

Review Article

Fragrance allergy and hand eczema – a review

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Because hand eczema and fragrance allergy are common both among patients and in the general population, simultaneous occurrence by chance must be expected. Fragrances are ubiquitous and a part of many domestic and occupational products intended for hand exposure. The present review is based on a systematic literature research using both a manual and a Medline based search. The search identified 39 studies, including epidemiological patch test studies, general population patch test studies, case studies, and studies of occupational groups. The published data indicate a possible association between fragrance allergy and hand eczema. In future studies, a more detailed exposure assessment is needed, combined with patch test studies among patients with hand eczema tested with relevant fragrance allergens, as well as experimental control exposure studies to specific fragrance allergens on the hands. As exposures to fragrances on the hands are often simultaneous exposures to irritants, this combined exposure approach needs to be considered.

Key words: fragrances; hand eczema; domestic fragrance exposure; occupational fragrance exposure; combined exposures. © Blackwell Munksgaard, 2003.

Accepted for publication 19 November 2002

In 1968, Rothenborg & Hjorth described allergy to toilet soaps and detergent perfumes as a contributing factor in hand eczema (1). Fragrances are ubiquitous and part of many domestic and occupational products intended for hand exposure. Recent analyses of 59 household products indicate that the fragrance mix (FM), the current diagnostic test, may not detect all fragrance allergies (2). Table 1 lists the 10 most frequently found fragrances in 59 household products and 70 deodorants. Only 2 of the listed fragrance allergens are FM constituents, and most of the fragrance allergens appear in significant concentrations. Even if fragrance allergens are moderate to weak allergens, contact allergy may be induced and elicited on the hands.

Fragrances are, following nickel, the most frequent patch test allergen (3,4). The FM, a mixture of 8 different fragrance ingredients, has been a screening test for fragrance allergy since its introduction in the late 1970s (5–7). The frequency in dermatological patients ranges worldwide from 2.4% to 11.3% (8–12), and 2 population studies found frequencies around 2% and 11%, respectively (13,14). Hand eczema is frequent in adults (15,16) and can be associated with severe socioeconomic disabilities (17). As hand eczema and fragrance allergy are common both among pa-

tients and in the general population, simultaneous occurrence by chance must be expected.

The aim of this review is to search the literature as to a possible significant association between fragrance allergy and hand eczema, including both domestic and occupational aspects.

Materials and Methods

We searched for scientific papers including data about fragrances and hand eczema or fragrances and hand eczema with occupational relevance.

The following scientific journals were searched manually for the last 10 years of publication:

Am J Contact Dermatitis
Contact Dermatitis
Dermatosen

PubMed was searched with the phrases fragrance or perfume allergy and hand dermatitis or hand eczema. The phrase occupation was added to the final search.

Studies with focus on contact urticaria, fungal infections, children, balsam of Peru or essential oils were not included, neither were studies in which both the variables hand eczema and fragrance allergy were not investigated for the same group.

The search resulted altogether in 39 studies.

Table 1. The 10 most frequent fragrance substances in 59 household products and in 70 deodorants

Fragrance substance	Frequency in 59 household products (2)	Frequency in 70 deodorants (53)	Concentration range (ppm) in	
			59 household products	70 deodorants
Limonene	78%	n.a.	6–9443	n.a.
Linalool	61%	97%	3–439	9–1927
Citronellol	47%	81%	18–1579	1–5585
Eucalyptol	41%	n.a.	15–446	n.a.
Geraniol*	41%	76%	53–1758	1–1178
α -pinene	39%	n.a.	5–157	n.a.
Galaxolide®	36%	n.a.	6–346	n.a.
Isoamylsalicylate	34%	n.a.	29–1157	n.a.
α -hexylcinnamic aldehyde	32%	71%	53–674	2–1684
Eugenol*	27%	57%	32–349	1–2355
Lilial®	27%	51%	36–214	1–3732
Linalyl acetate	27%	73%	n.a.	1–1810
Coumarin	25%	57%	45–309	1–1411
Citral	25%	n.a.	48–1088	n.a.
Hedione	24%	79%	n.a.	1–17587
Benzylacetate	14%	84%	n.a.	1–26960
Benzyl benzoate	10%	71%	51–223	1–1075
Lyrall®	10%	53%	36–103	1–1874
α -isomethyl ionene	8%	61%	n.a.	1–2765

n.a.: not analysed.

