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Review Article

Adverse reactions to fragrances

A clinical review

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This article reviews side-effects of fragrance materials present in cosmetics with emphasis on clinical aspects: epidemiology, types of adverse reactions, clinical picture, diagnostic procedures, and the sensitizers. Considering the ubiquitous occurrence of fragrance materials, the risk of side-effects is small. In absolute numbers, however, fragrance allergy is common, affecting approximately 1% of the general population. Although a detailed profile of patients sensitized to fragrances needs to be elucidated, common features of contact allergy are: axillary dermatitis, dermatitis of the face (including the eyelids) and neck, well-circumscribed patches in areas of "dabbing-on" perfumes (wrists, behind the ears) and (aggravation of) hand eczema. Depending on the degree of sensitivity, the severity of dermatitis may range from mild to severe with dissemination and even erythroderma. Airborne or "connubial" contact dermatitis should always be suspected. Other less frequent adverse reactions to fragrances are photocontact dermatitis, immediate contact reactions and pigmentary changes. The fragrance mix, although very useful for the detection of sensitive patients, both causes false-positive and false-negative reactions, and detects only 70% of perfume-allergic patients. Therefore, future research should be directed at increasing the sensitivity and the specificity of the mix. Relevance is said to be established in 50–65% of positive reactions, but accurate criteria are needed. Suggestions are made for large-scale investigation of several fragrances on the basis of literature data and frequency of use in cosmetics. The literature on adverse reactions to balsam of Peru (an indicator for fragrance sensitivity), essential oils (which currently appear to be used more in aromatherapy than in perfumery) and on fragrances used as flavours and spices in foods and beverages is not discussed in detail, but pertinent side-effects data are tabulated and relevant literature is provided.

Key words: perfume; fragrance; adverse reactions; fragrance mix; balsam of Peru; essential oils; allergic contact dermatitis; photosensitivity; immediate contact reactions; pigmented cosmetic dermatitis; occupational contact dermatitis.

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This article reviews side-effects of fragrance materials present in cosmetic products with emphasis on clinical aspects: epidemiology, types of adverse reactions, clinical picture, diagnostic procedures, and the sensitizers. Adverse reactions to balsam of Peru, a marker for fragrance sensitivity (1), which detects approximately 50% of patients allergic to fragrance materials (2), and to fragrances from non-cosmetic sources (e.g., flavours in food) are not discussed in detail. Essential oils seem to be more often used nowadays for medicinal (notably aromatherapy (3)) than for cosmetic purposes. Only the adverse reactions from their presence in cosmetic fragrances are included. However, because of their close relationship to fragrances these flavours, essential oils (which often co-react in patients allergic to fragrances (4)) and ingredients of balsam of Peru causing contact allergy and other side-effects are tabulated separately with reference to relevant articles.

Fragrance Materials

What are fragrances? (5)

Fragrances may be natural (balsams, essential oils, concretes/absolutes) or synthetic. Natural fragrances are, with few exceptions (animal products such as musk, ambergris, civet, and castoreum, which can also be produced synthetically nowadays), of botanical origin. A natural fragrance contains several hundred different chemicals, a few major and many minor ones, which are responsible for the complexity of the odour.

Balsams are viscous, coloured, and aromatic plant products soluble in alcohol but not in water. They are obtained from the exudate often artificially produced by incising the bark. Balsams with a characteristic odour can be obtained from trees rich in resins, e.g., balsam of Peru, balsam of Tolu, storax, galbanum, myrrh, and benzoin.

Essential oils come from a limited number of animals, from many different plants, and can be synthesized from 2 fossil fuels (coal and petroleum). Essential oils can become gaseous at room temperature; because they volatilize so easily, they are also known as *volatile oils*. There are 5 classic methods of extracting essential oils from plants and flowers: distillation, extraction, enfleurage, maceration and expression (6, 7). Examples of essential oils obtained by stem distillation of various plant raw materials, such as blossoms, leaves, and fruits of flowers, are oils of roses, laurel and lavender; from the wood and roots of trees come cedarwood oil and sandalwood oil.

Concretes or *absolutes* are obtained by solvent extraction of plant materials (which for absolutes is alcohol), with evaporisation of the solvent. Materials manufactured this way are subject to less change during their preparation than those that are distilled.

Synthetic fragrances are well-defined chemical compounds with a simple odour.

Until the 19th century, fragrances were manufactured from essential oils and alcohol extracts of plant origin. Nowadays, synthetic chemicals are far more used for reasons of cost, purity, compatibility and quality control; they may account for as much as 90% of the perfume composition . The history of fragrances has been well described by Guin (6) and Scheinman (7).

The blending of a perfume (5, 6, 8)

Perfumery is the art of making individuals and products attractive to the olfactory sense. Specific fragrances must be designed for individual products, as compatibility is essential and the product ingredients may affect the odour. These products may also be designed for a particular price range, which often determines the ingredients available to the perfumer. Among thousands of chemical substances which have an odour, about 3000 (of which 300–400 are of natural origin), are used in the fragrance industry (9).

A perfume is a creative composition of fragrance materials, of which it may contain from a few to over 300. On opening a bottle, the most volatile components of the "top note" will be smelled. After 5–20 min the "heart" or the "body" of the perfume is perceptible. With a good perfume this heart will last for 2–4 h. What is left is the "dry out", which will gradually disappear. There are distinct perfume materials that have a favourable influence on the perfume profile, tempering the top note, refinement and extension of the heart and strengthening the dry out. Such materials are called "fixatives" and include balsam of Peru, balsam of Tolu, storax, benzoin, coumarin and musk.

Perfumes contain approximately 12–20% of the perfume compound. They are expensive and actually too concentrated. The more diluted products (perfume lotion, perfume de toilette, eau de toilette, colognes) are therefore much more popular. There are no legally defined concentrations of the perfume compounds for these products, but in general, colognes will contain 2–5%, perfume lotion and perfume de toilette 5–8%. Most fragrance products are alcoholic solutions (70–96% ethanol), but perfume creams (sachets) and aerosols are also popular. Approximate concentrations of fragrance materials in cosmetics are 0.5% and in masking fragrances ≤0.1% (7, 8, 10, 11) (Table 1).

Fragrance materials most commonly used

Details of the composition of a particular fragrance are closely guarded by industry, which

Table 1. Concentrations of perfume in various products (7, 8, 11)

aerosol freshener	0.5%–2%
bathroom cleaners	≤5%
colognes	2%-5%
compressed powder	0.5%
dishwashing liquid	0.1%–0.5%
facial make-up	1.0%
hair pomade	0.5%
hair spray	0.1%–0.3%
laundry powder	0.1%–0.3%
lipstick	1.0%
liquid detergents	0.1%–1%
masking perfume	≤0.1%
perfume	12%–20% (or higher)
shower and bath formulations	0.5%–4%
skin care products (emulsions)	0.3%–0.5%
soap	0.5%–2%
toilet water	5%–8% (or higher)

Table 2. Most commonly found fragrances in cosmetics and toiletries

Rank order	Fragrances found in 400 products in the USA (12)#	* %	Rank order	Fragrances found in 300 products in the Netherlands (8)	* %
1	linalool	90	1	linalool	91
2	phenylethyl alcohol	82	2	phenylethyl alcohol	79
3	linalyl acetate	78	3	benzyl acetate	78
4	benzyl acetate	74	4	limonene	71
5	benzyl salicylate	74	5	citronellol	71
6	coumarin	68	6	linalyl acetate	67
7	terpineol	66	7	γ-methylionone	63
8	hedione	56	8	terpineol	52
9	hexylcinnamic aldehyde	51	9	β-pinene	51
10	γ-methylionone	51	10	geraniol	50
11	terpinyl acetate	50	11	hydroxycitronellal	49
12	lilial	49	12	benzyl benzoate	49
13	lyral	46	13	hexylcinnamic aldehyde	48
14	geraniol	43	14	lilial	48
15	heliotropin	43	15	coumarin	44
16	galaxolide®	41	16	benzyl salicylate	43
17	acetyl cedrene (Vertofix®)	41	17	benzyl alcohol	42
18	musk ketone	38	18	eugenol	36
19	citronellol	38	19	α-pinene	35
20	amyl salicylate	32	20	geranyl acetate	35
21	eugenol	26	21	α-amylcinnamic aldehyde	35
22	vertenex	25	22	musk ketone	34
23	isobornyl acetate	23	23	caryophyllene	33
24	α-amylcinnamic aldehyde	21	24	lyral	33
25	hydroxycitronellal	21	25	camphor	31

* % of products containing the fragrances listed.
# These fragrances may be present at a concentration of >1% in "fine perfumes" (12).

maintains that secrecy of the formulae is fully commensurate with investment in the development and marketing of a product (IFRA statement, vide infra).

2 studies have examined the nature of fragrance materials used in perfumes, cosmetics, household products, and soap. Fenn (12) examined the "aroma chemical usage trends in modern perfumery" by analysing the "Top 25" materials in 400 cosmetic products: "fine fragrances" (perfumes, toilet water, some creams), "household products" (fabric softeners, cleansers), and "soaps" (bar, tablet). In each group were commonly purchased products of the USA. The most frequently identified fragrances were linalool, present in 90% of products, phenylethyl alcohol (82%), linalyl acetate (78%), benzyl acetate (74%), and benzyl salicylate (74%) (Table 2). Weyland (8) analyzed 300 cosmetic products sold on the Dutch market, and also found linalool and phenylethyl alcohol to be the most frequently incorporated (Table 2). 17 of 25 of the American "Top 25" were also on the Dutch list and vice versa. 6 chemicals (linalool, phenylethyl alcohol, linalyl acetate, benzyl acetate, terpineol and γ-methylionone) were in both investigations in the "Top 10" of identified fragrance materials. Of the 8 fragrances present in the fragrance mix (vide infra), 4 belonged to the "Top 25": geraniol (43% and 50%), eugenol (26% and 36%) α-amylcinnamic aldehyde (21% and 35%), and hydroxycitronellal (21% and 49%) (Table 2).

Perfume Ingredient Safety Evaluation: RIFM and IFRA (13, 14)

Fragrances are relatively innocuous. Most ingredients have a long history of use, are chosen carefully and are subjected to rigorous screening prior to introduction. Even so, the chemical composition and the degree of exposure to individual fragrance ingredients should determine the type and extent of toxicological studies. The fragrance industry has established a system of industry self-regulation, based on 2 important organisations: the International Fragrance Association (8 Rue Charles-Humbert, CH-1205 Geneva, Switzerland), an association of national associations, whose Technical Advisory Committee (TAC) issues a Code of Practice for the industry and Industry Guidelines on ingredient usage, and the Research Institute for Fragrance Materials Inc. (2 University Plaza # 406, Hackensack, NJ 07601–6209, USA).

The Research Institute of Fragrance Materials (RIFM) was formed in the United States in 1966 to carry out definitive research on fragrance ingredients for the sole purpose of establishing fragrance safety. RIFM has compiled a computer

bank of data on the majority of fragrance ingredients currently in use (15). The results of RIFM findings are presented as ingredient monographs published in *Food and Chemical Toxicology*. To date, some 1500 monographs on the most frequently used fragrance materials have been prepared. Routine toxicological tests for the ingredient monograph include: (a) acute oral toxicity (rat LD_{50} or limit test), (b) acute dermal toxicity (rabbit LD_{50} or limit test), (c) dermal irritation (rabbit and human), (d) dermal sensitization (guinea pig and human) and (e) dermal phototoxicity (photoirritation and photosensitization). RIFM compiles and evaluates all available data and test results but does not issue guidance on safe levels. Such interpretation is left to member companies and to the International Fragrance Association.

