REVIEW ARTICLE

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Fragrance Contact Allergy

A Clinical Review

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Abstract

Most people in modern society are exposed daily to fragrance ingredients from one or more sources. Fragrance ingredients are also one of the most frequent causes of contact allergic reactions. The diagnosis is made by patch testing with a mixture of fragrance ingredients, the fragrance mix. This gives a positive patch-test reaction in about 10% of tested patients with eczema, and the most recent estimates show that 1.7–4.1% of the general population are sensitized to ingredients of the fragrance mix. Fragrance allergy occurs predominantly in women with facial or hand eczema. These women typically have a history of rash to a fine fragrance or scented deodorants. Chemical analysis has revealed that well known allergens from the fragrance mix are present in 15–100% of cosmetic products, including deodorants and fine fragrances, and most often in combinations of three to four allergens in the same products. This means that it is difficult to avoid exposure, as products labelled as 'fragrance free' have also been shown to contain fragrance ingredients, either because of the use of fragrance ingredients as preservatives or masking perfumes, or the use of botanicals.

About 2500 different fragrance ingredients are currently used in the composition of perfumes and at least 100 of these are known contact allergens. Therefore, it is advisable to supplement standard patch testing with the patient's own stay-on cosmetic products, as well as the fragrance chemical hydroxyisohexyl-3-cyclohexane carboxaldehyde, which on its own gives responses in 1–3% of tested patients. The focus in recent years on the ingredients of the fragrance mix will probably result in the fragrance industry changing the composition of perfumes, and thus make the current diagnostic test less useful. New diagnostic tests are under development to identify contact allergy to new allergens, reflecting the continuous developments and trends in exposure.

Fragrance ingredients are one of the most frequent causes of contact allergy in eczema patients and in the general population.[1-3] Contact allergy is a type IV immunological reaction involving the T lymphocytes of the immune system.[4] Reactivity may decrease, but contact allergy persists for life once acquired. So far desensitization experiments in animals and humans have shown only limited and transient effects. The problem is the complicated mechanism of type IV allergy, so even though the

receptors of specifically activiated T-cells may be blocked, naïve T-cells may be easily recruited from the relatively protected lymphoid tissue.[4] The clinical presentation is eczema, an inflammatory skin disease, causing erythema, swelling, vesicles and, in chronic cases, scaling. A contact allergic reaction starts at the primary site of skin contact, but may spread secondarily to other areas. Contact allergy is seen predominantly in women of young or middle age,[5] may cause socioeconomic problems and affect quality of life.[6]

1. Fragrance Ingredients

The International Fragrance Association defines fragrance ingredients as any basic ingredient used in the manufacture of fragrance materials for its odorous, odor-enhancing or blending properties. Fragrance ingredients may be chemicals, essential oils, natural extracts, distillates, etc. and these are used to create a fragrance formula, which is also called a perfume in popular terms. A perfume is a product composed of 10–100 or even more fragrance ingredients generally diluted with ethanol (ethyl alcohol). A deliberate selection and quantification of ingredients to form a specific olfactory shape creates the composition of a perfume. In order to achieve this the fragrance ingredients must be volatile and odorous.[7] The art of creating a perfume has been virtually unchanged since ancient times. More recent development lies in the number and quality of the available raw materials and a different way of compounding. Today 2500 different fragrance ingredients are in use for composing perfumes.[8] A fragrance ingredient can either be a simple chemical or a natural extract derived by extraction processes from botanical sources.[9,10] Previously, secretions from certain animal species were also used as fragrance ingredients, e.g. musk – a secretion of the male musk deer. Nowadays these are usually substituted by blends of chemicals. Botanicals are derived from special plant families that produce natural fragrance ingredients, e.g. rose, lavender and jasmine. The fragrance ingredients may be present in the flowers, leaves, stems, bark, fruit or any other part of the plants and are extracted by steam distillation or solvent extraction. A natural extract may consist of a few main ingredients or may be a complex composition of numerous ingredients.[10]

Chemical synthesis of the ingredients responsible for the odor in natural extracts began in the mid-1800s but, because of technical difficulties, commercial production was not possible until the turn of the century. In 1900, the advances in technology made the production of simple chemicals easier and less expensive than most natural extracts, and today many perfumes are based mainly on fragrance chemicals.

