

Fragrance allergy in patients with hand eczema – a clinical study

SIRI HEYDORN¹, JEANNE DUUS JOHANSEN², KLAUS E. ANDERSEN³, MAGNUS BRUZE⁴, CECILIA SVEDMAN⁴, IAN R. WHITE⁵,
DAVID A. BASKETTER⁶ AND TORKIL MENNÉ¹

¹Department of Dermatology, ²The National Allergy Research Centre for Consumer Products, University of Copenhagen, Gentofte Hospital, Hellerup, ³Department of Dermatology, Odense University Hospital, University of Southern Denmark, Odense, Denmark, ⁴Department of Occupational and Environmental Dermatology, Malmö University Hospital, Lunds University, Malmö, Sweden, ⁵St. John's Institute of Dermatology, St. Thomas' Hospital, London, ⁶SEAC Toxicology, Unilever Research, Sharnbrook, UK

Fragrance allergy and hand eczema are both common among dermatological patients. Fragrance mix (FM) and its constituents have a recognized relevance to exposure to fine fragrances and cosmetic products. Based on extensive chemical analysis and database search, a new selection of fragrances was established, including 14 known fragrance allergens present in products to which hand exposure would occur. A non-irritating patch-test concentration for some fragrances was established in 212 consecutive patients. 658 consecutive patients presenting with hand eczema were patch tested with the European standard series and the developed selection of fragrances. 67 (10.2%) of the 658 patients had a positive reaction to 1 or more of our selection of fragrance chemicals present in the new selection. The most common reactions to fragrances not included in the FM were to citral, Lyrall[®] (hydroxyisohexyl-3-cyclohexene carboxaldehyde) and oxidized L-limonene. A concomitant reaction to the FM identified potential fragrance allergy in less than 1/2 of these patients. Exposure assessment and a statistically significant association between a positive patch test to our selected fragrances and patients' history support the relevance of this selection of fragrances. Those with a positive reaction to our selected fragrances were significantly more likely to have 1 or more positive patch tests in the standard series. This observation is the basis for the hypothesis concerning cross-reactivity and the effect of simultaneous exposure. The study found that fragrance allergy could be a common problem in patients with eczema on the hands.

Key words: citral; fragrance allergy; fragrance; hand eczema; Lyrall[®]; oxidized limonene; patch testing. © Blackwell Munksgaard, 2003.

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Fragrance allergy, defined as a positive patch test to the fragrance mix (FM), is found in 2.4%–11.3% of patch-tested patients in Slovenia, Denmark, Germany, Italy and the rest of Europe (1–5). An association between hand eczema and contact allergy to fragrances has been suggested in a number of studies (6). The hands are exposed to fragrances present in cosmetic products such as lotions, after-shave preparations, shampoos and many others. Besides these types of exposure, however, the hands are in contact with fragrances in a multitude of other products both domestically and occupationally, such as detergents, dishwashing liquids, soaps and hard-surface cleaners.

Investigations of various cosmetic products demonstrated the presence of a wide range of fragrance chemical allergens (7, 8). More recently,

we analysed the contents of fragrances used in domestic and occupational products intended for hand exposure or for which hand exposure was probable (9). Although there was some overlap in fragrance chemicals used in these products compared to cosmetics, there were also clearly important differences between the 2 product types. The aim of this study was to investigate a large number of patients referred with hand eczema concerning their frequency of positive patch tests to allergens in a selection of fragrances and to the European standard series.

Materials and Methods

The basis for the present investigation was a thorough exposure assessment of fragrances

contained in products intended for hand contact or for which hand contact was probable. The study included a 2-step procedure comprising thorough chemical analysis of target products (9) and analysis of available industrial databases for the use (quantitatively) of possible fragrance contact allergens present in products aimed at hand contact. The selection of the final list was based on the relative contribution following 3 criteria: known human contact allergens, fragrances used in products associated with hand exposure and the quantities used in consumer products. From this, a balanced decision as to inclusion in our selection of fragrances was made between the authors.