The International Fragrance Association (IFRA) was formed in 1973 to ensure safety in use of fragrance materials by promoting industry compliance with internationally agreed regulations and standards for the use of fragrances in consumer products. IFRA has produced an Industry Code of Practice and circulates guidelines on specific fragrance materials, limiting or prohibiting their use in response to adverse specific evidence from

Table 3. IFRA-controlled fragrance materials (2, 13, IFRA Code of Practice, 1995)

Potential sensitizers
acetylated vetiver oil
acetyl isovaleryl#
alantroot oil#
allyl heptine carbonate
amylcyclopentenone
anisylidene acetone#
balsam of Peru#
benzylidene acetone#
p-tert-butyldihydrocinnamaldehyde
p-tert-butylphenol#
carvone oxide*
cassia oil
cinnamic alcohol
cinnamic aldehyde*
cinnamon bark oil Ceylon
citral*
colophony (rosin)
costus root oil#
cyclamen alcohol@
diethyl maleate#
dihydrocoumarin#
2,4-dihydroxy-3-methylbenzaldehyde#
dimethyl citraconate#
ethyl acrylate#
ethyl heptine carbonate
farnesol
fig leaf absolute#
trans-2-heptenal#
hexahydrocoumarin#
trans-2-hexenal
trans-2-hexenal diethyl acetal#
trans-2-hexenal dimethyl acetal#
α-hexylidene cyclopentanone
hydroabietyl alcohol#
hydroxycitronellal
isoeugenol
6-isopropyl-2-decalol#
menthadienyl formate
7-methoxycoumarin#
α-methylanisylidene acetone#
methyl crotonate#
6-methyl-3,5-heptadienone
methyl heptine carbonate
p-methylhydroxycinnamic aldehyde
3-methyl-2(3)-nonene nitrile
methyl octine carbonate
nootkatone
oakmoss extracts
1-octen-3-yl acetate (amylvinylcarbinyl acetate)
opoponax
pentylidene cyclohexanone#
perilla aldehyde
phenylacetaldehyde*
pinacea derivatives
propylidene phthalide
pseudo-ionone@
pseudo-methylionones@
rose ketones (1-(2,6,6-trimethyl-cyclohexenyl and cyclohexadienyl)-2-buten-1-one)
sclareol
styrax American and Asian
tree moss extracts
verbena absolute
verbena oil#

Dermotoxic agents
allyl esters
nitrobenzene#

Potential photoallergens
4,6-dimethyl-8-t-butylcoumarin#
7-methoxycoumarin#
6- and 7-methylcoumarin#
4-methyl-7-ethoxycoumarin#
musk ambrette

Phototoxic agents
5-acetyl-1,1,2,3,3,6-hexamethylindane
angelica root oil
bergamot oil expressed
citrus oils
cumin oil
fig leaf absolute#
grapefruit oil expressed
lemon oil cold pressed
lime oil expressed
marigold (tagetes) oil and absolute
methyl N-methylanthranilate
orange bitter oil, expressed
rue oil
verbena oil#

(Neuro)toxic agents
acetylethyltetramethyltetralin (AETT)#
cis- and *trans*-asarone@
dihydrosafrole@
isosafrole@
musk ambrette
nitrobenzene#
safrole@

Depigmenting agents
p-tert-butylphenol#
hydroquinone monoethyl ether#
hydroquinone monomethyl ether#

Miscellaneous
allyl isothiocyanate#$
cade oil (juniper tar)
chenopodium oil#$
cinnamylidene acetone#$
3,7-dimethyl-2-octen-1-ol (6,7-dihydrogeraniol)#$
diphenylamine#$
esters of 2-nonynoic acid, except methyl octine carbonate#$
esters of 2-octynoic acid, except methyl and allyl heptine carbonate#$
ethyleneglycol monoethyl ether (acetate)#$
ethylene glycol monomethyl ether (acetate)#$
furfurylidene acetone#$
massoia lactone#$
methyl methacrylate#$
phenyl acetone (methyl benzyl ketone)#$
phenyl benzoate#$
savin oil
thea sinensis absolute#$

* Should be used with quenching agents to reduce allergenicity.
\# Prohibited by IFRA.
@ Prohibited, but special exemptions exist.
#$ Prohibited because there is absence of reports on the use of these materials as fragrance ingredients and inadequate evaulation of possible physiological effects resulting from their use in fragrances.

RIFM and other sources (recommendations on "safe concentrations" in various product categories, usage in non-skin-contact products). RIFM and IFRA interact via a Joint Advisory Committee. Materials which are controlled by IFRA (prohibited, restricted, specifications) are given in Table 3.

The Code of Practice issued by IFRA is a loose-leaf folder, which is periodically updated in the light of new scientific data relating to fragrance materials. It makes recommendations on the limitation or non-use of certain materials, i.e., a restricted/negative list. It also defines the Industry Code of Practice covering aspects such as definitions, good manufacturing practice and use of fragrance materials. The Code also outlines a minimum set of toxicity tests which should be completed satisfactorily before introduction of a new fragrance chemical.

The efforts of the RIFM and the IFRA are extremely valuable. Nevertheless, they cannot prevent adverse effects from fragrances from occurring:

- Predictive tests for allergenicity on a limited number of test animals and persons will identify strong sensitizers. However, a negative test result does not exclude that sensitization will occur with widespread population exposure.
- The recommendations are not always followed. Despite a 1985 recommendation from IFRA that musk ambrette no longer be used in products that touch the skin, in 1988 the FDA reported an analysis of 125 fragrance compounds showing that 40% of the assayed products still contained musk ambrette (16).
- The sensitizing potential of certain fragrance allergens, such as cinnamic aldehyde, phenyl acetaldehyde and citral, can, according to RIFM (17, 18), be diminished by the addition of other fragrances. This phenomenon has been termed "quenching". As a consequence, cinnamic aldehyde and citral have always been used by the fragrance industry pre-quenched, for example with eugenol and/or limonene. However, Basketter and Allenby (19) could not confirm a quenching action in patients allergic to cinnamic aldehyde (elicitation phase), nor in guinea pig sensitization studies in the induction or in the elicitation phase (19). RIFM has not been able to provide accurate and convincing data proving the actual existence of quenching. Therefore, whether quenching in allergic contact dermatitis does exist and, if so, is effective, is rather doubtful (20). Eugenol *does* quench the production of *non-immune immediate contact reactions* to cinnamic aldehyde (21).
- Fragrances are complex mixtures of chemicals in which interactions and possibly the formation of new chemicals (which have not been investigated) may occur. Also, the presence of other chemicals in fragranced products may influence the sensitizing potential of fragrance materials.

In spite of this, the work of RIFM and IFRA is very laudable and useful, and dermatologists should positively, firmly and without bias cooperate with cosmetic chemists and other scientists in order to ascertain maximum (cutaneous) safety of fragranced products to consumers.

Contact with Fragrances and Fragranced Products (5)

Products

The use of fragrances is ubiquitous and not limited to cosmetic products primarily used for their scent, such as perfumes, eaux de cologne, eaux de toilette, deodorant and aftershave. Virtually all cosmetics and toiletries contain fragrance materials; even "unscented" or "fragrance-free" products may contain a "masking" perfume. Flavors used in oral hygiene products – toothpaste, mouthwash, and dental floss – are fragrance chemicals. Scented household products include detergents (22), cleaners, softeners, deodorizing sprays, polishes, solvents and waxes. In industry, cutting fluids (23), electroplating fluids, paints, rubber, plastics, insecticides, herbicides and additives used in air-conditioning water may all be scented. Eugenol is widely used by dentists. Paper and paper products – including diapers, facial tissues (24), moist toilet paper (25) and sanitary napkins (26, 27) – may cause a reaction. Fabrics and clothes may contain fragrance materials, especially after they are laundered or treated with a fabric softener.

Topical medicaments often contain perfumes (28, 29), and ventilating systems may spread fragrances (30). The distinction between fragrances and spices is often indistinct. Many synthetic fragrances are used as spices and flavours. Natural fragrances like cinnamon, clove, vanilla and cardamon, are added to foods, soft drinks, lozenges, chewing gum, sweets, ice cream and tobacco (31–33). Thus, it can be stated that virtually everyone is in daily contact with fragrance materials.

Modes of contact

Contact with fragrances may be from direct product application to the skin or mucous membranes (toothpaste, mouthfresheners, feminine hygiene sprays (34), perfumed eyedrops (35)), by occasional contact with an allergen-contaminated product such as towels and pillows, contact with products used by partners, friends or co-workers ("consort" or "connubial" contact dermatitis) (36–

38), airborne contact (39–42), and systemic exposure by inhalation and ingestion (fragrances, flavours and spices in foods and drinks, cough syrup).

Sites of contact with fragrances

Any part of the body may be in contact with fragranced cosmetics: scalp: shampoo, hair lacquer, hair gel (43, 44); face: skin care products (8, 44), aftershave (45), perfumed tissue handkerchiefs (24, 46), airborne from perfumes on clothing (42, 47); the eyelids: eye cosmetics (48); the lips: lipstick, toothpaste (49, 50); the neck: aftershave, perfume (39, 47); the trunk: body lotion (51); the axillae: deodorant and antiperspirant (47, 52–54); the arms and legs: body lotion (55); the perianal area: fragranced (moistened) toilet tissue (25, 27); the vulval area: feminine hygiene sprays (34, 56), sanitary napkins (26, 27), topical drugs (29); the hands: moisturizing creams (47), soap (57); and the feet: scented antiperspirants.

Frequency of usage

Perfumes are widely used. Of 811 female clients of beauticians, 91% used perfume/cologne and 82% deodorant (58). Of 35490 persons in the USA, 61% used deodorant, and 34% colognes (59). Usage of perfumes, aftershave and deodorant was also found to be very high in Swedish students (60). Other fragrance-containing products not primarily intended for their smell, such as soap, shampoo and toothpaste are used by virtually everybody.

Adverse Reactions to Fragrances in Cosmetics and Toiletries

Considering the extensive use of balsams, fragrances, spices, and flavour additives to food, the frequency of contact allergy to these groups of materials is relatively small. In absolute numbers, however, fragrance allergy is common. The prevalence in dermatitis patients seen by dermatologists is high; in most countries the "fragrance mix" (a composition of 8 commonly used fragrances to identify subjects with fragrance allergy) is among the "Top 5" of allergens, usually number 2 after nickel sulfate. Indeed, fragrances are major causes of allergic contact dermatitis. At least 35% of all allergic reactions to cosmetics are due to perfume ingredients (61–65), and approximately 1% of the unselected population is sensitized to fragrances (66, 67). Other adverse reactions include irritant contact dermatitis, photocontact dermatitis, immediate contact reactions (contact urticaria), and (de)pigmented contact dermatitis.

Frequency of adverse reactions in the general population

Adverse reactions to fragrances/fragranced cosmetics appear to be far from rare. Guin and Berry (68) conducted a questionnaire study in 90 student nurses; 29 (32%) gave a history of cutaneous fragrance intolerance. When tested with the fragrance mix (8×2%), 15/90 (18%) gave a positive reaction. Of these 15, 12 (80%) had indeed a positive history of fragrance sensitivity. Of the nurses with a negative patch test reaction, only 21% considered themselves to be fragrance sensitive (68).

De Groot et al. (69) interviewed 1609 adult subjects and 196 (12%) reported reactions to various kinds of cosmetics and toiletries in the preceding 5 years. 69 of these (35% of the reactors and 4.3% of the total population) attributed their reactions to products primarily used for their smell (45 deodorants, 16 aftershaves and 8 perfumes). Patch tests were not performed, but from a similar study in clients of beauticians it may be concluded that only a minority of all reactions (less than 10%) were caused by contact allergy (58).

In Denmark, 567 unselected individuals aged 15–69 were tested with the fragrance mix (TRUE Test™ system), and 6 (1.1%) had a positive reaction (66, 67). The frequency in men (1.1%) was identical to that in women (1.0%). In men, shaving with a razor is said to increase the risk of becoming sensitized by fragrances by a factor of 3, possibly by creating small cuts in the skin facilitating penetration of applied perfume substances derived from soaps, shaving foams and aftershave lotions (70).

Frequency of adverse reactions in patients consulting the dermatologist

The adverse reaction to fragrances seen most frequently by dermatologists is allergic contact dermatitis. In studies on allergic reactions to cosmetic products, perfumes account for 4%–18% of all reactions, and deodorants/antiperspirants cause 5%–17% of all cases of allergic contact dermatitis (8, 44, 61, 62,71–75). This may actually be an underestimation of the real importance of fragrance sensitivity. People rarely consult a dermatologist with a rash caused by perfume, toilet water, cologne, or deodorant. When this occurs, the culprit is usually obvious, and they simply stop using the fragrance on their skin.