A fragrance chemical can be nature-identical, meaning that it exists in nature, or it can be synthetic, which implies that a natural counterpart does not exist. Most fragrance ingredients known to cause contact allergy are natural extracts or nature-identical chemicals.[11]

2. Clinical Presentation and Diagnosis

Fragrance allergy occurs predominantly in women, probably because of a more intense use of scented products, especially cosmetics, by women than men.[5] The typical patient is in her mid-forties and has either facial[12] or hand eczema.[13] The history of the patient provides guidance as to the likelihood of fragrance allergy. A typical fragrance-allergic patient has a history of axillary eczema caused by perfumed deodorants or a history of rash to a fine fragrance[14] (figure 1 and figure 2). A previous rash from a scented deodorant increases the likelihood of contact allergy to fragrance ingredients by a factor of 2.4, a previous rash from cologne makes it 6.2 times more likely, and if both symptoms are present the risk increases 12.8 times.[14]

The basic diagnosis is made by patch testing with the standard patch-test series including the fragrance mix, which has been used as an indicator of fragrance contact allergy since the late 1970s.[15] The fragrance mix consists of a mixture of eight ingredients: seven

Fig. 1. Allergic contact dermatitis in the axilla caused by fragrance ingredients in a deodorant.

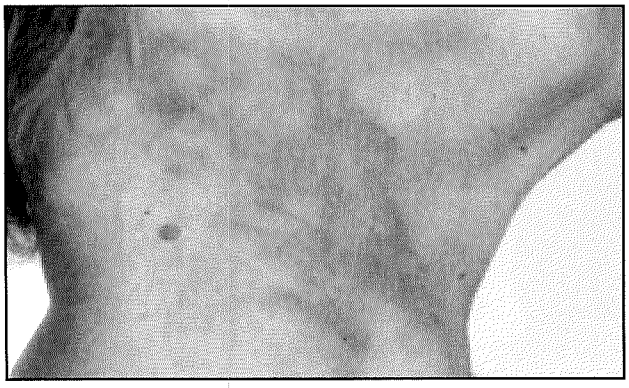

Fig. 2. Allergic contact dermatitis caused by cologne.

chemicals and a natural extract (table I). The fragrance mix is still a valuable indicator of contact allergy to fragrance ingredients; however, developments in the fragrance industry mean that it is relevant to also test other ingredients. In recent multinational studies extra candidates for testing have been identified,[16-20] including chemicals such as coumarin, farnesol, citral, α-hexylcinnamic aldehyde and natural extracts such as ylang ylang oil, narcissus oil, sandalwood oil, and jasmine absolute. Larsen found that jasmine absolute or synthetic was useful in detecting extra cases of fragrance contact allergy.[20] One substance, hydroxyisohexyl-3-cyclohexene carboxaldehyde (HMPPC; Lyral®[1]), has been shown to cause reactions in 1–3% of consecutively patch-tested patients.[16,21] Only one-half of these patients are also positive to fragrance mix, which means that the diagnosis of fragrance contact allergy would otherwise be missed.[16] HMPPC is now included in the standard patch-test series in many clinics, awaiting the development of new additional mixes or test series for patch testing. It is recommended, as is already done in Germany, to supplement the standard patch-test series with this substance, which is available from producers of patch-test materials.[21]

Balsam of Peru, a natural extract prepared from the exudation of the tree *Myroxylon pereirae*, has also been used in the standard series of tests for fragrance contact allergies for decades. At first it was used as an indicator of allergy to balsam of Peru, which was used for wound treatment and infections;[23] later it became clear that it was also an indicator of fragrance contact allergy.[24] In reality this was not surprising, as balsam of Peru was used as a fragrance ingredient. In 1974, the crude form was banned by the fragrance industry because of its allergenicity, however, to what extent it is used in modified forms in perfumes is unknown.[25]