Preliminary testing

The patch-test concentrations were based upon the available literature (Table 1). Where the patch-test concentration was undefined, several concentrations were included in the preliminary testing. The test series was evaluated for irritancy, partly by searching the literature and partly by testing 212 consecutive patients at St. John's Institute of Dermatology, St. Thomas' Hospital, London. The main study ran in 3 clinical centres (Gentofte, Malmö and Odense) during the period from March 2001 to September 2002.

Participants

Eligible participants were consecutive patients among the referrals in the 3 participating clinical centres, all of whom had eczema on the hands,

confined by the wrist, but who were also allowed to have eczema elsewhere on the body.

Questionnaire

On the 1st day (D) of patch testing, all participants were asked to fill in a short questionnaire with a cross for either 'Yes' or 'No' in most questions.

- Sex.
- Age.
- Did you have eczema in the elbow/knee folds (child eczema) as a child?
- Did you have asthma or hay fever as a child?

4 different questions concerning exposure-defined relevance:

- Have you ever had eczema after use of perfumed household and/or cleaning products?
- Have you ever had eczema after use of perfumed cosmetics or skin care products? (Examples given)
- Have you had eczema after use of perfumed products in the last 12 months?
- Do you think that use of perfumed products worsens your eczema?

The questionnaire also included the following questions:

- Do you use gloves when doing housework and/or cleaning?
- Do you have skin contact with household or cleaning products at work?
- Does your eczema worsen if you do housework and/or cleaning without gloves?

Table 1. Positive patch-test reactions to a selection of fragrances in 658 patients with hand eczema

Patch-test substances (CAS no.)	Patients with positive reactions [n (%)]
Citral 2% pet. (5392-40-5)	28 (4.3)
Hydroxycitronellal 5% pet. * (107-75-5)	20 (3.0)
Lyrall [®] 5% pet. (31906-04-4)	14 (2.1)
Eugenol 5% pet. * (97-53-0)	13 (2.0)
Oxidized L-limonene 3% pet. † (5989-54-8)	6 (0.9)
Geraniol 5% pet. * (106-24-1)	6 (0.9)
Citral 1% pet. ‡ (5392-40-5)	3 (0.8)
Citral 0.5% pet. ‡ (5392-40-5)	1 (0.3)
Oxidized D-limonene † 3% pet. (5989-27-5)	5 (0.8)
Lilial [®] 10% pet. (80-54-6)	3 (0.5)
Coumarin 5% pet. (91-64-5)	3 (0.5)
α-Hexylcinnamaldehyde 10% pet. (101-86-0)	3 (0.5)
Benzyl salicylate 5% pet. (118-58-1)	2 (0.3)
Galaxolide 10%, IPM 10% pet. (1222-05-5)	2 (0.3)
Citronellol 5% pet. (106-22-9)	2 (0.3)
Benzyl benzoate 5% pet. (120-51-4)	1 (0.2)

IPM (isopropyl myristate) was tested at 10% petrolatum (pet.) and was negative in those positive to Galaxolide[®]. Galaxolide[®] = 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopental[g]benzopyran; Lilial[®] = 2-methyl-3-(4-*tert*-butyl-phenyl) proanal; Lyrall[®] = 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene carbaldehyde and INCI (hydroxyisohexyl-3-cyclohexene carboxaldehyde).

*Part of the fragrance mix.

†n = 649.

‡n = 392.

- Where is your eczema located?
- How long is it since you had eczema for the first time?