Clinical picture of allergic contact dermatitis from fragrances

In spite of the daily contact of virtually everybody with fragrances, and despite the high frequency of

positive patch test reactions to the fragrance mix in patients routinely tested for suspected contact dermatitis (in women slightly more frequent than in men (vide infra)), literature on the clinical picture of perfume dermatitis is rather scant. In not a single study routinely testing the fragrance mix has the clinical picture of patients with positive reactions to the mix been investigated and compared with contact dermatitis patients *not* sensitized to fragrances, although it has been shown that patients with hand dermatitis and leg ulcers/stasis dermatitis have an odds ratio of 2.6 of being sensitized to the fragrance mix compared to patients with no hand dermatitis or stasis dermatitis (76). It can be expected, however, that the neck, the skin behind the ear and the axillae (77) are often implicated, being exposed to products with high concentrations of fragrances (perfume, deodorant). Also, the sensitive skin of the face and the eyelids should be particularly susceptible to developing allergic contact dermatitis from fragrances in skin care products, decorative cosmetics and cleansing preparations, and from airborne contact dermatitis (39, 40, 41). Micro-trauma from shaving facilitates (photo) contact allergy to aftershave fragrances (70). Indeed, among the 167 patients with suspect fragrance allergy investigated by Larsen et al. (78), the face was most frequently affected (40%).

Meynadier et al. (35) investigated 28 patients with fragrance sensitivity. 12 were sensitized to perfumes or perfumed products, 5 to perfumes in topical medicaments, 7 to both; in 4, the relevance was uncertain. One patient had pruritus sine materia on the eyelids from fragrance sprayed on her clothes. Several had allergic contact dermatitis on the face and chest. Most of these were erythematous, in some cases the eruption resembled nummular eczema, seborrhoeic dermatitis, sycosis barbae, or lupus erythematosus (35). More acute lesions with papules, vesicles and oozing may sometimes be observed. Lesions in the skin folds may be mistaken for atopic dermatitis. Dermatitis due to perfumes or toilet water tends to be "streaky" (79). Facial psoriasis may be induced/aggravated by allergic contact dermatitis from fragrances (80).

Hand eczema. Hand eczema is common in fragrance-sensitive patients. Santucci et al. (81) identified 54 patients sensitive to the fragrance mix. The hands were most frequently affected (41%), followed by the face (25%), diffuse (17%), axillae (9%) and legs (4%) (81). Malten et al. (82) also found the hands to be the most frequently affected in patients with suspected allergic cosmetic fragrance dermatitis. This may be explained by contact with fragranced cosmetics and toiletries (soap, shampoo, hand cream), perfumed topical medicaments, perfumed household products, flavouring materials used in the kitchen, and vegetable foods (83). Dyshidrotic eruptions are ascribed to ingestion of spices (35).

Recently, Johansen et al. investigated 11 patients with proven contact allergy to the fragrance mix and one or more personal products. Also in this study, the hands were most frequently affected (n=6), followed by the face (n=5), neck (n=3) and axillae (n=2) (47).

Although there is no published evidence confirming this, it is our personal experience that fragrances are rarely the sole cause of hand eczema. Usually, patients first have irritant contact dermatitis or atopic dermatitis (although it may be argued that a personal history of atopy is not a risk factor for allergy to fragrances (76)), which is later complicated by contact allergy to products used for treatment (fragranced topical medicaments) or prevention (hand creams and lotions) of hand dermatitis, or to other perfumed products in the household, hobby, or work environment.

Atopic dermatitis located at other body sites, perianal dermatitis (25), and vulval dermatitis (84) may also be complicated by fragrance allergy. The frequency of involvement of the face, neck and axillae in various studies may be an underestimate, as patients sensitized to perfumes applied there may recognize the culprit, stop using the incriminated products, and not consult a dermatologist.

Detecting allergic contact dermatitis from fragrances with the fragrance mix

A perfume may contain as many as 200 or more individual ingredients (85). This makes the diagnosis of perfume allergy by patch test procedures complicated. Screening agents such as the fragrance mix, balsam of Peru and, to some extent, colophony have been incorporated in the standard series to overcome the problem. However, the detection of fragrance sensitization by mixes means that no direct cause-effect relationship is established between the use of perfumed products, their content of different fragrance materials and allergic contact dermatitis. The fragrance mix, or perfume mix, was introduced as a screening tool for fragrance sensitivity in the late 70s following the important work of Larsen (28, 86). It contains 8 fragrance materials: eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, α-amylcinnamic aldehyde, cinnamic aldehyde and cinnamic alcohol. It is estimated that this mix detects 70%–80% of all cases of fragrance sensitivity (10). Originally formulated at 16% in petrolatum (2% of each constituent) it frequently produced irritant reactions. Therefore the concentration was lowered

Table 4. North American Contact Dermatitis Group perfume screening series (7)

α-amylcinnamic alcohol	5% pet.
anisyl alcohol	5% pet.
benzyl alcohol	5% pet.
benzyl salicylate	2% pet.
cinnamic alcohol	5% pet.
cinnamic aldehyde	1% pet.
coumarin	5% pet.
eugenol	5% pet.
geraniol	5% pet.
hydroxycitronellal	4% pet.
isoeugenol	5% pet.
musk ambrette	5% pet.
oak moss absolute	5% pet.
sandalwood oil	2% pet.

in July 1984 to 8×1%. Unfortunately, the currently used mix causes both false positive (irritant) (87, 88) and false-negative reactions (89, 90) (vide infra).

As of 1986, the North American Contact Dermatitis Group (NACDG) stopped using the fragrance mix (16%) and substituted a screening series of 14 individual fragrance allergens recommended for routine testing (Table 4).

Components of the fragrance mix (5)

α-amylcinnamic aldehyde is a greenish-yellow liquid with an intense jasmine odour not found in nature. It may be a constituent of several synthetic essential oils (e.g., jasmine oil synthetic). Found in perfumes, cosmetics, soap, and a wide range of industrial products, it is a weak sensitizer. It may cross-react or coreact with α-amylcinnamic alcohol.

Cinnamic alcohol in pure form may produce crystalline needles with the odor of hyacinth. It occurs as an ester in natural fragrance materials such as balsam of Peru, storax, cinnamon leaves, hyacinth oil, and propolis. It is found in perfumed cosmetic products, deodorants, paper, and laundry products and is often used in flavours. It cross-reacts with cinnamic aldehyde.

Cinnamic aldehyde is a yellowish oily liquid with a powerful, aromatic, warm, spicy odour and with the taste of cinnamon. It is a constituent of cinnamon oil, cinnamon powder, and patchouli oil and is found in bath oils and salts, tonics, hair cosmetics, lipsticks, mouthwash and breath fresheners, soaps, detergents, and as flavouring agent in toothpastes, sweets, soft drinks, and pastries. It is irritating at a concentration of 2%, and is a moderately strong sensitizer.

Eugenol is a colorless or light yellow viscous liquid, which darkens and thickens upon exposure to air. It has a powerful, spicy odour of clove, pungent taste – characteristic of the odour one associates with a dental surgery, where it is often used. It is found in oils of clove, bay, pimento, cinnamon leaf, sassafras, and patchouli. It is used in colognes, toilet waters, tonics, dressings, hair cosmetics, dentifrices, impression materials, and periodontal packings. It is a moderately strong sensitizer. It (pseudo)-cross-reacts with balsam of Peru and benzoin.

Geraniol is an oily, colourless liquid with a sweet, floral odour of rose. It constitutes the chief part of rose and palmarose oil, geranium oil, citronella oil, lavender oil, jasmine oil, and is present in most other essential oils. It is isomeric with linalool. It is used in perfumery, is an insect attractant, and is a weak contact allergen.

Hydroxycitronellal is a colourless viscous oil, a synthetic floral fragrance not found in nature. It has a sweet, fresh, green odour of lily of the valley. It is widely used in floralizing perfumes, many other cosmetic products (primarily in soaps), antiseptics and insecticides, and is a moderately strong sensitizer. It cross-reacts with citronellal and geranial.

Isoeugenol is a colourless oily liquid which turns yellow, with an odour of clove weaker than that of eugenol. It is a constituent of ylang-ylang oil and nutmeg oil. It is used in perfumery and is a moderately potent sensitizer.

Oak moss absolute, extracted from *Evernia prunastri* (oak moss) and *Pseudevernia furfuracea* (tree moss) is found in perfumes, colognes and aftershaves. It is used in many scented products marketed to men. Oak moss is a moderately strong allergen containing atranorin, evernic acid and fumarprotocetraric acid, and a photosensitizer.

Frequency of reactions to the fragrance mix and its constituents

Frequency of reactions to the mix. The response rate to the fragrance mix (FM) in dermatological patients nowadays ranges worldwide from 6% to 11%: Germany 7.5% (91) to 11.2% (92), Denmark 6.3% (93), Belgium 8.3% (cited by 87), Sweden 5.5% (94), Hungary 10.1% (95), Europe 7.8% (2455 patients in 8 centres (96)), Europe 8.3% (1069 patients in 12 centres (87)), Europe 7.5% (702 patients in 7 centres (88)), USA 11.4% (97), Australia 6.2% (98), UK 7.9% (99) and Greece 8.1% (100). Relevant data are summarized in Table 5. In most lists of frequent allergens, the FM ranges among the "Top 5", usually number 2 after nickel sulfate. An increase in the frequency of positive reactions has been noted in Copenhagen (4.7% in 1979–1983; 6.3% in 1988–1992) (93), and in Sin-

Table 5. Frequency of allergic reactions to the fragrance mix in patients routinely patch tested for suspected allergic contact dermatitis

Ref	Country	Year	No. Pat	Pos (%)	Men Pos (%)	Women Pos (%)	Relevance	Comments
87	Europe	1992–1994	1072	89 (8.3%)				*
97	USA	1992–1994	3478	396 (11.4%)			64% present, 9% past	
91	Germany	1990–1991	4140	310 (7.5%)	(7.1%)	(7.9%)	67% relevant	
92	Germany	1990–1993	18000	(7.7–11.2%)	(6.6–10.3%)	(8.5–11.6%)		
88	Europe	1993	702	53 (7.5%)			56% relevant, 17% possibly	*
95	Hungary	1992	1452	147 (10.1%)				*
93	Denmark	1979–1992	8215	449 (5.5%)				*
		1979–1983	2447	114 (4.7%)	(4.4%)	(5.1%)		
		1984–1987	2331	120 (5.1%)				
		1988–1992	3440	215 (6.3%)	(5.0%)	(7.4%)		
94	Sweden	1984–1990	3790	208 (5.5%)				
103	Germany	1987	1845	179 (9.7%)	69 (10.1%)	110 (9.5%)		*
96	Europe	1987	2455	(7.8%)				
98	Australia	1982–1989	3300	203 (6.2%)				
99	United Kingdom	1988	4721	372 (7.9%)				
101	Singapore	1986–1990	5557	738 (13.3%)				
		1984–1985	2471	208 (8.4%)				
102	Portugal	1980–1986	2411	192 (8.0%)				

* Patients also tested with ingredients of the mix. See Table 6.

Table 6. Reactions to the fragrance mix and its constituents

reference	87	88	95	89	93	103	81
country	Europe	Europe	Hungary	Netherlands	Denmark	Germany	Italy
year of study	1992–94	1993	1992–93	1991	1988–92	1987	1984–85
number of patients	1072	702	494	677	2540	1670	1500
positive to mix (%)	89 (8.3%)	53 (7.5%)	50 (10.1%)	61 (9%)	160 (6.3%)	162 (9.7%)	54 (3.6%)
oak moss	24 (2.2%)	18 (2.6%)	2 (0.4%)	21 (3.1%)	86 (3.4%)	14 (0.8%)	19 (1.3%)
isoeugenol	20 (1.9%)	23 (3.3%)	3 (0.6%)	15 (2.2%)	68 (2.7%)	27 (1.6%)	12 (0.8%)
eugenol	13 (1.2%)	6 (0.9%)	2 (0.4%)	12 (1.8%)	30 (1.2%)	11 (0.7%)	9 (0.6%)
cinnamic aldehyde	10 (0.9%)	6 (0.9%)	12 (2.4%)	21 (3.1%)	62 (2.4%)	34 (2.0%)	3 (0.2%)
geraniol	8 (0.7%)	5 (0.7%)	2 (0.4%)	8 (1.2%)	15 (0.6%)	4 (0.2%)	4 (0.3%)
hydroxycitronellal	8 (0.7%)	3 (0.4%)	5 (1.0%)	12 (1.8%)	27 (1.1%)	10 (0.6%)	9 (0.6%)
cinnamic alcohol	6 (0.6%)	1 (0.1%)	4 (0.8%)	19 (2.8%)	40 (1.6%)	9 (0.5%)	5 (0.3%)
α-amylcinnamic aldehyde	5 (0.5%)	6 (0.9%)	1 (0.2%)	3 (0.4%)	10 (0.4%)	2 (0.1%)	1 (0.1%)
sorbitan sesquioleate	5 (0.5%)	5 (0.7%)	NT	NT	NT	NT	NT
comments	1	2	3	4	5	6	7

NT: not tested.