The function of balsam of Peru as an indicator of fragrance contact allergy is more complex and heterogeneous than the fragrance mix, and may vary in different parts of the world because of local habits.[26] In some parts of the world, positive patch tests to balsam of Peru and the fragrance mix correlate,[27] while in others they are more dissociated.[28] fragrance mix is superior to balsam of Peru in detecting cases of fragrance allergy to ingredients in cosmetics, as most cosmetic products analyzed have been shown to contain one or more of the fragrance mix ingredients (table II). This means that the fragrance mix, by its composition, has a more direct relevance to exposure. Contact allergy to balsam of Peru has been shown to be more prevalent in eczema patients with reactions to the peel of citrus fruits.[29]

The fragrance mix is positive in 50–80% of eczema patients with reactions to perfumes in cosmetics;[30,34] the same applies if single fragrance allergens are tested.[16-18,35] As none of the current diagnostic tools are perfect, it is important to test with the cosmetic products, fine fragrances, etc. used by the patient. Testing should generally be confined to stay-on products, as wash-off products, because of their irritant nature, make the interpretation of patch-test reactions difficult.

Whenever a certain cosmetic product is suspected of causing an allergic reaction a repeated open application test (ROAT) should be performed. A ROAT is used to mimic the normal exposure, especially to cosmetic products.[36] The ROAT is used to evaluate if a given product has caused or contributed to an eczema; further, it is used for research purposes to define thresholds for elicitation.[37,38] Typically, the elbow flexure or the outer aspect of the upper arm are used as test sites with a test area of 25cm^2, but smaller areas may be used, which is relevant if a fine fragrance is tested.[30,36-38] An amount realistic to normal usage is applied, twice daily for 7 days,[36] but if there is a negative reaction the test

Table I. Ingredients of the fragrance mix

Ingredients	CAS No.[a]	Ranking[b] (%)
Oak moss absolute	Extract	24 (2.2)
Isoeugenol	97-54-1	20 (1.9)
Eugenol	97-53-0	13 (1.2)
Cinnamic aldehyde (cinnamal)	104-55-2	10 (0.9)
Hydroxycitronellal	107-75-5	8 (0.8)
Geraniol	106-24-1	8 (0.8)
Cinnamic alcohol	104-54-1	6 (0.6)
α-Amyl cinnamic aldehyde (amyl cinnamal)	101-85-9	5 (0.5)
Sorbitan sesquioleate (emulsifier)	8007-43-0	5 (0.5)

a Chemical Abstracts Service Registry Number.

b The ranking of ingredients is derived from a European multicenter study.[22] It is seen that oak moss is top ranking, followed by isoeugenol, eugenol and cinnamic aldehyde.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Presence of fragrance mix (FM) allergens in consumer products

Type of products	No. of products investigated	Products with fragrance mix allergens (%)	Four main ingredients in each product	No. of products containing each of the FM ingredients (%)	Concentration range of each FM ingredient (% w/v)
Fine fragrances[30]	10	100	Hydroxycitronellal	9 (90)	0.25–1.2
			Eugenol	9 (90)	0.04–0.89
			Geraniol	9 (90)	0.08–0.48
			Isoeugenol	7 (70)	0.05–0.34
Natural ingredient perfumes[31]	22	82	Geraniol	14 (64)	NS
			α-Amyl cinnamic aldehyde	8 (36)	0.19–3.0
			Eugenol	8 (36)	0.03–2.3
			Hydroxycitronellal	5 (23)	0.13–6.0
Deodorants[32]	70	17–73	Geraniol	53 (76)	<0.001–0.12
			Eugenol	40 (57)	<0.001–0.24
			Hydroxycitronellal	35 (50)	<0.001–0.10
			Cinnamic alcohol	27 (39)	<0.001–0.12
Domestic products[33]	59	2–41	Geraniol	24 (41)	0.005–0.17
			Eugenol	16 (27)	0.003–0.03
			Hydroxycitronellal	7 (12)	0.002–0.01
			α-Amyl cinnamic aldehyde	5 (8)	NS

