
2. clove bud oil
3. DL-citronellol CAS 106-22-9
4. isoeugenyl methyl ether CAS 93-16-3 (methyl isoeugenol)
5. synthetic ylang ylang oil
6. hydroxycitronellol CAS 107-74-4
7. nerol CAS 106-25-2
8. benzenepropanol, beta, beta, 3-trimethyl CAS 103694-68-4 (majantol)
9. benzyl mix:
benzyl alcohol CAS 100-51-6
benzyl salicylate CAS 118-58-1
benzyl acetate CAS 140-11-4
10. lavender oil CAS 8000-28-0
11. eucalyptus oil CAS 8000-48-4
12. eugenyl methyl ether CAS 93-15-2 (methyl eugenol)
13. 3, 7-dimethyl-7-methoxyoctan-2-ol CAS 41890-92-0 (osyrol)
14. ethylene dodecanedioate CAS 54982-83-1 (musk 144)
15. 3-phenyl-1-propanol CAS 122-97-4
16. cyclohexylacetate CAS 622-45-7
17. hexyl salicylate CAS 6259-76-3
18. linalool CAS 78-70-6

(16). The proportion of those reporting a past history of atopic dermatitis is almost double the 14% prevalence reported by the NACDG for atopic dermatitis (14).

Positive responses were elicited to 6 fragrance ingredients not reported as contact allergens previously (Table 2). These positive responses suggest that persons exposed to these materials should be evaluated for allergic response to them. Clove bud oil, nerol and hydroxycitronellol would have been identified by a positive response to FM. However, the other responses would not be adequately screened by patch testing with FM. The FM missed the following 10 fragrance materials that showed positive reactions. These patients were negative to the fragrance mixture but had positive reactions to the following chemicals:

- benzenepropanol, beta, beta, 3-trimethyl (majantol);
- hexyl-salicylate;
- dl-citronellol;
- synthetic ylang ylang oil;
- benzyl mixture;
- cyclohexyl-acetate;
- eugenyl methyl ether;
- isoeugenyl methyl ether;
- 3-phenyl-1-propanol, and;
- 7-dimethyl-7-methoxyoctan-2-ol.

The 1st part of our study (17) found significant reactions to:

- ylang ylang oil;
- narcissus absolute;
- sandalwood oil;
- sandela; and

- benzenepropanol, beta, beta, 3-trimethyl (majantol).

In Part II of our study, we found significant reactions to:

- jasmin absolute;
- geranium oil bourbon;
- spearmint oil;
- levo-citronellol;
- 1, 3, 4, 6, 7, 8-hexahydro-4, 6, 6, 7, 8, 8, -hexamethyl cyclopenta-gamma-2-benzopyran (galaxolide);
- omega-6-hexadecenlactone and
- dimethyltetrahydro benzaldehyde (isomer mixture) (triplal).

All of these chemicals should be tested by other investigators to corroborate their allergenicity.

Recently in Europe Frosch et al. (19) studied 11 fragrance materials in 1855 consecutive patients attending contact dermatitis clinics. They discovered that Lyrall (4-(4-hydroxy-4-methyl pentyl)-3-cyclohexane carboxaldehyde) was an important sensitizer. Lyrall sensitivity was found in many patients missed by the FM. Frosch and his co-workers recommend that Lyrall be used in addition to the FM in patients suspected of contact dermatitis.

Conclusion

The current fragrance mixture (FM) detects about 60–70% of fragrance allergic patients. The purpose of our studies is to find new fragrance allergens. By identifying new allergens, we can test with new screening chemicals and screening mixtures for fragrance allergy. The ultimate goal is to detect all cases of fragrance allergy.

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