Comments:

1. 32/89 reactions to the fragrance mix negative to ingredients (36%)*.
2. 29/53 reactions to the fragrance mix negative to ingredients (55%)*.
3. 50 patients from a population of 147 were retested. The number of patients (494) is therefore calculated as approximately. Test concentrations not certain.
4. Constituents tested 5% pet (cinnamic aldehyde 2%) without sorbitan sesquioleate.
5. 54% of the patients with a positive reaction to the FM mix had at least one positive reaction to ingredients; 72% if the doubtful reactions were also counted*.
6. 162 patients from a population of 179 were retested. The number of patients (1670) is therefore calculated as approximately. 69/162 reactions to the fragrance mix positive to ingredients (43%)*.
7. 9/54 reactions to the fragrance mix negative to ingredients (17%)*.

* FM-mix: 8×1%. Ingredients: 1% pet.

gapore (8.4% in 1984–1985; 13.3% in 1986–1990) (101).

Frequency of reactions to the constituents of the mix. Several studies have investigated the frequency of allergic reactions to the *ingredients* of the fragrance mix (81, 87,–89, 93, 95, 103). Although the results have varied widely, most reactions appear to be caused by oak moss, isoeugenol and cinnamic aldehyde (104), whereas geraniol, α-amylcinnamic aldehyde and hydroxycitronellal usually yield lower scores of positive reactions (Table 6).

Cinnamic aldehyde 1% pet. is routinely tested in the NACDG standard series, and yielded 2.7%

positive reactions in 1990–1992 (3.1% from 1985–1989) (97). Cinnamic alcohol 5% pet. scored 4.8% positive reaction in the USA from 1985–1989 (105).

Sensitivity to oak moss (102) is frequently induced by the use of aftershave lotions, because the integrity of the epidermis is lost during shaving, facilitating sensitization; lichens encountered in nature may also be implicated (45, 106). 31 patients allergic to oak moss were studied (102). In 20 of them, the origin of sensitization was attributed to perfumed products. Lichen acids were tested in 20 oak-moss-sensitive patients: 10 reacted to atranorin, 8 to usnic acid, 6 to evernic acid, 3 to fumarprotocetraric acid, and 2 to stitic acid (102). Other studies gave similar results (106, 107). Occasionally, reactions to physodes/physodalic acid and diffractaic acid have been observed (55). Photosensitivity is far less common (55).

Clinical relevance of a positive reaction to the fragrance mix

As with any contact allergen, the finding of a positive reaction to the fragrance mix should be followed by a search for its relevance. Often, however, correlation with the clinical picture is lacking and many patients can tolerate perfumes and fragranced products without problems. This may sometimes be explained by irritant patch test reactions to the mix. Alternative explanations include the absence of relevant allergens in those products or a concentration too low to elicit clinically visible allergic contact reactions. In addition, in the "ageing" proces of a perfume, the allergen may be inactivated (108). Whether the phenomenon of "quenching", in which the allergenicity of a fragrance compound is inhibited by the addition of a quencher fragrance, may play a rôle is uncertain (17, 19).

In various studies the relevance of positive patch test reactions to the mix has been investigated. However, criteria were usually not provided. In cases with concomitant positive reactions to perfumes or fragranced products used by the patient, interpretation of the reaction as "relevant" may be quite easy. Often, however, relevance may (correctly or incorrectly) only be assumed , as the role of fragrances is likely/cannot be excluded because of the ubiquitous occurrence of fragrances and multiple possible exposure moments from (in)-direct contact, airborne exposure, inhalation or ingestion (flavors, spices).

In an early study, 50% of 54 patients with a positive patch test to the fragrance mix considered the response consistent with their clinical history (81).

According to an EECDRG study (88), clinical relevance of a positive patch test reaction exists in at least 55%–65% of positive results. Strongly positive patch test reactions (++ or +++) are more likely to be associated with a positive fragrance history than a weak or doubtful reaction (88). A positive ROAT (repeated open application test, 2× daily application on the antecubital fossa for 1 week) (109, 110) with fragrance ingredients makes relevance of the reaction more likely. In patients with a positive reaction but a negative history of fragrance sensitivity, the ROAT is more likely to be negative (88). ROATs usually end after 7 days. It should be appreciated that this may not be long enough. With use tests involving cinnamic aldehyde, nearly 50% first reacted after day 7, sometimes even after 14 days (104).

In the USA, 64% of 396 reactions to the fragrance mix were considered to be of present relevance, and 9% of past relevance (97).

In Denmark, 23 products, which had either given a positive patch and/or use test in a total of 11 fragrance mix-positive eczema patients, were analyzed. In all cases, the use of these cosmetics completely or partly explained present or past episodes of eczema. Between 1 to 6 constituents of the fragrance mix were found in 22 of 23 products. The cosmetics of all patients sensitive to hydroxycitronellal, eugenol, cinnamic alcohol and α-amylcinnamic aldehyde were found to contain the respective substances. It was concluded that exposure to constituents of the fragrance mix is common in fragrance-allergic patients with cosmetic dermatitis (47). It should of course be realized that these patients were selected on the basis of cosmetic dermatitis, a positive patch test reaction and/or use test to a currently used leave-on cosmetic product. Therefore, this study does not say anything about the relevance of a positive reaction to the fragrance mix per se. Nevertheless, it does indicate that, in such patients with relevant cosmetic dermatitis caused by fragranced products, the fragrance mix is a good reflection of actual exposure (47).

Of 31 patients allergic to oak moss, in 20 the origin of sensitization was attributed to perfumed products (102). In 7 patients allergic to the fragrance mix, ROATs were performed with deosprays, deosticks and skin care creams containing the perfume mix fragrances (each product contained 4 fragrances each at a 1% concentration!). 5 of 7 had one or more positive use tests. However, only 2 of 7 patients had proven contact allergy to the ingredients of the mix, and the concentrations of the fragrances were excessively high, which makes this report difficult to interpret and of limited value (111).

The fragrance mix: very useful, but not ideal

The currently used mix causes false-positive (irritant) (87, 88), but also false-negative reactions (89, 90).

Discrepancies between reactions to the fragrance mix and to its constituents. Investigators studying reactions to the fragrance mix and its constituents found that in only 40%–60% of patients with a positive reaction to the fragrance mix (8×1% containing 5% sorbitan sesquioleate) 1 or more of the constitutents of the mix (1% pet. without sorbitan sesquioleate), when tested separately, also gave positive patch test reactions (93, 103, 112). Possible explanations for this discrepancy include (88, 93, 103, 113) the following:

(i) False-positive (irritant) reaction to the mix.

(ii) False-negative reaction to the constituents. The test concentration in testing the individual constituents may be too low (89, 90, 93), as: (a) the mix contains chemically related substances, which may cross-react; (b) unrelated allergens in combination, as in the mix, may have a lowering effect on the concentration needed for the individual allergens to elicit reactions (113); (c) the absorption of the constituents in the mix may be enhanced by the presence of the emulsifier sorbitan sesquioleate; (d) a marginally irritant constituent in the mix may enhance the absorption of other constituents.

(iii) Two or more ingredients in the mix form a new allergen ("compound allergy").

Enders et al. (114) investigated the influence of adding 1% sorbitan sesquioleate (SSO) to the individual ingredients. Of 423 patients tested with the mix, 39 (9.2%) had a positive reaction. When tested with the individual ingredients **without** sorbitan sesquioleate, 20 of these 39 (51%), reacted to 1 or more ingredients. In a second series of 721 patients, 53 (7.4%) had positive reactions to the mix. When these 53 were tested with the ingredients **with** sorbitan sesquioleate, 49 (92%) had 1 or more positive reactions (versus 51% in the first series). Moreover, 15 patients from the 1st series, positive to the mix but negative to the ingredients without sorbitan sesquioleate, were retested. All 15 again had a positive reaction to the mix, 14 (93%) reacted to one or more ingredients **with** SSO, but only 3 (20%) to ingredients **without** SSO. The authors concluded that the addition of sorbitan sesquioleate enhances the diagnostic power of the individual ingredients, and that the negative reactions to ingredients (without SSO) in patients with a positive reaction to the mix are largely false-negative. The discrepancy can almost entirely be overcome by addition of 1% SSO to the ingredients used for patch testing (114). As a result, Hermal (Reinbek, Germany), producer of Trolab® allergens, from January 1991 on added 1% SSO to the individual ingredients of the mix (oak moss already contained it) (115).

Frosch et al. in a multicentre study also investigated the influence of adding SSO, by testing patients with the Trolab mix, a "self-made" mix of the same composition, the 8 ingredients **with**, and the 8 ingredients **without** 1% SSO, and SSO itself (20% pet) (88). 709 patients were tested. 5 patients (0.7%) had a reaction interpreted as allergic to the emulsifier SSO itself, 2 were irritant. Thus SSO should always be tested in the standard series in order to avoid misinterpreting a positive reaction to the mix as "fragrance allergy".

Of the remaining 702 patients, 53 (7.5%) reacted to one or both mixes. When tested with the constituents **without** SSO, 41% of these showed an allergic reaction. This figure became 55% when the constituents also contained SSO. 7 ingredients increased in the number of positive reactions by adding SSO, but the number of positive reactions to cinnamic alcohol actually **de**creased. Addition of SSO also increased the number of irritant reactions.

Although this study thus confirmed the value of adding SSO to the ingredients, still some 45% of positive reactions to the mix had negative "breakdowns". This phenomenon currently remains unexplained.

De Groot et al. (89) investigated the reverse situation: a negative reaction to the mix with a positive reaction to 1 or more ingredients, i.e., a false-negative reaction to the mix. Previously (90), these authors had found that, of 179 patients suspected of cosmetic allergy, 13 reacted to ingredients of the mix tested at a higher concentration (7×isoeugenol, 4×oak moss, 1×geraniol, and 1 combination), in the absence of a positive reaction to the mix itself. In the more recent study (89), patients with a negative reaction to the mix, but a positive reaction to 1 or more ingredients (5% pet. without SSO, cinnamic aldehyde 2% pet. without SSO) were retested with the ingredients in a dilution series (5%–3%–1%, for cinnamic aldehyde 2%–1.2%–0.4%) to confirm allergy. Of 677 patients tested, 6 had a positive reaction to ingredients, but a negative reaction to the mix. With serial dilution tests, 4 (0.6% of all patients and 6.2% of all fragrance-sensitive patients) had positive reactions to cinnamic alcohol, geraniol, isoeugenol and oak moss, 1 reaction each, which indicated that false-negative reactions to the mix occurred in them (89). Although these %s are rather small, the authors state that, given the large number of patients allergic to perfumes, several fragrance-sensitive patients allergic to ingredients of the mix are missed with the mix of current composition. Therefore they suggest that more research should be

done to increase the sensitivity of the mix. One possibility is to increase the concentration of the ingredients of the mix. It may of course be argued that this is not feasible as, in the past, the 8×2% mix caused many cases of false-positive reactions. Possibly, however, these were "pseudo-false-positive reactions" due to the absence of sorbitan sesquioleate in the ingredients (103, 114). Another possibility would be to divide the 8 ingredients into 2 mixes, possibly allowing higher concentrations. A 3rd possible way, to avoid missing fragrance sensitivity is to test the individual ingredients at the higher concentrations in any patient suspected of fragrance sensitivity (positive history, positive reaction to the indicators of fragrance sensitivity: balsam of Peru, colophony) with a negative reaction to the mix itself.