NS = not stated; **w/v** = grams per 100ml of solution.

should be continued for another week.[39] All stay-on cosmetic products can be tested in this way, while there is no standard open test for wash-off products. An allergic response often starts with itching papules and, after a few more days, erythema may develop and spread outside the area of application.[38] A scale of reading ROATs has been developed for research purposes.[40]

3. Epidemiology

The fragrance mix has been used as an indicator of fragrance contact allergy in studies of the general population. Results of positive patch tests to the fragrance mix have ranged from a prevalence of 1–11% (table III). In Denmark, fragrance mix sensitivity was found in 1.1% (95% CI 0.3–2.1%) of 567 persons drawn as a sample from the general Danish population; only nickel sensitivity was more prevalent.[3] In a recent study from Germany, the morbidity of contact allergy to fragrance ingredients has been assessed using a clinical epidemiology and drug-utilization research (CE-DUR) approach. This is a procedure based on the results of the sales of patch-test materials combined with the data from the surveillance system on contact allergy in Germany.[41] It was possible by a best-case and a worst-case scenario to estimate a disease prevalence ranging from 1.7–4.1% of the population, which means that 1.4–3.4 million individuals in the German population are sensitized to fragrance mix ingredients.[41] In considering this, it should be born in mind that only 50–80% of people with fragrance contact allergy are picked up by the fragrance mix.[16,30,35]

Fragrance contact allergy is not rare in children. In an investigation of 1200 school children aged 12–16 years, 1.6% of girls and 2.1% of boys had a positive reaction to the fragrance mix.[44] One out of three children had already had clinical symptoms from their fragrance allergy. In comparison, 0.3–0.2% of these children were allergic to preservatives, none of whom had experienced any symptoms from their preservative allergy.[44]

Approximately 11.7% of eczema patients in North America have a positive patch-test reaction to the fragrance mix;[2] 87% of these are judged as currently relevant. In a German multicenter study of more than 36 000 patients with eczema, it was found that an average of 10.2% of those tested reacted to the fragrance mix in the period of 1990–1995.[46] In a multicenter European study, the corresponding figure was 11.3% of eczema patients with a positive patch test to the fragrance mix,[1] making fragrance ingredients one of the leading causes of contact allergy together with nickel. The North American Contact Dermatitis Group has created an index combining the prevalence and the clinical relevance of different allergens, which indicates the relative importance of the allergen.[27] The leading allergens in terms of clinical importance were

fragrance mix followed by a preservative, quarternium-15, and balsam of Peru.[27]

4. Sensitivity to Fragrance Mix Ingredients

The fragrance mix consists of seven fragrance chemicals and one natural extract (table I). If the fragrance mix patch test is positive, breakdown testing of the individual ingredients is done, if possible. The rank order of the ingredients depends on the geographical region and era. Cinnamic aldehyde has been a top-ranking allergen in Europe for many years although the frequency seems to have decreased.[5,47] In North America, it has been used in the standard series and has given positive results in 2.8% of consecutive eczema patients.[2] Cinnamic alcohol is probably metabolized in the skin to cinnamic aldehyde and it is less frequently positive.[48] It has been debated whether the decrease in cinnamic aldehyde positives could be because of the recommendations of the fragrance industry to only use cinnamic aldehyde together with other specified allergens in order to block the allergen effect – a phenomenon called quenching. The original data to support quenching being effective are not reported in detail. In other studies no quenching effect was found in animals or in elicitation studies in humans.[49] In a review of the literature, it was concluded that quenching of fragrance allergens is a phenomenon still awaiting positive evidence of its existence.[50] An alternative explanation of the decreased frequency of cinnamic aldehyde positives would be a decreased usage of this chemical, which seems to be supported by exposure investigations, showing that cinnamic aldehyde is the least used of the fragrance mix ingredients.[23]

