

Content and reactivity to product perfumes in fragrance mix positive and negative eczema patients

A study of perfumes used in toiletries and skin-care products

J. D. JOHANSEN¹, S. C. RASTOGI², K. E. ANDERSEN³ AND T. MENNÉ¹

¹Department of Dermatology, Gentofte Hospital, University of Copenhagen, Denmark ²National Environmental Research Institute, Department of Environmental Chemistry, Denmark

³Department of Dermatology, Odense University Hospital, Denmark

The aim of the study was to investigate the elicitation potential of perfumes from 17 commonly sold lower-price cosmetic products. 8 of the perfumes were from stay-on cosmetics and 9 were from wash-off cosmetics. Each perfume was tested in 500 consecutive eczema patients, who also were tested with the European standard patch test series. 4.2% reacted to 1 or more of the wash-off product perfumes and 3.2% to 1 or more of the stay-on product perfumes. Concordant positive reactions between the fragrance mix and the product perfumes were found in 81.3% of positive reactions to the stay-on product perfumes and in 52.4% of the reactions to the wash-off product perfumes. Compared to the fragrance mix alone, only 1 additional case of contact allergy to the product perfumes was detected by balsam of Peru. Chemical analysis revealed that between 1 and 5 of the chemically-defined constituents of the fragrance mix were present in all of the product perfumes. Geraniol was found in 12 of the 17 perfumes and was most often detected. The concentration of the target fragrance materials ranged from 0.005%–1.35 w/v%. It is concluded that the allergenic constituents of the fragrance mix are impossible to avoid if perfumed cosmetics are used. Furthermore, patients suspected of perfume allergy need to be tested with their own perfumed products, as far from all cases of perfume allergy are detected by the fragrance mix and/or balsam of Peru in the European standard patch test series.

Key words: perfumes; allergic contact dermatitis; fragrance mix; balsam of Peru; gas chromatography-mass spectrometry. © Munksgaard, 1997.

Accepted for publication 27 February 1997

Contact allergy to fragrances is frequent. In 9835 eczema patients tested during 1994 by members of the German Contact Allergy Group, 15.3% had a positive reaction to the fragrance mix (1). In comparison, reactions to nickel, the most frequent contact allergen, occurred in 16.9% of the population. From 1993 to 1994, an increase was found, mostly in women, from 13.5% positive to fragrance mix in 1993 to 17.1% in 1994. A similar rising trend is found in other European countries (2). Fragrances are used in many different types of cosmetic products. Some are used for the purpose of the pleasures of smell, others have cleansing or beautifying effects as well.

In Europe, the sale of perfumes constitute 16% of the market of cosmetic products, while toiletries, hair/skin care and decorative cosmetics comprise the rest (3). It has previously been shown that widely sold prestige perfumes, i.e. eau de parfum/ eau de toilette, were able to provoke eczema in 1

out of every 15 female eczema patients (4). In the present study, the elicitation potential of perfumes used in popular, everyday products, within the groups of toiletries and hair/skin care products, was assessed. In addition, the content of selected fragrance allergens in the perfumes was determined by quantitative chemical analysis.

Materials and Methods

Study population

Consecutive eczema patients being patch tested either at the Department of Dermatology, Gentofte Hospital, University of Copenhagen, or Odense University Hospital were included in the study. 500 patients from Gentofte and 500 from Odense participated. Background variables are given in Table 1. The study was approved by the local ethical committees.

Table 1. Background information on the study populations

Variables	Odense (n=498)	Gentofte (n=497)
Sex		
male	179 (35.9%)	211 (42.5%)
female	319 (64.1%)	286 (57.5%)
ever rash from perfumed cosmetics	138 (28.3%) ¹	145 (31.0%) ²
daily use of perfumed cosmetics	374 (77.2%) ³	394 (84.5%) ⁴
distribution of eczema:		
face/neck	50 (10.1%)	57 (11.5%)
hands/arms	182 (36.5%)	144 (29.0%)
axilla	5 (1%)	13 (2.6%)
legs, no ulcer	31 (6.2%)	27 (5.4%)
legs, + ulcer	6 (1.2%)	12 (2.4%)
trunk	27 (5.4%)	18 (3.6%)
face+hands	27 (5.4%)	30 (6.0%)
hands+legs	71 (14.3%)	65 (13.1%)
anogenital	8 (1.6%)	12 (2.4%)
universal	64 (12.9%)	70 (14.1%)
data missing	27 (5.4%)	49 (9.9%)

Missing data for¹: 12 persons, ²: 30 persons, ³: 14 persons, ⁴: 31 persons.