Alternatives to the fragrance mix. From the discussion above, it is quite clear that the currently used fragrance mix (8×1% with 5% sorbitan sesquioleate) is very useful but not ideal. It causes irritant reactions (87, 88), irrelevant positive reactions (88, 93, 103, 112), false-negative reactions (89, 90), and leaves 20–30% of fragrance sensitivities undetected (10). Therefore, future research should be directed at both optimizing the test concentration of the mix and its ingredients and at finding more suitable allergens for a screening fragrance mix (89). Geraniol and α-amylcinnamic aldehyde would be the first candidates to be replaced, as they yield relatively few reactions in most relevant studies (87, 89, 93).

Several studies have indeed aimed at identifying fragrances which would be, by their frequency of sensitization, more suitable for inclusion in a fragrance mix. With the possible exception of citral and dihydrocoumarin (96), all these efforts have yielded no suitable candidates (87, 90), and the constituents of the fragrance mix have now remained the same for over 15 years. Testing additional fragrances may result in identification of more fragrance-sensitive individuals (78). Other test vehicles have been investigated including isopropyl myristate (87) and diethyl phthalate (87). Isopropyl myristate produced irritant reactions, and diethyl phthalate was considered to be unsuitable because of false-negative reactions (87).

Less common fragrance allergens

Routine testing with fragrances not present in the fragrance mix. Sugawara et al. (116) presented their results of 18 years testing with ylang-ylang oil 5% pet. The highest % of positive reactions in patients with cosmetic dermatitis was seen between 1975–1977 (19.8%); later (1987–1989) the frequency fell to 6.1%, due to the elimination by the industry of the main sensitizer dehydro-isoeugenol. In "controls" (patients with non-cosmetic dermatitis), the prevalence of senzitization ranged between 0.5% and 6.1% (116).

Frosch et al. (87) in a multicentre study tested 48 fragrances, each in at least 100 patients suspected of contact dermatitis, usually at concentrations of 1% and 5% pet. Only 10 reactions to 7 materials were observed: Iso E Super® (1,1,6,7–tetramethyl-6–acetyl decalene (isomers)) (n=2), Lyral (4-(4-hydroxy-4-methylpentyl)3-cyclohexenel-1-carboxaldehyde) (n=3), Cyclacet® (tricyclodecen-4-yl 8-acetate) (n=1), DMBCA (dimethylbenzyl carbinyl acetate) (n=1), Vertofix® (acetyl cedrene) (n=1), citronellol (n=1) and amyl salicylate (n=1). The remaining 41 fragrances were negative. Clinical relevance of positive reactions to any of the fragrances was not proven in a single case. The fragrances had been chosen because they were most commonly found in cosmetics on the US market (12), and therefore it was concluded that the "Top 25" fragrances commonly found in various cosmetic products cause few reactions in dermatological patients. One obvious criticism of this study however, as the authors themselves admit, was the relatively small number of patients tested (only 100 in most centres) (87).

Of 685 patients tested with lilal (lily aldehyde) in Japan, 3 (0.4%) had a positive patch test (117). Other prevalence rates of positive reactions (number of patients not specified) to fragrances in Japan were given as follows: oil of bergamot 1.5%, rose oil 3.9%, ylang-ylang oil 3.1%–8.1%, jasmine absolute 7.3%, benzyl alcohol 0.5%, benzyl salicylate 2.3%, oil of sandalwood 0.9%, santalol 0.9%, and musk ambrette 0.7% (117).

44 of 3152 Japanese patients (1.4%) tested with sandalwood oil 2% pet., 47 of 3123 (1.5%) tested with santalol 2%, and 25 of 1949 (1.3%) tested with isobornyl cyclohexanol (synthetic sandalwood) between 1979 and 1990 had positive patch test reactions (118). Of 456 patients tested with 5% farnesol in the same study, 7 (1.5%) had a positive patch test.

Paulsen et al. (119) tested 541 consecutive patients with *l*-carvone, one of the main constituents of spearmint oil. 15 (2.8%) had positive and 12 doubtful (?+) reactions to carvone. The strongest reactions were observed in 9 patients with concomitant Compositae sensitivity. When re-tested with *l*-carvone at the same or lower concentration, only 2 of 8 patients had positive reactions. The relevance of the reactions remained unknown, and no link to fragrances could be made (119).

Santucci et al. tested 1200 patients with 14 fragrance materials and observed 13 (1.1%) reactions to jasmine absolute, 12 (1.0%) to jasmine synthetic, 4 (0.3%) to musk ambrette, 3 (0.3%) to peppermint oil, 3 (0.3%) to limonene, 2 (0.2%) to bergamot oil,

2 (0.2%) to α-terpineol, 2 (0.2%) to β-pinene and 1 (0.1%) to menthol and sandalwood oil. Clinical relevance was not established (81).

Coumarin has occasionally caused positive patch test reactions in patients routinely tested with it, but relevance was not established (86, 120).

De Groot et al. (90) tested a series of 12 (mixtures of) fragrances in 179 patients suspected of cosmetic dermatitis. There were positive patch test reactions to α-amylcinnamic alcohol (n=7), a mixture of α-amylcinnamic aldehyde and α-hexylcinnamic aldehyde (n=7), Lilial® (n=5), Galaxolide® (n=3), cuminaldehyde (n=3), a mixture of ionone (mixed isomers) and γ-methylionone (n=2), d-limonene (n=2), nopyl acetate (n=2), carvacrol (n=2), isoamyl salicylate (n=1) and phenylethyl alcohol (n=1). However, some of the rarer reactions were considered to be irritant (excited skin syndrome), and relevance was not established (90).

Malten et al. (82) tested 182 patients suspected of cosmetic allergy to a series of 17 fragrances not included in the fragrance mix . There were positive reactions to coumarin (n=12), hydroabietyl alcohol (n=10), dihydrocoumarin (n=7), dimethyl citraconate (n=7), benzyl cinnamate (n=6), diethyl maleate (n=6), neral (n=5), propylidene phthalide (n=5), citral (n=5), benzyl alcohol (n=3), anisylidene acetone (n=2), farnesol (n=2), methyl heptine carbonate (n=2), phenyl acetaldehyde (n=2), ethyl acrylate (n=1) and methyl anisate (n=1) (82).

The North American Contact Dermatitis Group found prevalence rates of positive reactions of 1% for benzyl benzoate, 1.7% for citral, 1% for methyl heptine carbonate and 1.5% for methyl salicylate in patients routinely tested with these fragrances (121). Previously, the NACDG had routinely tested approximately 200 patients with 11 fragrances and found the following prevalence rates: jasmine synthetic (15.3%), jasmine absolute (10.8%), coumarin (5.4%), benzyl salicylate (2.1%), methyl salicylate (1.6%) and musk ambrette 1.6% (120).

Most recently, Larsen et al. (78) tested 167 patients suspected of fragrance allergy with 22 fragrance materials not present in the mix. Most reactions were seen to ylang-ylang oil (17%), narcissus oil (7%), sandela (7%), sandalwood oil (7%), majantol (5%), benzyl salicylate (5%) and galbanum resin (5%).

Other reported fragrance allergens. Documented fragrance allergens are listed in Table 7, with their test concentrations and relevant reference(s).

Occupational allergic contact dermatitis from fragrances

It may be expected that fragrances will cause dermatological problems in workers in the cosmetics industry (cosmetic chemists, workers handling the raw materials and the final products, salespeople), in beauticians, hairdressers, and aromatherapists. Housewives, health personnel and cleaning personnel may also be endangered by frequent contact with soap, cleansers, dishwashing liquids and other fragranced products. In spite of this, surprisingly little information on occupational allergic contact dermatitis from fragrances can be found in the literature, although in an early study all workers in a factory became sensitized to cinnamic aldehyde (148). This may be because, in the majority of people at risk, a definite relationship between dermatitis and fragrances is hard to prove. In many occupations (hairdressers, beauticians, housewives, health personnel, cleaning personnel) irritant factors may also be relevant in the etiology of dermatitis, and sometimes other allergens are also considered of paramount importance. In addition, non-occupational exposure to fragrances occurs in virtually everybody.

Most pertinent information is available on hairdressers. Holness and Nethercott (149) did find a very high frequency (18%) of allergic reactions to the fragrance mix in hairdressers, but the frequency in controls was as high. Reactions to cinnamic alcohol and cinnamic aldehyde occurred less frequently in hairdressers than in referents (149). Guerra et al., in Italy, considered 9 reactions to fragrance mix relevant in 184 hairdressers with allergic occupational contact dermatitis (150). Van der Walle & Brunsveld (151). In the Netherlands, saw 8 positive reactions in 103 hairdressers, but did not comment on their relevance.

Gola et al., in Italy, found the fragrance mix to be the 2nd most frequent allergen in **non**-occupational contact dermatitis, whereas it was not part of the "Top 10" of allergens in occupational contact dermatitis (152). Holness and Nethercott tested 601 individuals in their occupational contact dermatitis clinic, and found almost 20% positive reactions to the fragrance mix (16%). However, in only 3% of the positive reactors was the allergy felt to be work-related (153). In Australia, in 3 of 103 women with occupational allergic contact dermatitis were perfume fragrances listed as allergens (154). In none of 265 such men were fragrances implicated. Sun et al., in Taiwan, found 6 reactions (8.8%) to the fragrance mix to be relevant in 68 patients with occupational allergic contact dermatitis: 4 in hairdressers, 1 in construction and 1 in medical work (155).

Goodfield & Saihan (156) found a 44% prevalence of sensitivity to one or more fragrances in 35 coal miners, compared to 22% in male and 17% in female non-miner controls. The high frequency was attributed to the use of a highly perfumed

Table 7. Fragrances reported as allergens in cosmetics and toiletries[$]

Name of fragrance	Test conc/veh (209)	Ref.
1 acetyl cedrene (Vertofix®)	1%-5% pet.	(87, 122)
5-acetyl-1,1,2,3,3,6-hexamethylindan (Phantolide®)	3% pet.	(35)
amyl cinnamate	8% pet.	(123)
α-amylcinnamic alcohol	5% pet.	(28, 90, 124)
α-amylcinnamic aldehyde[#]	3%–5% pet.	(87, 124)
amyl salicylate	5% pet.	(86, 87)
anethole	5% pet.	(86)
anisyl alcohol[#]	5% pet.	(78, 86)
anisylidene acetone	2% pet.	(82)
atranorin (in oak moss)[&]	0.5% pet.	(55, 102, 125)
benzyl acetate	5% pet.	(86)
benzyl alcohol[#] *	5% pet.	(78, 82, 86, 117)
benzyl benzoate[#]	5% pet.	(86, 121)
benzyl cinnamate	5% pet.	(82)
benzylidene acetone	0.5% pet.	(35, 123, 126)
benzyl salicylate*	1% pet.	(22, 78, 86, 117, 127)
carvacrol (isothymol)	5% pet.	(35, 90)
cashmeran (6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone)	5% pet.	(78)
cedramber (cedrol methyl ether)	5% pet.	(78)
cinnamic alcohol[#]*	3%–5% pet.	(87, 128)
cinnamic aldehyde[#&]	1% pet.	(87)
cinnamyl benzoate	5% pet.	(123)
cinnamyl cinnamate[#]	5% pet.	(123)
citral	2% pet.	(82, 96, 121, 123)
citronellol	5% pet.	(62, 86, 87, 129)
coumarin[#]	5% pet.	(61, 78, 82, 86, 129, 130)
cuminaldehyde	5% pet.	(90)
dehydro-isoeugenol (in ylang-ylang oil)		(131)
diethyl maleate	2% pet.	(82)
diffractaic acid (in oak moss)	1% pet.	(55)
dihydrocoumarin	5% pet.	(82, 96, 123)
dimethyl citraconate	10% pet.	(82)
DMBCA (dimethylbenzyl carbinyl acetate)	3% pet.	(87)
ethyl acrylate	0.1% pet.	(82)
ethyl anisate	4% pet.	(132)
eucalyptol (1,8-cineole, cajeputol)	5% pet.	(133)
eugenol[#&]	3%-5% pet.	(87)
evernic acid (in oak moss)[&]	0.1% pet.	(55, 102)
farnesol	5% pet.	(82, 117)
fixolide	3% pet.	(35)
floropal (acetaldehyde 2-phenyl-2,4-pentanediol acetal)	5% pet.	(78)
fumarprotecetraric acid (in oak moss)	0.1% pet.	(102)
galbanum resin	2% pet.	(78)
geranial	1%–5% pet.	(134)
geraniol[#] *	3%–5% pet.	(87)
helional (α-methyl-3,4-methylene dioxyhydro- cinnamic aldehyde)	5% pet.	(78)
heliotropin	5% pet.	(86)
1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-2-benzopyran (Galaxolide®)	15% pet.	(90)
cis-3-hexenyl salicylate	3% pet.	(51)
α-hexylcinnamic aldehyde	10% pet.	(86, 90)
hexyl salicylate	12% pet.	
hydroabietyl alcohol (Abitol®)	10% pet.	(82)
hydroxycitronellal*[&]	3%–5% pet.	(87)
ionone	8% pet.	(90, 136)
isobornyl cyclohexanol (synthetic sandalwood)*	2% pet.	(118, 128, 137)
isoeugenol	3%–5% pet.	(87)
isopulegol	5% pet.	(86)
jasmine (absolute, synthetic) *	5%–10% pet.	(81, 86, 117)
ligustral ((methyl-(2,4(3,5)-dimethyl-3-cyclo-hexen-1-yl)-methylene anthranilate)	5% pet.	(78)
lilial (lily aldehyde, *p*-tert-butylmethylhydrocinnnamic aldehyde)	5% pet.	(52, 78, 81, 90, 117)
d-limonene	2% pet.	(90, 138)
linalool	2%–30% pet.	(3, 62, 80)
lyral (4-(4-hydroxy-4-methylpentyl)3-cyclo-hexenel-1-carboxaldehyde)	5% pet.	(44, 62, 87, 122, 135)
majantol (2,2-dimethyl-3-(3-methylphenyl)-propanol)	5% pet.	(78)