Isoeugenol and the natural extract oak moss absolute have been top ranking for many years. Both have shown significant increases in prevalence of contact allergy over long time periods. The rate of positive patch tests to either ingredient increased by 5% per year in a study from the UK.[5] In response to the documented high levels of isoeugenol sensitivity, the fragrance industry lowered the limit for the recommended level of isoeugenol in products from 0.2% to 0.02% in 1998.[51] Whether a decrease in sensitization to isoeugenol will follow depends on the alternatives used to produce the isoeugenol scent.[52] If very similar chemicals, such as isoeugenyl acetate, are used the desired effect may not be seen, as certain isoeugenol derivatives give cross-reactions in isoeugenol-sensitive individuals.[52]

The relatively high rates of contact allergy to oak moss absolute have resulted in a search for modifications leading to hypoallergenic forms of the extract,[53] but with little success. Oak moss absolute is an extract derived from lichen growing on oak trees in the Mediterranean area. It has a complex composition and has been used in many fragrance products, often mixed with other cheaper extracts, but still sold under the name oak moss absolute.[54] This has caused confusion as allergens from other lichens were found in oak moss absolute patch-test materials at one time.[55] Oak moss absolute has been the subject of intense research for identification of the responsible allergens.[56] A program supported by the European Commission has been based on a bioguided fractionation procedure, where individuals allergic to oak moss absolute have been tested with fractions of the oak moss extracts. The positive fractions have been further broken down chemically and tested again in individuals, until single substances have been identified. So far, several allergens have been detected in oak moss absolute and some of these seem to be relatively potent.[56] This opens the possibility of preventing contact allergy by removing the allergen from the extract and monitoring exposure from other sources.

5. Fragrance Contact Allergens in Cosmetic and Domestic Products

Cosmetics are the most prominent source of exposure to fragrance ingredients and include toiletries, decorative cosmetics, hair products and hydro-alcoholic products such as colognes and perfumes. Most people in modern society are exposed daily to fragrance ingredients from one or more sources.[57] Fragrances are

Table III. Prevalence of positive patch-test reactions to fragrance mix (FM) in population groups

Country	Period	Selection criteria	No. of patients tested	Patients positive to FM (%)	Reference
Italy	1990	Military recruits without history of eczema	593	0.5	42
Denmark	1990–1991	Random sample of an adult population, aged 15–69 years	567	1.1	3
Portugal	1991	Children aged 5–14 years from four schools	562	1.8	43
Denmark	1995–1996	Adolescents aged 12–16 years in the municipality of Odense	1146	1.8	44
Germany	1997–1998	Case-control study, adults aged 28–78 years, in Ausberg	1141	11.4 (estimate)	45
Germany	1992–2000	Drug-utilization research method	Not applicable	1.7–4.1 (estimate)	41

also added to other products such as laundry and cleansing agents, air fresheners, pharmaceutical preparations and industrial products such as cutting oils.[11]

Exposure to nearly 400 fragrance substances used in major commercial products marketed around the world has been studied. The results from fine fragrances, household products and soaps were published in 1989.[58] The 25 most frequently detected fragrance substances with a concentration exceeding 1% in the product were listed. Three of these substances were constituents of the diagnostic test, the fragrance mix: geraniol, which was found in 43% of the fine fragrance products in an average concentration of 3.2%; eugenol, which was found in 26% of the products in an average concentration of 2.0%; and hydroxycitronellal, which was in 21% of the products in an average concentration of 3.0%.[58] Since 1987, the International Fragrance Association (IFRA) guideline has restricted the use of hydroxycitronellal to 1% in consumer products to prevent contact allergic reactions.[59]