* constituent of FM.

Lilial®: 2-methyl-3-(4-tert-butyl-phenyl)proanal.

Lyrall®: 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene carbaldehyde.

Galaxolide®: 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopental[g]benzopyran.

Clinical studies

Fragrance allergy and hand eczema has been evaluated in clinical patch test studies, with or without statistical analyses, as well as in case reports.

Studies including statistical analyses

Christophersen et al. patch tested 2166 consecutive patients with the European standard series (3). Applying a logistic regression model, hand eczema was an independent variable for the possibility of a positive FM ($p < 0.05$). The relative risk was higher when hand eczema and leg ulcer/eczema were combined (possibility of positive FM = 10%). They considered important characteristics like age, sex, atopy, location of eczema, but did not include duration of hand eczema, multiple allergies and exposure-defined relevance. Multiple allergies tend to increase the risk of chronic contact dermatitis (18) and with resent exposure assessments we know that fragrance allergens are common in products designed for hand exposure.

Johansen et al. patch tested 884 consecutive patients with the European standard series (19). A positive FM was compared to replies from a self-administered questionnaire, filled out prior to patch testing, using a logistic regression model. Rash on the hands perceived by the patients to

have been caused by scented products increased the probability of a positive FM (odds ratio = 2.15). The authors considered variables like age, sex, childhood eczema, 'scented products as cause of or exacerbation of skin disease', and 'rash from scented products'. As in the above-mentioned study, multiple allergies, duration of eczema and exposure-defined relevance were not included. Furthermore, the self-diagnosis of hand eczema using the term rash could overestimate (20) or underestimate (21) the actual number of patients with hand eczema; though the relatively high odds ratio indicates a significant association.

Larsen et al. tested 752 referred patients in 5 centres worldwide with FM, balsam of Peru 25%, a mixture of 7 of the 8 FM ingredients and other fragrances including jasmine absolute, and a mixture of 5 natural fragrances (5). Chi-square test with Yates' continuity correction found hand eczema to be more frequent in fragrance-allergic patients (56%) than in non-fragrance-allergic patients (38.5%; $p = 0.001$). Corrections for multiple comparisons were not performed (22), but the result is in accordance with the studies mentioned above.

Uter et al. analysed patch test data from 57779 referred patients with a Poisson regression analysis (23). They found an estimated adjusted prevalence ratio for hand eczema and at least a + reaction to

Table 2. List of descriptive studies

Study	Patch test material	Number with positive patch test	Number patch tested	Age, years	Atopy/ asthma, rhinitis	Sex (m or f)	Location of dermatitis				
							Hands	Face	Neck	Legs	Generalised
Buckley et al. (27).	FM constituents	934	1112	n.a.	n.a.	325 m 609 f	^m 35% ^f 28%	^m 22% ^f 25%	*	n.a.	^m 13% ^f 18%
Katsarma et al. (29)	FM, its constituents, 14 other fragrances, own perfume	91 85 (FM)	n.a. (744 to FM)	48.4±18.6	24%/17%, 15%	^r 23 m 65 f	31%	26%	*	12%	12%
Paulsen et al. (30)	l-carvone 5% pet.	15	541	^c 56± n.a.	^c 13%/n.a.,n.a.	5 m 10 f	^c 87%	^c 53%	^c 20%	^c 13%	^c 27%
Larsen et al. (32)	FM, and 17 other fragrances	^c 154 (FM) ^c n.a. (17 other fragrances)	218 (204 FM) (All suspected fragrance allergic patients)	46.3±14.7 (n=218)	26.7%/13.6%, 24.0% (n= 191, 198 and 196)	^c 32 m ^c 185 f (n= 217)	†26.1%	†28.0%	†10.6%	†6.0%	†3.7%
Temesvari et al. (31)	FM	294	3604	n.a.	21.5%/2%, 10.2%	63 m 183 f (n=246)	§30.1%	§26.8%	n.a.	n.a.	§15.9%
Buckley et al. (28)	FM, its constituents	1813 (FM), 934 (its constituents)	24 046 in total. 1112 (its constituents)	44.2±n.a.	n.a./n.a., n.a.	636 m 1177 f	27.9%	23.6%	*	n.a.,	n.a.