Contd.

Table 7 (contd.)

Name of fragrance	Test conc/veh (209)	Ref.
o-methoxycinnamic aldehyde	4% pet.	(123)
methoxycitronellal *	10% pet.	(139)
methyl anisate	4% pet.	(82, 132)
methyl heptine carbonate	0.5% pet./ 1% MEK	(82, 121, 123, 140, 141)
methylionantheme	0.04% alc.	(136)
γ-methylionone	10% pet.	(62, 90, 136)
methyl octine carbonate	1% MEK	(140)
methyl salicylate	2% pet.	(121, 142)
musk ambrette[&]*	5% pet.	(81, 117, 128, 143)
musk moskene[&]	5% pet.	(143)
musk xylene[&]	5% pet.	(143)
narcissus oil	2% pet.	(78)
neral	2% pet.	(82)
nopyl acetate	10% pet.	(90)
oak moss[&]	3%–5% pet.	(87, 102)
patchouli oil*	2% pet.	(78, 144)
phellandrene	?	(145)
phenylacetaldehyde (hyacinthin)	0.5% pet.	(82, 123)
phenylethyl alcohol	5% pet.	(86, 90)
physodes/physodalic acid (in oak moss)	0.1% pet.	(55)
β-pinene	15% pet.	(81)
propylidene phthalide	2% pet.	(82)
rhodinol (mixture of 1-citronellol and geraniol)	3% pet.	(144)
rose oil (Bulgarian)	2% pet.	(146)
sandalore (5-(-2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol)	5% pet.	(78)
sandalwood oil	2% pet.	(61, 78)
sandela (isobornyl cyclohexanol + 3-*trans*-isocamphyl cyclohexanol)	5% pet.	(78)
santalol*	2% pet.	(117, 118, 137)
stitic acid (in oak moss)	0.1% pet.	(102)
α-terpineol	5% pet.	(81, 86)
1,1,6,7-tetramethyl-6-acetyl decalene (isomers) (Iso E Super®)	1%–5% pet.	(87)
thymol	1% pet.	(86)
tree moss absolute	5% pet.	(86)
tricyclodecen-4-yl 8-acetate (Cyclacet®)	5% pet.	(87)
usnic acid (in oak moss)	0.1% pet.	(54, 55, 101)
violet leaves absolute	2% pet.	(78)
ylang-ylang oil*	5% pet.	(78, 116, 147)

[$] Presence in cosmetics not always proven; contact allergy sometimes established by routine testing.
* Has caused pigmented cosmetic/contact dermatitis.
[&] Has caused phototoxicity/photoallergy (8).
[#] Has caused immediate contact reactions (contact urticaria).

body lotion provided at the pit-head bath, and the frequent occurrence of irritant contact dermatitis from working in the coalmines facilitating contact sensitization (156).

5 cases of respiratory and cutaneous disorders in the perfumery industry caused by allergy to abelmusk seeds (*Hibiscus abelmoschus,* Malvaceae), characterized by conjunctivitis, coryza, cough, asthma, pruritus, urticaria and eczema have been observed. However, the odorous substances of abelmusk used in perfumes and cosmetics were *not* the allergens in these patients (157).

On the basis of these data, we conclude that fragrances may play a role in some patients with occupational contact dermatitis, but in no single occupation is it a major cause of occupational allergic contact dermatitis, and rarely is it the sole etiological factor. However, fragrances may play an important role in aggravating hand eczema of other origin (atopic hand eczema, irritant contact dermatitis, allergic contact dermatitis) by contact with hand cleansers, barrier creams, moisturizing preparations, etc. In addition, flavours and spices may be involved in occupational contact dermatitis in bakers, cooks, caterers, and others working in the food industry (not discussed here).

Documented case reports of occupational allergic contact dermatitis from fragrances

Bergamot oil (158) and lovage oil (159) each sensitized 1 worker in the fragrance industry. 13 cases of contact allergy to cinnamic alcohol in a fragrance plant were collected by Gutman & Somov (160).

A woman packing cosmetics was sensitized by

ylang-ylang oil (147). 2 patients handling cosmetic ingredients developed hand dermatitis. One had positive patch test reactions to the perfume he came in contact with, and also reacted to the fragrance mix, ylang-ylang oil, aniseed oil, and oak moss absolute. The other reacted to the fragrance mix, citronella oil, cinnamon oil, eugenol and isoeugenol, but not to the perfume he handled (161).

A handyman employed in a hotel developed airborne allergic contact dermatitis from the fragrance in the air conditioning system that he had to clean (98). A chemical product mixer was sensitized to the fragrance that was used in his work to combat the bad smell of the insecticide produced at the plant he worked (98). A nurse developed airborne allergic contact from a perfume which she sprayed on a patient after washing her (98). A laboratory assistant mixing fragrances was occupationally sensitized to methyl heptine and methyl octine carbonate (140). A hairdresser was sensitized to lavender oil in lavender shampoo (162). A worker adding fragrances to a dispensing machine making air-fresheners was sensitized to cinnamic aldehyde with which he came in contact (163). A nurse developed hand dermatitis from applying an aftershave lotion to disabled patients. She was allergic to oak moss present in the aftershave (45). A physiotherapist became sensitized to the lavender fragrance in a massage gel used on her clients (164).

Irritant Contact Dermatitis

Few well-documented cases of irritant contact dermatitis from fragrance materials are found in the literature (165). A large number of people broke out after the introduction of a lemon-scented detergent in a hospital. The temperature-dependent, primary irritant reaction from the lemon perfume was due to the chemical citral. The problem was solved by doing the manual dishwashing in colder or lukewarm water rather that hot water (166).

Meynadier et al. (35) state that irritant reactions occur frequently and are caused especially by products with high concentrations of perfume, notably deodorants and antiperspirants. The most frequently affected sites are the upper eyelids, axillae and perineum. However, these authors provide no clinical data nor literature references to substantiate their statements (35). Of course, deodorants and antiperspirants are an important cause of irritation, favoured by the humid climate in, and anatomical occlusion of, the axillae (69). However, this may well be caused by the alcohol content or other ingredients rather than by the fragrance materials.

Photocontact Dermatitis

Compared to allergic contact reactions, photocontact dermatitis from fragrances is unusual. Only musk ambrette , a fragrance fixative used both in the food and cosmetics industry, has caused a considerable number of photocontact allergy reactions since its first description in 1979 (143, 166, 167). It is present in colognes, toiletries and perfumes, especially for men, and in fragrant oil used by Muslims before prayers (168). Pigmented photoallergic contact dermatitis (169), airborne pigmented contact dermatitis (170) and lichenoid photocontact dermatitis have all been described (171). Persistent light reactions are not rare (172–176), sometimes leading to erythroderma (175). Photocross-reactions have been observed to musk moskene and musk xylene (143). Photodermatitis may be acquired by "connubial" or "consort" exposure (38). In 1985, the International Fragrance Association (IFRA) recommended that musk ambrette not be utilized in products in contact with skin. In other products a concentration of 4% or less was recommended.

The photoallergenic and phototoxic properties of coumarin derivatives, notably 6-methylcoumarin, are well-known (177–181). Coumarin itself, which is widely present in fragrances (Table 2), does not appear to induce clinical photosensitization. 6-Methylcoumarin is not used anymore by the cosmetics industry (183).

Occasionally, positive photopatch tests have been observed to the fragrance mix (167, 184, 185), and some phototoxic reactions were noted (185).

Reactions to oak moss and its ingredients lichen acids are usually of the allergic contact type, but photosensitivity may occur to oak moss (185), atranorin and evernic acid (186). In patients with persistent light reactions in chronic actinic dermatitis, a greater incidence of contact sensitivity reactions to certain fragrance materials than in patients with polymorphic light eruption and in patients with non-light contact dermatitis was found (177). Immediate and delayed photopatch test reactions were also observed, notably to oak moss, musk ambrette, eugenol, cinnamic aldehyde, 6-methylcoumarin, costus root oil and hydroxycitronellal. These reactions were (tentatively) interpreted as phototoxic rather than photoallergic (177). The authors suggested that in some subjects with persistent light reaction a significant factor is likely to be exposure to substances such as fragrance materials which have the ability to produce dermatitis, not only from contact allergic sensitivity but also through photocontact reactions involving either phototoxic or photoallergic mechanisms (177).

Recently, 21% of 89 patients with chronic actinic dermatitis were found to be allergic to fragrances and 6% had photocontact allergy to musk ambrette, which seems to confirm the association (187). Even more of these patients (36%) were found to be allergic to the sesquiterpene lactone mix, containing allergenic constituents of Compositae plants. Some fragrance materials may cross-react with Compositae (188), and indeed, sesquiterpene lactones have been suggested as "screening agents" for fragrance sensitivity (6, 79).

Immediate Contact Reactions (Contact Urticaria)

Contact urticaria to fragrances is usually non-allergic (non-immune immediate contact reactions (21)), caused by a non-allergic histamine-liberating effect. Well-known causes are balsam of Peru, cinnamic aldehyde (21), cinnamic acid, cinnamyl cinnamate, benzyl benzoate and benzyl alcohol. Immediate contact reactions can also affect the respiratory tract, as some individuals suffering from chronic respiratory problems experience worsening or precipitation of their symptoms on exposure to certain fragrance materials (68) (vide infra under "Other adverse reactions"). Becker et al. tested 50 patients with a positive patch test reaction to the fragrance mix with its constituents. In 27, "immediate reactions" were observed, mainly to cinnamic aldehyde and cinnamic alcohol. 1 reaction was observed to eugenol, 1 to α-amylcinnamic aldehyde and 1 to geraniol. There were also positive reactions to salicylaldehyde and benzaldehyde. Clinical details and the relevance of these reactions were not provided (95).