Patch test materials

17 perfumes were used for patch testing in addition to the European standard patch test series. All 17 perfumes were supplied by a cosmetic company manufacturing popular lower-price products for daily use. 9 of the perfumes came from wash-off products (Table 2) and were tested in Odense, 8 came from stay-on cosmetics and were tested in Gentofte (Table 3).

Patch test concentrations

25 healthy control persons were tested with the 9 and another 25 with the 8 perfumes dissolved in petrolatum at 1%, 2% and 5%. The control persons were 48 women and 2 men, mean age 41.3 years (range 19–56), with no history of prior skin symptoms from using perfumed products. 1 woman reacted to 7 of the wash-off product perfumes in several concentrations on day 3 and was considered to be a case of allergic sensitivity. Another had a doubtful reaction to 1 perfume at 2% and 5%. 2 of the stay-on product perfumes (2% and 5%) gave a doubtful reaction on day 3 in 1 person. Based on these results, 5% in petrolatum (pet.) was selected as the test concentration for all the perfumes. The fragrance mix consisted of 8 fragrance materials: cinnamic aldehyde, cinnamic alcohol, α -amyl cinnamic aldehyde, eugenol, isoeugenol, geraniol, hydroxycitronellal and oak moss, each 1% pet. together with the emulsifier sorbitan sesquioleate 5% (Hermal, Reinbeck, Germany), which was used in

Gentofte. In TRUE Test (ALK-Abello), which was used in Odense, the fragrance mix had an identical composition of fragrances and was tested at 450 $\mu\text{g}/\text{cm}^2$. The test concentration of balsam of Peru was 25% pet. from Hermal in Gentofte and 800 $\mu\text{g}/\text{cm}^2$ as supplied by ALK-Abello (TRUE Test) in Odense.

Patch test methods

The test substances were applied to the upper back for 2 days under occlusion. Readings were made on the 2nd, 3rd and 5th–7th day according to the ICDRG's scale.

Relevance of patch test reactions

Prior to patch testing, all participants were asked if they had ever experienced a rash from cosmetic products and if they had used perfumed cosmetic products daily before the outbreak of their eczema.

Chemical analysis

All perfumes and the corresponding cosmetic products were analyzed for their content of fragrance mix constituents, except oak moss. Quantification was made by gas chromatography - mass spectrometry (5). The analysis was done without knowledge of the results of patch testing.

Statistics

Fisher's test was used for comparison between 2 rates. The chosen level of significance was $p \leq 0.05$.

Results

Non-participants

81 patients did not want to participate in Gentofte (14%), 57 women and 24 men. 7 of these were fragrance mix positive (8.6%). No significant difference in fragrance mix sensitivity among those who participated and the non-participants were found. 50 patients did not want to participate in Odense (10%), 39 women and 11 men. 7 of these were fragrance mix positive (14%), which is significantly more than in the group of participants ($p=0.004$).

Eliciting capacity of the perfumes

A significant relationship between previous rash and a positive patch test reaction to 1 or more of the extra perfumes was found ($p=0.001$). 21 of 498 (4.2%, 95%-confidence interval 2.6%–6.4%) reacted to 1 or more of the wash-off product perfumes and 16 of 497 (3.2%, 95%-confidence inter-

val 1.9%–5.2%) reacted to 1 or more of the stay-on product perfumes. The stay-on product perfumes gave a total of 54 positive reactions, mean 2.6 positive reactions/subject. The wash-off product perfumes gave 57 reactions, mean 3.6 positive reactions/subject). Results from the single perfumes are given in Tables 2, 3. No major difference in reactivity to the single perfumes was seen. The same age distribution was found in the group of perfume-positive as in the negative group in both centres. A little more of the women (4.3%) than of the men (2.8%) reacted to the product perfumes, but the difference was not significant.