Patch-test material

Except for prepared syringes with oxidized D- and L-limonene at 3% white petrolatum (pet.) without antioxidant (tocopherylacetate), donated by Prof. A.-T. Karlberg (Gothenburg, Sweden), all fragrance chemicals were donated by Dr. D. Basketter, Unilever Research (Sharnbrook, UK) and dispersed in white pet. according to protocol by the same laboratory technician in Gentofte throughout the study period. Specifications of purity according to labelling or product sheet were: α -hexylcinnamaldehyde (101-86-0), 85%; citral (5392-40-5), 95%; hydroxycitronellal (107-75-5), unknown; Lyrall[®] (hydroxyisohexyl-3-cyclohexene carboxaldehyde, 31906-04-4), 99.4%; Lilial[®] (80-54-6), 98.5%; Galaxolide[®] (1,3,4,6,7, 8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c] pyran, 1222-05-5), 94.9%; isopropyl myristate (Merck-Schuchardt Eurolab, Hohnbrunn, Germany), 98%; benzyl salicylate (118-58-1), 99%; benzyl benzoate (120-51-4), 99%; coumarin (91-64-5), unknown; geraniol (106-24-1), 98%; eugenol (97-53-0), 99%; and dL-citronellol (106-22-9), 95%. The purity of oxidized D-limonene (5989-27-5) and oxidized L-limonene (5989-54-8) was reported as following by Prof. A.-T. Karlberg: 'after 10 weeks of air exposure 34% of the original compound remained in the oxidation mixture of D-limonene as well as in the oxidation mixture of L-limonene according to analysis with gas-chromatography'. The patch tests were applied to the skin of the upper back for 2 D, using Finn Chambers[®] (Epitest, Helsinki, Finland) on Scanpor[®] tape (Norgesplaster A/S, Venne, Norway). Readings were taken on D2 and/or D3-4 and on D7. ICDRG recommendations were followed (10). A patch test was considered positive when the reading was +, ++ or +++. A + patch-test reaction was defined as homogeneous erythema and infiltration, whereas only erythema was not.

The standard series used in Gentofte was from Hermal[®] (Reinbek, Germany) apart from sesquiterpene lactone mix, which became unavailable from Hermal[®] and was therefore obtained from Chemotechnique[®] (Malmö, Sweden). In Odense, the standard series was TRUE Test[™] (Chemotechnique[®]), supplemented by test substances from Hermal[®]. In Malmö, the standard series was from Chemotechnique[®]. In Odense, they tested 229, in Gentofte 220 and in Malmö 209 patients with hand eczema. As seen in tables 2 and 3, patch-test results from Hermal[®],

Chemotechnique[®] and TRUE Test[™] were combined for each allergen in the standard series.

Statistical methods

For tabulation and calculation, the strongest positive patch-test reaction at any of the readings was used. We used logistic regression (full model and backward elimination with a 5% significance level) with at least 1 positive patch test to our selected fragrances (Table 1) as the dependent (response) variable in the SAS[®] system for Windows[®] release 8.02 TS level 02MO© 1999–2001 by SAS Institute Inc. (Cary, NC, USA). Replies from the questionnaire (age, sex, child eczema, asthma/hay fever, time since the 1st onset of eczema, axillary dermatitis and facial/neck dermatitis) were entered as explanatory variables along with a variable termed a positive fragrance history, defined as at least 1 positive answer on the questionnaire to the 4 different questions regarding exposure-defined relevance. A variable termed other positive patch tests than our selection of fragrances was also entered. It was defined as the number of positive patch tests from 0 to 23 in the European standard series.

55 participants had no information regarding patch testing to the standard series. The logistic regression (full model and backward elimination) was repeated, excluding the missing data and excluding FM from the variable termed other positive patch tests. That is to say, the same dependent variable (at least 1 positive patch test to our selected fragrances) but with only 603 included participants and the explanatory variables age, sex and other positive patch tests excluding the FM.

Afterwards, this logistic regression was repeated with $n = 601$, excluding a further 2 participants who reacted to citral 0.5% and citral 1% but to none other of our selected fragrances. Finally, we repeated the logistic regression again with $n = 596$, adding the explanatory variable fragrance history and excluding participants who had missing values on the issue of fragrance history.

Ethical considerations

The study was carried out according to the Helsinki Declaration II and approved by the local ethics committees at each centre. Every research subject was required to give verbal and written informed consent.

Results

A total of 658 patients with hand eczema referred to 1 of the 3 participating clinics were tested with a selection of 14 fragrances found in household

Table 2. Characterization of 658 consecutive hand eczema patients patch tested with a selection of fragrances