Abifadel et al. (188) observed immediate contact reactions to the perfume mix (see also 21), balsam of Peru, cinnamic aldehyde, vanillin, and clove oil. They interpreted these as non-immunological immediate contact reactions, the relevance of which remained obscure (188). Emmons & Marks (189) performed open tests with 14 fragrances and balsam of Peru on 50 volunteers: 16 with a history of cosmetic intolerance, 15 with dermatitis and 19 controls. There were positive immediate reactions to cinnamic alcohol (n=39), cinnamic aldehyde (n=38), geraniol (n=35), anisyl alcohol (n=35), benzyl alcohol (n=32), balsam of Peru (n=32), coumarin (n=24), eugenol (n=18), and α-amylcinnamic aldehyde (n=3). However, these reactions were only macular and erythematous and were no more frequent in a group with cosmetic intolerance than in the other groups. Relevance was not established (189). A patient with contact urticaria to rouge was found to be contact allergic to γ-methylionone contained in it (190), and terpinyl acetate in spray starch caused contact urticaria (191). Several cases of immediate contact reactions to commercial deodorants (192) and perfumes (165,192,193) have been reported.

Non-immune immediate contact reactions to cinnamic aldehyde can be diminished ("quenched") by eugenol. The mechanism is unclear (21).

Pigmented Cosmetic Dermatitis (134, 139, 194)

In Japan, in the 1960s and 1970s, many women with bizarre hyperpigmentations of the face were observed. Before the relationship with cosmetics was discovered, such patients had been diagnosed as suffering from Riehl's melanosis or "melanosis feminae faciei" (194). The skin manifestations of (what was later called) pigmented cosmetic dermatitis consisted of diffuse or patchy brown hyperpigmentation on the cheeks and/or forehead; sometimes the entire face was affected. Occasionally, erythematous macules or papules, suggesting a mild contact dermatitis, were observed. Itching was sometimes present. The dermatosis was differentiated from chloasma (melasma), because pigmented cosmetic dermatitis does not have the spectacle-shape configuration seen in melasma, and dermatitis and itching are absent in melasma patients. In 1964, contact allergy to cosmetics was first suspected to be the cause of melanosis feminae faciei (195); yet it would take nearly 10 years before the term "pigmented cosmetic dermatitis" was coined by Nakayama et al (139). From 1969 on, systematic investigation of patients suffering from pigmented cosmetic dermatitis, with patch testing and photopatch testing of cosmetic ingredients (134), confirmed that many patients with "melanosis feminae faciei" had contact allergy to cosmetics. It was found that the major sensitizers in cosmetics were coal tar dyes (used in decorative cosmetics) and fragrances. Common causative fragrance materials included jasmine absolute, ylang-ylang oil, cananga oil, sandalwood oil, benzyl salicylate, benzyl alcohol, methoxycitronellal (a derivative of hydroxycitronellal), β-santalol, geraniol, geranium oil, and patchouli oil (139). Photocontact allergy was less important in the development of pigmented cosmetic dermatitis.

On the basis of their clinical and patch testing experience, Nakayama et al. (134) developed the "allergen controlled system" for the production of safer cosmetics, and major cosmetic companies in Japan began to stop using various sensitizers in their products in 1977. Since 1978, the number of patients suffering from pigmented cosmetic dermatitis has decreased remarkably, and the rate of positive reactions to some cosmetic allergens has begun to decrease (139, 196).

Pigmented cosmetic dermatitis was and is hardly

observed in Western countries, as the persistent secondary hyperpigmentation to contact dermatitis, which causes the clinical picture, is common in Mongoloids but is not observed in Caucasians. Nowadays, (possible (197)) cases of pigmented cosmetic dermatitis from fragrances are reported infrequently (170, 198, 199).

Berloque dermatitis

Berloque dermatitis is characterized by pigmentation, classically in a droplet or pendant-like configuration, usually over the sides of the neck in adult females. This cosmetic reaction used to be very frequent, and was caused by a phototoxic reaction to 5-methoxypsoralen (bergapten) in bergamot oil present in perfumes, resulting in hyperpigmentation with or without preceding erythema. This incidence of berloque dermatitis had already declined by the 60s, by the reduction of the concentration of natural bergamot oil in perfumes and the use of bergamot oil free of bergapten. Nevertheless, cases were still reported in 1981 (200). At that time, 21% of a random sample of 108 perfumes still contained 10 ppm or more of bergapten (200). It was suggested that other (more or less distinct) pigmentary disorders such as melasma, Riehl's melanosis, pigmented peribuccal erythema of Brocq and poikiloderma of Civatte may also be induced or aggravated by bergapten photosensitivity (200). Indeed, in a recent review article (201) on melasma, perfumes were considered to be an important etiological factor. However, we think this claim cannot be substantiated.

Other Adverse Reactions

Depigmented airborne contact dermatitis from santalol and musk ambrette released from burning incense has been observed (202). A pemphigoid-like allergic reactions was thought to be caused by cinnamic aldehyde (203). 1 patient, who had an erythema-multiforme-like contact dermatitis from clothing, had positive reactions to several allergens including the fragrance mix. Cutaneous histopathological features of biopsies of the lesions and several patch test reactions were consistent with erythema multiforme. It should be stressed, however, that the fragrance allergy was not relevant to the eruption (204).

Contact dermatitis from the application of spray cologne to the chest and the abdomen in a female patient resulted in the development of erythema multiforme, with progression to toxic epidermal necrolysis and, ultimately, her death (205). Erythema-multiforme-like allergic contact dermatitis was also caused by a deodorant (206).

Possibly, fragrances can induce or worsen respiratory problems (207, 208). Guin & Berry (68) interviewed 90 student nurses. In 4, asthma was thought to be aggravated or precipitated by exposure to fragrances, 25 would develop rhinitis, and 5 ascribed (worsening of) episodes of urticaria to contact with fragrances. These questionnaire results were not further explored by tests. Shortness of breath and sneezing from inhalation of fragrances was also found in a similar interview study (69). People with respiratory allergy may commonly experience aggravation around cosmetic counters, candle shops, and perfumes worn by other people, e.g., in church. This is thought to be due to a direct release of histamine rather than an allergic mechanism, caused by fragrance ingredients known to cause non-immunologic immediate contact reactions (68).

The "Work-up"of Patients Suspected of Allergic Contact Dermatitis from Fragrances

Patient history

On the basis of information provided by the patient, contact allergy to fragrances may be suspected. This is especially the case when products are used at sites of dermatitis which contain high concentrations of fragrances and few other allergenic ingredients: perfumes, colognes, eaux de toilette, and deodorants. A history needs to include a complete accounting of cosmetic usage and details regarding exacerbating factors such as work, hobby, or exposure to light.

Physical examination

Dermatitis on the face, behind the ears, on the neck (especially when it is streaky), in the axillae, on the chest, and perianal/vulval should alert to the possibility of fragrance allergy. However, any other part of the body can be affected by sensitivity to fragrances, and any other form of dermatitis (irritant, atopic) may be complicated by sensitization to perfume.

Patch testing

The patient should be patch tested with the standard series of allergens (EECDRG or NACDG) and the patient's own contact materials, including all relevant cosmetics, perfumes, and other perfumed contactants. Most perfumes can be tested at concentrations of 10% to 30% in petrolatum or alcohol. Individual components, however, should be diluted to concentrations of 1% to 5% (8, 79, 209, 210). When fragrance allergy is strongly suspected on the basis of the patient's history, ad-

Table 8. Fragrance allergens commercially available

Allergen	Trolab	Chemo-technique
abitol® (hydroabietyl alcohol)	10% pet.	10% pet.
alantolactone (helenin)	0.1% pet.	0.1% pet.
α-amylcinnamic aldehyde	1% pet.	2% pet.
anethole		5% pet.
atranorin	0.5% pet.	0.1% pet.
balsam of Peru	25% pet.	25% pet.
balsam of Tolu	20% pet.	10% alc.
benzaldehyde	5% pet.	
benzyl alcohol	1% pet.	1% pet.
benzyl cinnamate	5% pet.	
benzyl salicylate	1% pet.	2% pet.
cananga oil		2% pet.
cedarwood oil	10% pet.	
cinnamic alcohol	1% pet.	2% pet.
cinnamic aldehyde	1% pet.	1% pet.
clove oil	2% pet.	
dipentene (*dl*-limonene)	2% pet.	1% pet.
eucalyptus oil	2% pet.	
eugenol	1% pet.	2% pet.
evernic acid		0.1% pet.
geraniol	1% pet.	2% pet.
geranium oil Bourbon		2% pet.
hydroxycitronellal	1% pet.	2% pet.
isoeugenol	1% pet.	2% pet.
jasmine absolute, egyptian		2% pet.
jasmine synthetic		2% pet.
laurel oil	2% pet.	
lavender absolute		2% pet.
lemon grass oil	2% pet.	
lemon oil	2% pet.	
lichen acid mix		0.3% pet.
– atranorin		0.1% pet.
– usnic acid		0.1% pet.
– evernic acid		0.1% pet.
menthol		2% pet.
6-methylcoumarin		1% pet.
musk ambrette	5% pet.	1% pet.
musk ketone		1% pet.
musk mix		5×1% pet.
musk moskene		1% pet.
musk tibetene		1% pet.
musk xylene		1% pet.
neroli oil	2% pet.	
oak moss absolute	1% pet.	2% pet.
orange oil	2% pet.	
peppermint oil	2% pet.	
phenyl salicylate	1% pet.	1% pet.
rose oil, Bulgarian	2% pet.	
salicylaldehyde	2% pet.	
sandalwood oil		2% pet.
storax		2% pet.
usnic acid	0.1% pet.	0.1% pet.
vanillin	10% pet.	10% pet.
ylang-ylang oil		2% pet.

ditional fragrances can be tested concomitantly: the ingredients of the mix and possibly a fragrance screening series (Table 4). Over 50 fragrance allergens are currently commercially available for patch testing (Table 8).

Positive patch test reactions to the fragrance mix and/or the "indicators" of fragrance sensitivity, balsam of Peru and colophony (rosin), suggests the existence of contact allergy to fragrance materials. A single weak (?+ to +) reaction to the fragrance mix, in the absence of any other reaction to the indicators, other fragrance materials (if tested) or fragranced products brought in by the patient, may well be irritant in nature and should never be accepted as proof of fragrance contact allergy. In such cases, the fragrance mix should again be tested, preferably together with its fragrance ingredients (3–5% pet., with the exception of cinnamic aldehyde, 1% pet.) and sorbitan sesquioleate 20% pet. Fragranced products, to which weak positive patch test reactions are observed, should also be retested. Control tests in unexposed persons should exclude irritancy from personal products (false-positive reactions). Repeated open application tests may be helpful in diagnosing or confirming contact allergy and establishing relevance (vide infra). Other fragrances may be tested in a fragrance screening series (Tables 4 and 8).

In cases of suspected photosensitivity, photopatch tests should be performed (211, 212). When immediate contact reactions have occurred, appropriate tests should be performed (213–218).

Relevance

Positive patch test reactions to the fragrance mix and other fragrance materials should be followed by establishing the relevance of the reaction. This may be quite easy in cases where patients' fragranced products also reacted upon patch testing. A strongly positive patch test reaction to the mix is more likely to be relevant than a weak one (88). In cases of doubt, use tests or repeated open application tests (ROATs) with suspected products and/or fragrance materials may be helpful. Classically, the ROAT (109, 110) involves applying the product to the antecubital fossa 2× daily for 7 days. Recent information suggests that this time span is too short and should be extended to 14 days (104) as otherwise positive reactions may be missed! Often, the relevance will remain uncertain. Because of the ubiquitous occurrence of fragrance materials and multiple exposure possibilities, a role for fragrances is often assumed, even when not definitely proven.