Concordant positive reactions between the fragrance mix, balsam of Peru and the product perfumes

Concordant positive reactions to the extra perfumes and the fragrance mix were found in 13 cases in Gentofte and 11 cases in Odense. Of the positive reactions to the stay-on product perfumes, 81.3% were detected by the fragrance mix (Gentofte) and 52.4% of the reactions to the wash-off product perfumes (Odense) (Table 4). Fewer of the reactions were detected by Peru bal-

sam (Table 4) and, compared to the fragrance mix alone, only 1 additional case was detected by balsam of Peru.

Content of fragrance mix constituents in the perfumes

All the investigated perfumes, both from the wash-off and stay-on cosmetics, contained at least 1 of the chemically defined constituents of the fragrance mix. An average of 2.8 allergens/wash-off product perfume and 2.6 allergens/stay-on product perfume was found. The range of known allergenic substances was 1–5 and 1–4 respectively. Geraniol was found in 12 perfumes, α -amyl cinnamic aldehyde in 10, cinnamic alcohol and eugenol in 8. Hydroxycitronellal was found in 6 and isoeugenol in 2 perfumes. Cinnamic aldehyde was not detected (detection limit 1 ppm). The concentration of the target fragrance materials ranged from 0.01–1.35 w/v% in the wash-off perfumes and from 0.005–0.24 w/v% in the stay-on product perfumes. The mean allergen concentration was 0.23% in the wash-off perfumes and 0.08% in the stay-on perfumes (Tables 2, 3).

Table 2. Results from patch testing with and chemical analysis off the wash-off product perfumes

	Patch test results with perfume 5% pet. number of patients with:		Product type	Contents of fragrance mix constituents	concentration in perfume % (w/v)
	?+	+ / + + / + + +			
1	20	4	baby bath	geraniol	0.0500
2	30	5	body shampoo	geraniol	0.1187
				cinnamic alcohol	0.3288
				eugenol	0.0252
				α -amyl cinnamic aldehyde	0.0134
3	22	8	hair shampoo	geraniol	+
				cinnamic alcohol	0.1020
				eugenol	0.2740
				isoeugenol	0.1350
4	31	7	shower baths	hydroxycitronellal	0.0990
				cinnamic alcohol	0.1000
				eugenol	0.1028
				α -amyl cinnamic aldehyde	+
5	20	9	creme rinse	geraniol	0.0695
				eugenol	0.3878
				α -amyl cinnamic aldehyde	1.3477
6	28	7	shampoo	α -amyl cinnamic aldehyde	0.8462
7	21	4	creme rinse	geraniol	+
8	27	4	skin tonic	geraniol	+
				hydroxycitronellal	+
				eugenol	+
				isoeugenol	0.1702
				α -amyl cinnamic aldehyde	0.0832
9	29	6	shampoo	geraniol	0.0954
				cinnamic alcohol	0.0610

+: detected, but quantification not possible due to interference.

Table 3. Results from patch testing with and chemical analysis of the stay-on product perfumes

	Patch test results with perfume 5% pet. number of patients with:		Product type	Contents of fragrance mix constituents	concentration in perfume % (w/v)
	?+	+ / + + / + + +			
1	5	4	body lotion	geraniol hydroxycitronellal	+ 0.007
2	6	7	sun lotion	cinnamic alcohol eugenol α -amyl cinnamic aldehyde	0.0827 0.1090 0.1747
3	13	7	body lotion	α -amyl cinnamic aldehyde	0.0050
4	11	7	moisturizer	geraniol hydroxycitronellal cinnamic alcohol α -amyl cinnamic aldehyde	+ 0.0636 0.0163 0.0356
5	7	7	antiperspirant	geraniol cinnamic alcohol eugenol α -amyl cinnamic aldehyde	0.1866 0.0183 0.0581 0.0367
6	10	12	deo stick	geraniol	+
7	13	8	deo stick	geraniol hydroxycitronellal eugenol	+ 0.1408 0.0563
8	9	5	moisturizer	hydroxycitronellal cinnamic alcohol α -amyl cinnamic aldehyde	0.2444 0.0119 0.1461

+: detected, but quantification not possible due to interference.