n.a.: not analysed.

^m or ^f Information separated for males (m) and females (f).

* Face and neck combined.

^c Calculated from data in the publication.ⁿ *n* = 162; at least one positive patch test to either FM, its constituents, 14 other fragrances, colophony or propolis.[#] *n* = 150 (location tabulated).^r Remaining participants had not recorded sex.† Location of dermatitis is reported for *n* = 218 patients.

§ only 246 of the 294 FM positive have data tabulated.

Patient characteristics covers the patch test positive.

Table 3. List of case reports on fragrance, hand eczema and occupation

Occupation	Sex	Age (years)	Atopy	Positive patch tests	Product gives eczema and contains an allergen?	Improve during vacation?
(54) Handyman at a hotel	Male	49	No	Balsam of Peru 25%, FM, epoxy resin 1%.	Fragrance injected into air-conditioning system, fragrance for carpets, and aerosol room fresheners.	Yes
(54) Chemical product mixer in an insecticide factory.	Male	32	No	FM, isoeugenol 1%, eugenol 1%, oak moss absolute 1%, masking perfume used in insecticide 1%.	He wiped the masking fragrance from the insecticide on face before working	Yes.
(55) Physiotherapist	Male	32	No	FM, eugenol, 'Balsam from ash extract' cream and the components cinnamon oil 0.5%, and clove oil 1% pet.	Massaged with 'Balsam from ash extract' cream. Discontinuation led to improvement.	n.a.
(56) Hairdresser	Female	41	n.a.	Acid perm solution 5%, isoeugenol, oak moss, lemon grass oil, clove oil, cedarwood oil, and oak moss component from acid perm solution.	Dermatitis on scalp after a perm with the perm solution she also worked with.	Maybe
(57) Engineer grinding components for printing press. Use a coolant (soluble oil).	Male	47	Yes	FM, balsam of Peru, sodium metabisulfite, diethanolamine, oak moss absolute, the coolant (soluble oil) and to the component oak moss resin and mono-ethanolamine.	Rash deteriorated until coolant (soluble oil) was withdrawn. Symptom-free ever since	Yes
(58) Cook for 10 years. The last 9 years a barman.	Male	47	No	Lemon essence, lemongrass essence, essence of neroli, and geraniol.	Authors believe essential oils of orange and lemon peel could explain the rash.	Yes
(59) Histopathology medical laboratory science officer	Male	53	n.a.	Diluted solvent and dl-limonene (dipentene1%)	Solvent contained d-limonene. Eczema improved with avoidance.	n.a.
(60) Mechanic	Male	42	n.a.	Oxidized 2% and 1% d-limonene	d-limonene in his hand cleanser. Discontinuation and resolved.	n.a.
(61) The last 6 months weighed cosmetic components (plant producing cosmetics).	Male	25	No family history	FM, ylang-ylang oil, aniseed oil, oak moss absolute, perfume composition he worked with and bromonitropropanediol 0.5%	Handled 0.1 kg bromonitropropanediol and 3–5 kg of the patch tested perfume composition monthly. Eczema gone after new job. Own soap also gave eczema.	Yes
(62) The last month made room 'air-fresheners' (Added various fragrances to a machine.)	Male	43	n.a.	FM 16%, and cinnamic aldehyde 2%	Analyses of the used fragrances gave: cinnamic aldehyde and others.	n.a.
(62) Nurse	Female	n.a.	n.a.	Atranorin 0.1%	Aftershave applied on patient gave her eczema. Composition of it unknown.	Yes

n.a.: not analysed.