Chemical analysis of almost 200 products of international brands and of different types have shown that the allergens known from the diagnostic test, the fragrance mix, are widespread in consumer products (table II), even in natural-based perfumes[31] and toy cosmetics.[60] All prestige perfumes were found to contain at least three of these allergens[30] and between 17% and 73% of deodorants contained one or more of the allergens.[32] A case study showed that cosmetic products, which were thought to fully or partly explain the dermatitis of fragrance mix-allergic individuals, all contained fragrance mix ingredients.[29]

A general finding was that three to four of the allergens from the fragrance mix were found in the same cosmetic product. This increases the risk of provoking allergic contact eczema, as exposure to combinations of fragrance allergens have a synergistic effect on the inflammation and extent of eczematous reactions provoked in individuals sensitized to the fragrances in question.[61] The effect of allergen combination on the induction of contact allergy is unknown. It seems that cosmetic products intended for children are more carefully formulated than other products, as the fragrance mix ingredients were either not present or were present in fairly low concentrations in children's shampoos, shower gels and lotions.[60]

In domestic products, such as dishwashing liquids, substances other than the fragrance mix ingredients dominate.[33] Firstly, limonene, a citrus-smelling substance, was found most frequently. It is allergenic in its oxidized state.[33] Secondly, isoeugenol was only found in 5% of domestic products compared with 70% of fine fragrances.[30] This means that a different screening series for reactions to fragrance ingredients in domestic products could be relevant.

Air-borne exposure to perfumes may elicit an allergic reaction in very sensitive individuals, but this is an extremely rare phenomenon.

5.1 Sensitivity to Fragrance Contact Allergens in Cosmetic Products

Fragrance ingredients account for 30–45% of the allergic reactions to cosmetics in eczema patients, and are the most frequent cause of contact allergy to cosmetic products, followed by preservatives.[62,63] Fine fragrances and deodorants are the products most often indicated as the initiator of skin reactions in individuals with fragrance contact allergy in comparison with two different control groups (a random sample of the general population and fragrance-mix-negative eczema patients).[14] Both fine fragrances and deodorants have been the subject of clinical and experimental studies (table IV). In the 1960s and 1970s, formulated colognes were regarded as useful indicators of fragrance contact allergy.[64,65] These were replaced by the introduction of the fragrance mix.[15] In the 1990s, fine fragrances were still good indicators of fragrance contact allergy; international brand perfumes were shown to give an allergic reaction in 6.2–6.9% of patch-tested consecutive eczema patients.[30,66] A clinical study on deodorants in fragrance mix-positive eczema patients with a history of axillary dermatitis from a particular deodorant, revealed that the reaction could be reproduced in 60% of the patients within 7 days.[67] A series of clinical controlled studies using deodorants spiked with the individual allergens, cinnamic aldehyde, isoeugenol or hydroxycitronellal in realistic usage concentrations, have shown that 79–100% of sensitized individuals react to these products compared with none of the non-sensitized control individuals.[68] These experimental studies confirm the history of patients reporting, in particular, reactions to scented deodorants or fine fragrances.[14] Furthermore, they show that the usage concentrations of allergens are at a level that produces allergic reactions in a considerable proportion of sensitized patients with eczema.

Scented creams and lotions also have a role to play in fragrance allergic contact dermatitis. This has not yet been explored experimentally, but in clinical studies skincare products are often identified as a cause of contact allergy.[71,72]

6. Factors Influencing Fragrance Contact Allergy

Table V provides a list of factors that are important in eliciting allergic contact dermatitis including fragrance contact allergy. The crucial factor for induction and elicitation of fragrance contact allergy is the dose of allergen per unit area of skin (table V).[73] The risk of getting sensitized is greater with exposure to products used in small areas with a high concentration of the allergen than to

Table IV. Clinical and experimental studies with products in fragrance-sensitized patients