	At least 1 positive patch test to a selection of fragrances (%)	No positive patch tests to a selection of fragrances (%)	Both groups (%)	Non-responders in the 3 categories (%)
Sex	45 females (67) 22 males (33)	359 females (61) 232 males (39)	404 females (61) 254 males (39)	0/0/0
Age (years)				
0–20	0	31 (5)	31 (5)	0/0/0
21–30	14 (21)	139 (24)	153 (23)	
31–40	13 (19)	159 (27)	172 (26)	
41–50	11 (16)	117 (20)	129 (20)	
51–60	20 (30)	99 (17)	118 (18)	
>61	9 (13)	46 (8)	55 (8)	
Eczema in elbow/knee folds as a child	13 (19)	134 (23)	147 (23)	0/8/8
Hay fever/asthma as a child	4 (6)	106 (18)	111 (17)	0/9/9
Time since onset of eczema				
0–3 months	2 (3)	23 (4)	25 (4)	0/3/3
4–12 months	11 (16)	147 (25)	158 (24)	
13 months to 5 years	20 (30)	181 (31)	201 (31)	
>5 years	34 (51)	237 (40)	271 (41)	
Axillary eczema	7 (14)	59 (13)	66 (13)	16/132/148
Facial/neck eczema	18 (33)	138 (29)	156 (29)	13/108/121
Use gloves when cleaning/house working	34 (54)	288 (52)	322 (52)	4/40/44
Positive fragrance history by questionnaire	48 (72)	276 (47)	324 (50)	0/5/5
Other positive patch tests than the selection of fragrances (European standard series without FM)	44 (69)*	168 (31)*	212 (35)*	64/537/601*

FM = fragrance mix.

*For details, see *Materials and methods*.

products according to our previously published work (9). Basic characteristics of the 658 participants (61.4% women and 38.6% men) are summarized in Table 2. Most of the participants were in the working age group and more than 40% had first experienced their eczema >5 years ago. 22.6% indicated flexural dermatitis as a child and 17.1% hay fever/asthma as a child.

67 (10.2%) of the patients with hand eczema had 1 or more positive patch-test reactions to our selection of fragrances (Table 1). The most frequent positive fragrance patch-test reactions were to: citral, 28 patients (4.3%); hydroxycitronellal, 20 patients (3%); Lyrall[®], 14 patients (2.1%); and eugenol, 13 patients (2.0%). The remaining fragrances all gave a frequency below 1%. 30 patients (45.5%) of those with at least 1 positive reaction to our selection of fragrances also had a positive patch test to the fragrance mixture (Table 3).

A positive fragrance history, as defined earlier, was found in 71.6% of those participants with at least 1 positive patch test to our selection of fragrances, compared to 47.1% of those negative to our selection of fragrances. In the European standard series, 80.3% of those participants with at least 1 positive patch test to our selection of fragrances had 1 or more positive reactions, in contrast to only 33.7% of those negative to our

selection of fragrances. Logistic regression (full model, $n=658$) with the explanatory variables age, sex, childhood eczema, asthma/hay fever, time since onset of eczema, axillary dermatitis, facial/neck dermatitis and positive fragrance history and with the dependent variable participants with at least 1 positive patch test to the selection of fragrances found the following significant variables: a positive fragrance history ($P=0.0103$) and other positive patch tests (European standard series including FM, $P<0.0001$). A backward elimination model confirmed the significance of the variables a positive fragrance history ($P=0.0287$) and other positive patch tests ($P<0.0001$), but the variable hay fever/asthma as a child was just about significant ($P=0.0384$).

Logistic regression (full model and backward elimination) with $n=603$. The full model as well as the backward elimination model found that the significant variable was other positive patch tests (European standard series excluding the FM this time) than our selection of fragrances ($P<0.0001$). The logistic regression with $n=601$ showed the same result. Logistic regression with $n=596$ found the following significant variables: other positive patch tests (European standard series excluding FM) ($P<0.0001$, full and backward model) and the variable positive fragrance history