FM above 1 (1.24, 95% confidence intervals (95% CI) = 1.07–1.46). The patients were characterized according to the important variables age, sex, past or present history of atopic dermatitis, location of eczema and occupational exposure. In future databases it might be of interest to record and investigate the effect of eczema duration, multiple allergies, and exposure-defined relevance.

Two studies from 1980s, including 1016 and 721 patients respectively, did not identify any association between fragrances and hand eczema (24,25). The latter study compared the 721 hand eczema patients with 1389 referred non-hand eczema patients.

A thorough characterization of the study participants may reveal other differences or indications of explanation(s) between the results from various analyses, or it may identify important subgroups of patients clarifying certain associations of particular interest such as fragrance allergy and hand eczema.

Nethercott et al. used logistic regression to analyse patch test data from 3074 referred patients in North America (26). Only fragrances like cinnamic aldehyde 1% pet. and cinnamic alcohol 5% pet. were used for patch testing. Hands were over-represented for 10 substances, not including any fragrances, and under-represented for cinnamic alcohol and p-tertiary-butylphenol-formaldehyde resin. The odds ratio for cinnamic alcohol and hand eczema was 0.57 ($p < 0.01$). This lack of association may be caused by the selection of allergens with limited relevance for hand eczema (2).

Clinical patch test data comprise patients with contact dermatitis of sufficient severity for those patients to be referred to a patch test centre. The types of patients referred might differ on a regional basis depending on the organisation of the health care system. The patch test series can undoubtedly be improved according to assessment of hand exposure to fragrance chemicals. Such measures might strengthen an association between fragrance allergy and hand eczema. A certain standardization of the selection of statistical methods used for clinical patch test data is desirable, but the overall impression from the studies, notwithstanding the inherent weaknesses of the materials, is the possible existence of an association between contact allergy to fragrances and hand eczema.

Descriptive studies

Five descriptive studies have found hand eczema to be the most frequent site of eruption in patients with fragrance allergy (27–31) and 1 found facial eczema to be most common (Table 2) (32). No statistical analysis was attempted in these studies. The

remarkably similar frequencies of hand eczema and facial eczema (Table 2) in these studies mirror the regional occurrence of contact dermatitis as well as the relative importance of fragrance allergy.

Case reports

Seven case reports have focused on the possible association between hand eczema and fragrance allergy (33–38). Re-exposure to the product confirmed the hand eczema association in 1 case (34). Case studies can be extremely valuable in clinical medicine if they contain detailed information such as patch testing with own products, chemical analysis of suspected products, ingredient patch testing and re-exposure at the previously involved skin sites.

Occupational studies

Studies of patients representing different occupations are of particular importance, as occupational exposure is often more uniform and intensive and may therefore be expected to show a stronger association between fragrance allergy and hand eczema, as compared to domestic exposure.

Epidemiological studies

Sun et al. described occupational hand eczema found in 164 (36.6%, $n = 448$) patients referred to a clinic in Taipei (39). 68 (15.2%) of these had allergic contact dermatitis. A positive patch test to FM was considered relevant to the occupational dermatitis in 4 hairdressers, 1 in construction and 1 in the medical profession.

Meding et al. reported on hand eczema in a Swedish population study (40). 5.8% of 1081 patients with hand eczema were positive to FM. Service work had a significantly higher 1-year period prevalence of hand eczema among the occupational groups (15.4%, $p < 0.001$). The outcome of patch testing and occupation was not associated except for colophony, which was more frequent in women doing administrative work ($n = 11$, $p < 0.01$). This very extensive study did not include a population group without hand eczema, which might have provided further insight.

Hairdressers

Sutthipisal et al. described 143 hairdressers with hand eczema referred to St. John's Institute of Dermatology, London, UK. 4 (2.8%) were positive to FM (41). Conde-Salazar et al., in Madrid, Spain, found 7 (3.1%) FM-positive hairdressers out of 223 hairdressers with hand eczema (42).