Product type	Study group and method	Results	Reference
Deodorants	Case study. Re-exposure to deodorants tested in FM-positive patients	60% reacted to the incriminated deodorant within 7 days	67
Deodorants	Experimental studies of deodorants spiked with three different allergens in realistic use concentrations and tested in groups of patients sensitized to the allergen in question	79–100% of the case group reacted to the deodorants containing the allergen in question vs none in the non-sensitized control groups	68
Fine fragrances	1823 consecutive patients patch tested with perfume from aftershave (3% in petroleum)	3.6% gave a positive reaction	65
Fine fragrances	335 consecutive female eczema patients patch tested with ten fine fragrances (undiluted)	6.9% gave one or more positive reactions	30
Fine fragrances	1000 consecutive eczema patients patch tested with ten international brand perfumes (undiluted)	6.2% gave one or more positive reactions	66
Various products	498 consecutive eczema patients patch tested with fragrances from lower-price cosmetics, wash-off and stay-on products (5% in petroleum)	4.2% reacted to perfumes from wash-off products and 3.2% to perfumes from stay-on products	69
Various products	Seven FM-positive eczema patients did a repeated open application test with different products formulated with the same fragrance ingredients	Deodorants gave most reactions	70

FM = fragrance mix.

products spread over large surfaces with a low concentration of allergen, even if the total amount of allergen delivered is the same.[73] This means that the fine fragrances, which are typically used on small areas, but contain high concentrations of fragrance ingredients,[30] are products with a significant potential for causing contact allergy.

Individuals sensitized by a high concentration of allergen acquire a greater degree of sensitivity than those who have been sensitized by a low concentration and will thus be more likely to respond with allergic eczema at re-exposure to the allergen.[73] In most normal usage situations a cosmetic product is applied repeatedly over time. Sensitized individuals may tolerate allergen exposure depending on their individual level of sensitivity, the exposure concentration of the allergen, and the time period of exposure. This means that if the allergen level is low, the exposure may be tolerated by more individuals and for longer periods of time. In a study of isoeugenol-sensitized individuals, exposure to 0.2% applied repeatedly to healthy skin at the flexor side of the forearm elicited a reaction in a median of 7 (range 2–26) days, while a 0.05% solution took a median of 15 (range 3–28) days to elicit a reaction in the same individuals.[39]

The region of application is another variable. The axilla is more sensitive than the outer aspects of the upper arm,[67] possibly because of the occlusion effect. Shaving with razors has been shown to increase the risk of fragrance contact allergy.[80] This is relevant to axillary exposures in women and facial exposures in men, as shaving these sites is almost always followed by exposure to fragrance ingredients in deodorants or aftershaves.

In cosmetic products, allergens are present in combination, and in some products such as shampoos they are also combined with irritants. Such combined exposures may give a response in allergic individuals greater than would be expected from the effects of the exposure to the single ingredients.

Combining fragrance allergens in individuals allergic to fragrances has been shown to give a synergistic response,[61] and the combination of an irritant with an allergen, in this case nickel, has resulted in a synergistic response of a similar magnitude.[79] Nickel is an inorganic and water-soluble allergen, while fragrance allergens are organic and less water soluble, so it is not known if irritants produce the same effect together with fragrance ingredients as does nickel. Many domestic products combine detergents, which cause irritation, with fragrance allergens and patients with hand eczema may be exposed daily to products such as dishwashing liquids. These products are diluted with water in the handling process and the effective concentration may be very small, and it is not known if pre-existing hand eczema can be aggravated by such exposure.

7. Advising Patients with Fragrance Contact Allergy

The advice given to the patient depends on the clinical presentation. Some may have a weak degree of allergy and can tolerate some scented products on the skin, others are more sensitive and