Table 3. Frequency of reactions to the European standard series

	At least 1 positive patch test to a selection of fragrances (%)	No positive patch tests to a selection of fragrances (%)	Both groups (%)
Potassium dichromate	8 (12.1)	23 (4.3)	31 (5.2)
Neomycin sulfate	2 (3.0)	7 (1.3)	9 (1.5)
Thiuram mix	2 (3.0)	11 (2.1)	13 (2.2)
<i>p</i> -Phenylenediamine	1 (1.5)	9 (1.7)	10 (1.7)
Cobalt chloride	7 (10.6)	28 (5.2)	35 (5.8)
Benzocaine	0	0	0
Formaldehyde	2 (3.1)	10 (1.9)	12 (2.0)
Colophonium	10 (15.2)	16 (3.0)	26 (4.3)
Clioquinol		1 (0.5)	1 (0.5)
Myroxylon Pereirae resin	15 (22.7)	15 (2.8)	30 (5.0)
Black rubber mix	1 (1.5)		1 (0.2)
Amerchol L-101-/lanolin	2 (3.1)	4 (0.7)	6 (1.0)
MBT mix	2 (3.0)		2 (0.3)
Epoxy resin	4 (6.1)	3 (0.6)	7 (1.2)
Parabens		1 (0.2)	1 (0.2)
PTBPF resin	3 (4.6)	4 (0.7)	7 (1.2)
FM	30 (45.5)	28 (5.24)	58 (9.7)
Sesquiterpene lactone mix	4 (6.8)	8 (1.6)	12 (2.2)
Quaternium-15	2 (3.1)	6 (1.1)	8 (1.3)
Nickel sulfate	18 (30.5)	79 (15.1)	97 (16.7)
MCI/MI	7 (10.6)	20 (3.7)	27 (4.5)
Mercaptobenzothiazole	2 (3.0)		2 (0.3)
Primin	1 (1.6)	3 (0.6)	4 (0.7)

FM = fragrance mix; MBT = mercaptobenzothiazole; PTBPF = *p*-tert-butyl-phenol-formaldehyde.
55 participants had no information regarding patch testing with the standard series.

[$P=0.0007$ (full model) and $P=0.0033$ (backward model)].

Use of gloves when doing housework and/or cleaning (Table 2) was reported by 54% and 52.3% of those replying to the question and being positive or negative to our selection of fragrances, respectively. 42.2% and 41.3% of the same groups had skin contact with household or cleaning products at work, whereas 56.7% and 56.2%, respectively, indicated that their eczema worsened following housework and/or cleaning without gloves.

The frequencies of a positive reaction to the various standard allergens for the whole group and the 2 groups of patients with hand eczema being positive versus negative to the selection of fragrances are summarized in Table 3.

Discussion

Of the 658 patients tested, 67 (10.2%) reacted to our selection of fragrance allergens. The relevance in the individual patient cannot be confirmed, as product labelling for household products is not mandatory. Chemical analysis of products brought in by patients is possible in selected cases but not economically feasible in a large-scale study (or in normal dermatological practice). Based on the general relevance assessment

performed (9), it must be assumed that nearly all the positive reactions are of present or past relevance. Around 10% of patients with hand eczema react to the selected fragrances. The FM in the standard series would have picked up only 45.5% of these as possible fragrance-sensitive individuals. That is to say, 5.6% of all the patients tested would have had an inadequate diagnostic work up if the present extra fragrances had not been added, probably adding to the chronicity of their disease. This finding suggests the value of testing patients with hand eczema with the supplementary selection of fragrance allergens together with the European standard series. Such a supplementary selection of fragrances will tend to be modified over the years, depending on the industrial use of fragrance allergens in products.

Of the new fragrance allergens tested, citral was most commonly positive, followed by hydroxycitronellal, Lyrall[®] and eugenol. Previously, Frosch et al. (11) found 1.1% positive to citral 2% pet. among the 1855 consecutive patients patch tested in 6 European centres. Citral is a weak/moderately potent allergen in animal and human predictive tests (12–14) but also an irritant (15). Due to this distinct irritant potential, care is needed in the reading of a citral patch test (unpublished data). The present dataset includes only positive patch tests meeting at least the

minimum criteria of redness and homogeneous infiltration. Hydroxycitronellal, eugenol and geraniol are included in the FM. Sensitization to these fragrances can be caused by contact with a wide range of products, including cosmetics. The same holds true for the newly recognized fragrance allergen Lyrall[®] (16). Nearly, 1% of patients with hand eczema reacted to geraniol. Limonene and its oxidation products have an increasing significance, as they are used in both consumer and industrial products at high concentrations, as a solvent and as a fragrance ingredient. 1 or more of these oxidation products deserves a place in the standard series (17).