These frequencies are no higher than among eczema patients in general, though this clearly does

not exclude the fact that fragrances could be an occupational allergen in the individual hairdresser. A more detailed exposure assessment and aimed patch testing might have revealed more such cases.

Pottery industry

Lear et al. in the UK reported 24 cases of hand eczema in pottery workers using oil of turpentine in their local ceramic decoration industry (43). 14 were positive to Indonesian turpentine, 8 to α -pinene, 4 to Δ -3-carene and 2 to turpentine peroxides. According to the authors, the main sources of turpentine in use in the United Kingdom are Portugal, Indonesia and Brazil. Turpentine contains a mixture of α -pinene, Δ -3-carene, and dipentene. The main constituent of Portuguese and Indonesian turpentine is α -pinene; 78% and 85%, respectively. The authors conclude that oil of turpentine can still be a potent cause of occupational allergic contact dermatitis, though its irritant nature must also be remembered.

Wilkinson et al. described 26 workers with hand eczema referred from the pottery industry (44). 1 male mould-maker with hand eczema showed allergy to additives in oils used to ease the plaster moulds from the castings, but also to unspecified fragrance.

Other occupations

Shah et al. in the UK patch tested 64 metal workers referred with hand dermatitis with the European standard series (45). According to the authors, FM and balsam of Peru overlap with constituents of some soluble oils, and hence may be relevant to occupational dermatitis in metal workers; but none of the 5 positive to FM were thought to be from occupational exposure.

Fischer et al. studied 299 household painters from 8 selected companies in mid-Sweden and found 1 non-relevant reaction to FM (46). It is uncertain if patch testing with terpene-containing solvents was done.

Meding et al. studied a cohort of 84 male woodwork teachers (47). The diagnosis of allergic contact dermatitis was made in 3 out of 16 patients diagnosed with hand eczema, but in none of them was this due to fragrances.

Kanerva et al. brought the attention to allergic hand eczema in 5 food workers in contact with spices (48). The causative agents were garlic, cinnamon, ginger, allspice, and clove.

Case reports of allergy to fragrances, hand eczema and occupation

Besides the above-mentioned descriptive studies, case reports entailing fragrance allergy, hand ec-

zema and occupational dermatitis are available (Table 3). The overall impression from these studies is that fragrance allergy might have had a contributory effect on the hand eczema. As long as such studies do not include detailed chemical analysis, defining exposures qualitatively and quantitatively, and controlled re-exposure, the association in the individual case is left to clinical judgement.

Conclusion and further investigations

An association between exposure to contact allergens and clinical disease can be evaluated in epidemiological studies, clinical controlled exposure studies and carefully conducted case studies. Attempts to investigate such associations for nickel allergy and thiuram allergy have been done using both epidemiological methods (3, 49) and clinical controlled exposure (48a, 50, 51). Extensive studies on fragrance allergy during the last decade (52) have established a firm correlation between exposure to fragrances in cosmetic products and allergic contact dermatitis.

The question asked in the present paper is important, as hand exposure to fragrances is widespread both occupationally and domestically and often in combination with irritants.

The published data indicate a possible association between fragrance allergy and hand eczema. But due to the complex exposure situation with multiple contact allergens other types of studies need to be designed. Studies including large numbers of hand eczema patients patch tested with series of allergens specifically relevant to hand exposure need to be performed. Further controlled exposure studies including hand eczema patients with contact allergy to specific fragrance ingredients, and exposure to the allergen in question in a multiple dosage design, are essential for the risk assessment of fragrance allergy and hand eczema. Finally, the potential combined effects of fragrance allergens and irritants need to be considered.

Acknowledgement

The present study was supported by the Quality of Life and Management of Living Resources programme of the European Commission under the key action Environment and Health – Contract QLK4-CT-1999-01558 'Fragrance chemical allergy: a major environmental and consumer problem in Europe.

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