Table V. Factors influencing the elicitation of fragrance contact allergy

Factor	Comments
Allergen concentration (dose/unit skin)[39,73,74]	Also important in induction
Individual level of sensitivity[22,38,39]	Depends on the exposure concentration at induction. Severity of patch-test reactions to standard patch-test materials (FM) indicates the sensitivity of the individual
Time of exposure (number of applications)[39]	Low concentrations require longer exposure periods to elicit a reaction than high concentrations
Anatomical skin site[67,75]	The axilla is more sensitive than the arms
Occlusion[76]	Occlusion facilitates penetration for some allergens, but not for others
Skin hydration[77]	Pre-treatment of the skin with a moisturizer produces stronger patch-test reactions to nickel. Not known if this applies to fragrance ingredients
Product matrix[70,78]	Different product types have a different ability to elicit reactions in spite of a similar content of allergens
Combination with irritants or allergens[61,79]	Combination of fragrance allergens gives a synergistic response in FM-allergic individuals. Combination of nickel and an irritant gives a synergistic response. The effect of irritants with fragrance ingredients is not known
Abraded skin[80]	Shaving with razors increases the risk of FM allergy
Pre-irritated skin[81,82]	Pre-irritation of the skin with sodium laurilsulfate (sodium lauryl sulphate) gives stronger responses to allergens. Not studied for fragrance ingredients
Previous allergic eczema[83,84]	Previous allergic eczema caused by the allergen in question increases the skin reactivity to the allergen. Nickel has been used as a model. Fragrance ingredients have not been studied

FM = fragrance mix.

have to abstain from fine fragrances and scented deodorants, while some cannot use any scented products at all, including wash-off products such as shampoos. Patients with strong patch-test reactions to the standard patch-test fragrance mix are more likely to react to low concentrations of allergen[38,39] and to have a positive history of adverse reactions to scented products.[22] This also applies to patients with patch-test reactions to their own cosmetic products. Such patients often have to abstain from using scented products, which may not be so easy, firstly, because fragrances are used in many industrial and consumer products, and secondly, because the label 'fragrance free' may be misleading.[85,86] Products marketed as fragrance free, including products sold for sensitive skin, may, in spite of this, contain fragrance ingredients.[85,86] These are often various flower or plant extracts or chemicals acting as preservatives, e.g. geraniol and farnesol. Masking perfumes have also been found in products termed fragrance free.[86] Regardless of the reason for adding such ingredients, the consequences to the fragrance-allergic individual may be severe if they are using products that are misleadingly labelled as being unscented.

In response to requests from dermatologists in general and consumer organizations, a change has been made to the cosmetic legislation in Europe. This means that fragrance ingredients known to cause allergic reactions in humans will have to be included on the label of cosmetic products, like all other cosmetic ingredients.[19,87,88] This legislation is expected to be in full force in 2005.

8. Conclusion

The most recent estimates show that contact allergy to fragrance ingredients is detected in 1.7–4.1% of the general population[41] and 1.8% of adolescents.[44]Fragrance allergy is diagnosed in 10–12% of eczema patients seen by dermatologists.[1,2,46]

Fragrance allergy occurs predominantly in women with facial or hand eczema. They will typically give a history of previous rash to a fine fragrance or scented deodorant. Chemical analysis has revealed that well known allergens are present in 15–100% of cosmetic products, including deodorants and fine fragrances, and most often in combinations of three to four allergens in the same product. It has been shown that normal usage concentrations of these allergens in solution or incorporated into products will provoke contact eczema in two out of three individuals sensitized to the allergen in question. This means that it may be difficult for individuals with contact allergy to fragrance to avoid exposure. It also explains the high prevalence of reactions to fragrances in different population groups.

The current standard diagnostic tests, the fragrance mix and balsam of Peru, are indicators of fragrance contact allergy. How-

ever, it is advisable to supplement testing with the patient's own stay-on cosmetic products. Furthermore, the fragrance chemical hydroxyisohexyl-3-cyclohexene carboxaldehyde should be included in the standard test series as it gives positive responses on its own in 1–3% of tested patients. The focus in recent years on the ingredients of the fragrance mix will probably result in the fragrance industry changing the composition of perfumes, and thus make the current diagnostic test less useful. New diagnostic tests are under development to identify contact allergy to new allergens, reflecting the continuous developments and trends in exposure.

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