Hand eczema is common both in the general population (18, 19) and among patients investigated by dermatologists (20). The present material (Table 2) may differ from an average clinical material, as it contains a large number of cases with a time of onset more than 1 year ago. This could be related to the fact that the present cases are selected from 3 tertiary referral centres. The age and sex are as expected in a population of hand eczema patients. In the hand eczema study in the general population by Meding and Swanbeck (19), 23% had continuous symptoms from the onset of the hand eczema to the time of examination and the average time from onset of hand eczema to examination was 11.6 years (range 0–63 years) (19).

Visible flexural dermatitis is the only physical sign to be recorded along with 5 historical features in a UK working party's diagnostic criteria for atopic dermatitis (21). The childhood frequency of flexural eczema (knee or elbow) was 22.6% (Table 3). Data resembling ours were reported by Schultz et al. (22), whereas a study from Singapore found a lower frequency of a history of atopy in hand eczema patients (23). Dermatitis in the axillae, which is a known indicator of possible fragrance allergy, was present in 12.9% (24).

The patch testing was performed in 3 university centres within the same geographical area. Years of collaboration between the centres and a common educational background in dermatology may ensure a uniformity of the patch-test reading (10). It should be noted that the present study does not contain patch-test data from patients without hand eczema, as such a comparison is outside the scientific questions asked, although it might well be of interest.

The questions used in the study were based on clinical experience and have not been standardized further. Patients with hand eczema should be carefully evaluated based on exposure-defined relevance data.

The patient material was divided into 2 groups—those with a positive patch test to the selected fragrances and those without such a reaction. Significant differences appear by making comparisons between these 2 groups of patients collected using uniform criteria. The patients in the present material generally have multiple positive patch-test reactions. It is known from both human experimental sensitization studies and general population epidemiology that individuals with 1 positive patch test have a significant risk of having a 2nd contact allergy (25, 26). In the present material, other mechanisms such as exposure to multiple allergens (metals, fragrances, preservatives, etc.) and finally cross-reactivity between fragrance chemicals may all be operational in individual patients. The detailed analysis showed that 80.3% of the patients with a positive reaction to the selection of fragrances had 1 or more positive patch tests in the European standard series, while this was the case in only 33.7% of those without such a reaction. Among those reacting to the selection of fragrances, 71.6% gave a positive fragrance history compared to only 47.1% among those who did not react to the selection.

The hands are exposed to different types of fragrance chemicals used in cosmetics, domestic products (cleaning) and occupational products. 67 (10.2%) of 658 patients with hand eczema had 1 or more positive patch-test reactions to the selected fragrances present in products intended for hand exposure. This group of patients with hand eczema seem more often to have had a positive fragrance history and seem more often to have had 1 or more positive patch tests in the standard series than the group of patients with hand eczema negative to the selected fragrances. The study found that fragrance allergy could be a common problem in patients with eczema on the hands. Experimental hand exposure studies with specific contact allergens would add further insight into the overall significance of allergy and hand eczema. Future studies might also address the combined effects of irritants and fragrance allergens.

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Research participants: J.P. Lepoittevin and E.G. Arnau, University Louis Pasteur, Strasbourg, France. A.-T. Karlberg, M. Matura, M. Sköld and A. Börje, National Institute for Working Life, Stockholm, Sweden. D. Basketter and G. Patlewicz, SEAC Toxicology, Unilever Research, Sharnbrook, UK. T. Menné, J.D. Johansen, S. Heydorn, Department of Dermatology, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark. P. Frosch, Department of Dermatology and University of Witten/Herdecke, Dortmund, Germany. I. White, Department of Contact Dermatitis and Occupational Dermatology, St. John's Institute of Dermatology, St. Thomas' Hospital, London, UK. S. Rastogi, National Environmental Research Institute, Roskilde, Denmark. K.E. Andersen, Department of Dermatology, Odense University Hospital, Odense, Denmark. M. Bruze and C. Svedman, Department of Occupational and Environmental Dermatology, University Hospital, Malmö, Sweden. A. Goossens, Department of Dermatology, University Hospital KU Leuven, Leuven, Belgium.

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Address:
Siri Heydorn
Department of Dermatology
Gentofte Hospital
University of Copenhagen
Niels Andersens Vej 65
2900 Hellerup
Denmark
e-mail: sihe@gentoftehosp.kbhamt.dk