Table 4. Concordant reactions to fragrance mix, balsam of Peru and the product perfumes

	Odense	Gentofte
No. positive reactions to the product perfumes detected by: fragrance mix	52.4% (11/21)	81.3% (13/16)
by: balsam of Peru	9.5% (2/21)	37.5% (6/16)
No. fragrance mix positive persons reacting positively to 1 or more of the extra perfumes	73.3% (11/15)	31% (13/42)
No. balsam of Peru positive persons reacting positively to 1 or more of the extra perfumes	28.6% (2/7)	35.3% (6/17)

Discussion

Patch testing with commercial perfumes has been found a useful and relevant tool in diagnosing perfume allergy (6, 7). Rothenborg & Hjorth (6) patch tested 1943 consecutive eczema patients with 4 perfumes, 2 from toilet soaps and 2 from detergents, which were the 4 most common brands on the market. They used 5% pet. for the soap perfumes and 2.5% pet. for the detergent perfumes. Of the 1943 patients examined, 78 (4%) were found to react positively to patch testing with 1 or more of the toilet soap or detergent perfumes. An equal % was found among women and men (6). Hannukse-la et al. (7) used a perfume from an aftershave lotion as an additional fragrance screening test besides balsam of Peru. Of 1823 tested patients, 3.6% were positive to the perfume. We found a similar

frequency of reactivity to perfumes from commonly sold stay-on and wash-off cosmetics. 4.2% (21/498) reacted to 1 or more of the perfumes from the wash-off products and 3.2% (16/497) to the stay-on product perfumes. The patients were recruited for testing consecutively; however, in Odense, where the wash-off product perfumes were tested, some of the patients with known fragrance allergy did not want to participate in the study. This may have given slightly less reactivity to the tested wash-off-product perfumes than otherwise could be expected.

In a previous study, the 10 most sold prestige perfumes in Europe elicited a reaction in 6.9% of 335 consecutive female eczema patients on patch testing (4). This was significantly more reactions than was found in the current study to the stay-on product perfumes, which were also tested in

consecutive patients. It does not necessarily mean that the elicitation potential of the lower-price product perfumes is less than the prestige perfumes, as the prestige perfumes were tested as is, which gives a 20-fold higher patch test concentration than in the current study, where 5% pet. was used. However, if the actual use conditions are taken into account, the prestige perfumes are likely to produce more allergic reactions as they are applied to the skin undiluted, whereas the perfumes tested in the current study are usually dissolved in a product in maximum concentrations of 1–2% before use.

The fragrance mix was composed as an imitation of a perfume used in a popular product 20 years ago (8). The current study shows that the constituents of the fragrance mix, isoeugenol, geraniol, hydroxycitronellal, cinnamic alcohol, eugenol and α -amyl cinnamic aldehyde, are still used extensively (Tables 2, 3). All 17 perfumes contained at least 1 and on average 2.6–2.8 of the allergenic ingredients from the fragrance mix. In a study by Fenn, geraniol, eugenol, α -amyl cinnamic aldehyde and hydroxycitronellal were found in more than 1% concentration in 20–40% of fine fragrances sold in the US (9). The above-mentioned prestige perfumes contained 3–6 of the fragrance mix ingredients, mean 4 ingredients/product (4), which is more than the perfumes in the current study. Constituents of the fragrance mix have also been found in most of the products causing skin reactions in fragrance mix positive eczema patients, as well as in natural ingredient based cosmetics (10, 11). This shows that fragrance allergens are ubiquitous and thus virtually impossible to avoid if perfumed cosmetics are used.

The fragrance mix is part of the standard patch test series and is used as a screening agent for fragrance contact allergy together with the balsam of Peru. All patients suspected of allergic contact dermatitis are tested with these 2 indicators of fragrance allergy, but only occasionally are the patients own products used for patch testing. It is thus important to know how many cases are missed if only the screening agents for fragrance contact allergy are employed.

In Odense, where the wash-off product perfumes were tested, 52.4% of those positive to the product perfumes were also positive to the fragrance mix, a value similar to that found in the study of the prestige perfumes (4). In Gentofte, 81.3% of the reactions to the stay-on product perfumes were detected by the fragrance mix, a value similar to that found by testing with single fragrance chemicals and natural extracts (12–14). Balsam of Peru detected only a minority of the reactions to the product perfumes and had almost no additional value

in diagnosing fragrance contact allergy, compared to the fragrance mix.

The study shows a variation in the detection ability of the fragrance mix depending on the perfumes and population tested. It also clearly demonstrates that the patients' own perfumed products need to be tested if all cases of perfume allergy are to be diagnosed. In this context, it should be noted that a statistically significant association was found between a previous rash from perfumes and a positive patch test reaction to the product perfumes, indicating clinically relevant allergy. On the other hand, as many as 70% of the fragrance mix positive subjects did not react to the product perfumes (Table 4). This shows that even though patients react to the fragrance mix, perfumes containing these constituents may in some cases be tolerated. It is a subject for future research to determine whether this discrepancy may be due to low reactivity to the allergens in question, or if these subjects constitute a subgroup of patients with a different type of allergy.

Acknowledgements

We thank the nurses at both clinics for technical assistance in performing the patch tests, Eva Tiedemann for preparing the test materials, and Gitte Jensen for assistance with the chemical analysis. Financial support from The Danish Environmental Protection Agency, The Chemicals Group under The Nordic Council, and Professor Niels Hjørth's Foundation is gratefully acknowledged.

References

1. Schnuch A, Geier J. Die häufigsten Kontaktallergene im Jahr 1994. *Dermatosen* 1995; 43: 275–278.
2. Johansen J D, Menné T. The fragrance mix and its constituents: a 14-year material. *Contact Dermatitis* 1995; 32: 18–23.
3. The European Cosmetic Toiletry and Perfumery Association. European sale statistics 1993/94.
4. Johansen J D, Rastogi S C, Menné T. Contact allergy to popular perfumes; assessed by patch test use test and chemical analysis. *Br J Derm* 1996; 135: 419–422.
5. Rastogi S C. Analysis of fragrances in cosmetics by gas chromatography-mass spectrometry. *J High Res Chromatogr* 1995; 18: 653–658.
6. Rothenborg H W, Hjørth N. Allergy to perfumes from toilet soaps and detergents in patients with dermatitis. *Arch Derm* 1968; 97: 417–421.
7. Hannuksela M, Kousa M, Pirilä A. Allergy to ingredients of vehicles. *Contact Dermatitis* 1976; 2: 105–110.
8. Larsen W G. Perfume dermatitis. A study of 20 patients. *Arch Dermatol* 1977; 113: 623–626.
9. Fenn R S. Aroma chemical usage trends in modern perfumery. *Perfumer & Flavorist* 1989; 14: 1–10.
10. Johansen J D, Rastogi S C, Menné T. Exposure to selected fragrance materials. A case study of fragrance-mix-positive eczema patients. *Contact Dermatitis* 1996; 34: 106–110.

11. Rastogi S C, Johansen J D, Menné T. Natural ingredient based cosmetics: content of selected fragrance sensitizers. *Contact Dermatitis* 1996; 34: 423-426.
12. De Groot A, Liem D H, Nater J P, Ketel W G. Patch tests with fragrance materials and preservatives. *Contact Dermatitis* 1985; 12: 87-92.
13. Frosch P J, Pilz B, Andersen K E, Burrows D, Camarasa J G, Dooms-Gossens A et al. Patch testing with fragrances. Results of a multicenter study of the European Environmental and Contact dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis* 1995; 33: 333-342.
14. Larsen W, Nakayama H, Lindberg M, Fischer T, Elsner P, Burrows D et al. Fragrance contact dermatitis: A worldwide multicenter investigation (Part I). *Am J Contact Dermatitis* 1996; 7: 77-83.

Address:

Jeanne Duus Johansen
Department of Dermatology
Gentofte Hospital
2900 Hellerup
Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.