Management of the patient (30)

The patient should be fully informed of his/her allergy, and the names of the allergens should be provided. A patient information leaflet and written instructions are very helpful (5). The patient should be instructed to avoid, as far as possible, fragranced cosmetic products including flavoured

Table 9. Reported (allergic) cutaneous adverse reactions to essential oils and their ingredients

Name of essential oil (ingredient)	Test conc/veh (209)	Adverse reaction	(Ref)
Abies alba oil	2% pet.	CA in routine testing	(4, 223)
angelica root oil#	2% pet.	CA in routine testing, ACD	(4, 223)
anise oil	0.5% pet.	ACD and stomatitis	224
aromadendrene (in tea tree oil)	1%–5% pet.	ACD	(225)
avocado oil	as is	ACD	(71)
basil oil	1%–5% pet.	ACD	(226)
bay oil	2% pet.	CA in routine testing	(35)
benzoin oil	1%–5% pet.	ACD	(226)
bergamot oil &	2% pet.	CA in routine testing	(81, 117, 223)
bitter orange oil&	2% pet.	CA in routine testing	(4, 223)
calamus oil	2% pet.	CA in routine testing	(4)
cananga oil*	2% pet.	CA in routine testing	(4, 223)
caraway seed oil	2% pet.	"sub-shock"	(224)
cassia oil (cinnamon oil)#	2% pet.	CA in routine testing	(4, 223, 227)
		allergic contact cheilitis	(224)
		contact urticaria	(95)
cedarwood oil&	10% pet.	CA in routine testing	(4, 127, 223)
chamomile oil	3% pet.	ACD	(226)
chamomile oil German	3% pet.	CA in routine testing	(4, 223)
chamomile oil Roman	3% pet.	ACD	(228)
cherry pit oil	2% pet.	ACD	(61)
citronella oil	2% pet.	CA in routine testing, ACD	(4, 129, 223, 227)
clary sage oil	2% pet.	CA in routine testing	(4, 223)
clove oil	2% pet.	CA in routine testing	(4, 223)
		contact urticaria	(189)
		permanent local anesthesia and anhidrosis	(229)
coriander oil	2% pet.	CA in routine testing	(4, 223)
costus oil	0.5% pet.	CA in routine testing, ACD	(61, 142)
p-cymene (in tea tree oil)	1%–5%pet.	ACD	(225)
cypress oil	1%–5% pet.	ACD	(226)
eucalyptol (1,8-cineole) in tea tree oil	5% pet.	ACD	(230)
eucalyptus oil	2% pet.	CA in routine testing, ACD	(4, 127, 223, 3)
frankincense oil	1%–5% pet.	ACD	(226)
geranium oil*	2% pet.	CA in routine testing	(4, 35, 223)
geranyl acetate (in citronella oil)	1% pet.	ACD	(129)
green grass oil	10% o.o.	ACD	(231)
guiac wood oil	2% pet.	CA in routine testing	(4, 223)
jasmine oil	2% pet.	ACD	(3)
juniper berries oil	2% pet.	CA in routine testing	(4)
juniper oil	2% pet.	CA in routine testing	(4, 223)
laurel oil	2% pet.	allergic contact cheilitis, ACD	(3, 224)
lavandin oil	2% pet.	CA in routine testing	(4, 223)
lavender oil*&	2% pet.	ACD	(3, 4, 35, 162, 164, 226)
lemongrass oil	2% pet.	ACD	(83, 226)
lemon oil#	2% pet.	CA in routine testing, ACD	(4, 83, 223)
d-limonene (in tea tree oil)	1%–5% pet.	ACD	(225)
Litsea cubeba oil	2% pet.	CA in routine testing	(4, 223)
lovage oil	2% pet.	ACD	(159)
marjoram oil	1%–5% pet.	ACD	(226)
myrrh oil	1%–5% pet.	ACD	(226)
narcissus oil	2% pet.	CA in routine testing	(78)
neroli oil&	2% pet.	ACD	(83, 226)
niaouli oil	1% alc.	ACD	(8, 232)
Nigella sativa black seed oil	use test as is	ACD and pigmented CD	(233)
orange oil&	2% pet.	CA in routine testing	(35, 127)
patchouli oil*	2% pet.	ACD	(35, 78, 144)
peppermint oil	2% pet.	ACD, contact urticaria	(4, 223, 226, 234)
petitgrain bigarade oil&	2% pet.	CA in routine testing	(4, 223)
α-phellandrene (in tea tree oil)	1%–5% pet.	ACD	(225)
pine needle oil	2% pet.	CA in routine testing	(4, 223)
Pinus pumilio oil	2% pet.	CA in routine testing	(35)
Pinus sylvestris oil	2% pet.	CA in routine testing	(35)
pomerance flower oil	2% pet.	ACD	(3)

Contd.

Table 9 (contd.)

Name of essential oil (ingredient)	Test conc/veh (209)	Adverse reaction	(Ref)
rosemary oil	2% pet.	CA in routine testing	(4, 223)
rose oil (Bulgarian)	2% pet.	ACD, CA in routine testing	(117, 146)
rosewood oil	1%–5% pet.	ACD	(3, 226)
safrole (in star anise oil)	5% pet.	CA in routine testing	(235)
sage oil	1%–5% pet.	ACD	(226)
sandalwood oil*&	2% pet.	depigmented airborne ACD	(78, 81, 202)
		CA in routine testing	(4, 117, 118, 137)
		(photocontact) ACD	(137, 236)
santalol in sandalwood oil	2% pet.	depigmented airborne ACD	(202)
		CA in routine testing	(137)
spearmint oil	2% pet.	allergic contact cheilitis stomatitis	(224)
spike oil	2% pet.	CA in routine testing	(4, 223)
star anise oil	0.5% pet.	CA in routine testing	(235)
suxiaoye-baojianxiangjin oil	use test as is	ACD	(237)
sweet orange oil	2% pet.	CA in routine testing	(4, 223)
Tagetes patula (French marigold) oil#	2% pet.	ACD	(238)
tea tree oil (melaleuca oil)	10% pet.	ACD (also airborne)	(225, 229)
α-terpinene (in tea tree oil)	1%–5% pet.	ACD	(225)
terpinen-4-ol (in tea tree oil)	1%–10% pet.	ACD	(225)
thuja oil	1%–10% pet.	ACD (erythema multiforme)	(239)
thyme oil	2% pet.	CA in routine testing, ACD	(4, 8, 232)
vetiver oil	2% pet.	ACD	(223, 226)
ylang-ylang oil*	5% pet.	ACD, CA in routine testing	(4, 78, 117, 223, 226)
zdrawetz oil	2% pet.	CA in routine testing	(223)
zhenghonghua oil	as is	ACD	(237)

ACD: allergic contact dermatitis.
CA: contact allergy.
* Has caused pigmented cosmetic dermatitis.
& Has caused phototoxic/photoallergic reactions.
# Phototoxic according to IFRA (2, 8).

toothpastes and mouthwashes (219) (especially for those allergic to cinnamic aldehyde) (220). Cosmetics used by the patients (and possibly, also the patient's partner) should preferably be unscented. The possibility of the presence of a "masking" fragrance therein should be explained. On the other hand, total avoidance of fragranced products is often not necessary; many will say that some fragranced products are well-tolerated. This may be because the allergenic fragrances are either not present in the particular product, or in a concentration too low to elicit an allergic reaction. Rinse-off products such as shampoo (135) and soap are rarely the cause of allergic contact dermatitis, even in fragrance-sensitive patients, although the possibility that frequent contact may contribute to (persistence or worsening of) dermatitis cannot be excluded. Some patients can safely apply the perfume to their clothes or hair (*cave* airborne contact dermatitis).

In patients with hand eczema we recommend the use of definitely non-scented proprietary ointments (e.g., Vaseline® or Eucerin®, cold cream USP) for some time in order to establish a possible role of fragrance sensitivity in this often multifactorial dermatitis.

Use tests (under normal circumstances of use) and ROATs for up to 14 days will help the patient decide which fragranced products can be maintained or purchased. The patient should also be instructed that household products, topical drugs and occupational contact materials may contain fragrances.

In some fragrance-sensitive patients who also react to balsam of Peru (some 50%) and in those reacting to fragrances that are also used as flavours and spices such as cinnamic aldehyde, cinnamic alcohol, vanilla and eugenol, foods and drinks may exacerbate symptoms, either local (worsening of hand eczema, cheilitis, stomatitis) or systemic (e.g., pompholyx) (31–33). Foods and medications that may cause such reactions in patients allergic to balsam of Peru include (33):

- citrus peel: oranges, lemon, grapefruit, bitter orange, tangerine, mandarin oranges
- essence-flavored products: baked goods, sweets, chewing gum
- wine, scented tea, tobacco
- cough medications and lozenges
- eugenol
- ice cream
- colas and other soft drinks

- spices: cinnamon, cloves, vanilla, curry (products from these include: ketchup, chili sauce, chutney, pickled herring, pickled vegetables such as beets and cucumbers, baked goods, paté, liver paste, vermouth, bitters, spiced beverages).

In some patients, especially in those presenting with stomatitis, cheilitis, recalcitrant pompholyx or widespread dermatitis, elimination diets may be indicated (31–33). However, the benefits of a flavour-avoiding diet are regarded as questionnable by some (221), and may be observed in a small number of patients allergic to balsam of Peru and/or the fragrance mix only (222). Therefore, only when the patient's history or clinical picture definitely suggests that flavours and spices may exacerbate symptoms, elimination diets should be considered. This should preferably be confirmed by (blinded) oral provocation tests before a diet is prescribed.

Fragrances from non-Cosmetic Sources

Essential oils are used both in fragrances, in foods, and for (alternative) medicinal purposes including aromatherapy. Those that have been reported as causes of allergic contact dermatitis or other adverse reactions are listed in Table 9, with at least 1 reference. Fragrance materials used in foods and drinks as flavours, which have caused allergic contact dermatitis or other adverse reactions are listed in Table 10, with at least 1 reference. Balsam of Peru as such is not used anymore in cosmetics (IFRA recommendation). Nevertheless, it contains fragrance materials that have been shown to be sensitizers and several of them are used in perfumes. They are listed in Table 11, with at least 1 reference.

Conclusions

Virtually everyone is exposed continually to fragrances through contact with perfumes, cosmetics, toiletries, oral hygiene products, household products, paper products, topical drugs, industrial contact materials and through contact with flavours and spices in foods and beverages. Cutaneous adverse reactions to fragrances include allergic contact dermatitis, immediate contact reactions (contact urticaria), and photosensitivity. Considering the ubiquitous occurrence of fragrance materials, the risk of such side-effects is relatively small. In absolute numbers, however, fragrance allergy is common. Approximately 1% of the unselected population is sensitized to fragrance materials. Indeed, fragrances are the most common causes of allergic contact dermatitis from cosmetics. Any part of the body may be affected. Classic localizations are the face, behind the ears, the neck, and the axillae. Hand dermatitis is also frequent in fragrance-sensitive subjects. In the authors', experience, fragrances are rarely the sole cause of hand eczema. These patients usually have irritant or atopic hand dermatitis first, which is later complicated by fragrance contact allergy to products used for treatment or prevention, or to other perfumed products in the household, hobby or work environment. Occupational contact dermatitis from fragrances seems to be relatively uncommon.

The currently used fragrance mix (eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, α-amylcinnamic aldehyde, cinnamic aldehyde, cinnamic alcohol, each 1% with 5% sorbitan sesquioleate) is very valuable in diagnosing fragrance sensitization. Between 6–11% of patients routinely tested because of suspected allergic contact dermatitis react to it, and in most centres the mix ranges among the "Top 5" of frequent allergens, usually number 2 after nickel sulfate. However, false-positive reactions are not rare, and a single weak (?+ or +) reaction to the mix should not be taken as evidence of fragrance contact allergy, but should be substantiated with other tests (ROAT, use tests, patch testing with the ingredients of the mix or other fragrances and personal fragranced products). Relevance is established in 50–65% of all cases, but more strict criteria should probably be applied, and there is a need for further investigation of the profile of the fragrance-sensitive patient.

False-negative reactions to the mix also occur, and as possibly 30% of patients allergic to fragrances are *not* detected by the mix, future research should be aimed at increasing the sensitivity of the mix. Up to now, no other fragrances have been identified that would, on the basis of frequency of allergic reractions to them, be suitable candidates for inclusion in the mix. We suggest that the following fragrances be investigated in large-scale studies: *on the basis of literature data:* benzyl salicylate, citral, coumarin, dihydrocoumarin, hydroabietyl alcohol, jasmine absolute/synthetic, lilial, methyl salicylate, and ylang-ylang oil; *on the basis of their widespread presence in perfumes (8, 12):* benzyl acetate, linalool, linalyl acetate, lyral, hexylcinnamic aldehyde, γ-methylionone, phenylethyl alcohol, and terpineol.

The industry-based Research Institute for Fragrance Materials (RIFM) and the International Fragrance Association (IFRA) make serious efforts in providing adequate safety guidelines to the fragrance industry. However, cooperation with dermatologists should be further improved and initiated at an early stage of product development. Free exchange of information and joint research

Table 10. Adverse reactions to fragrances & flavours from non-cosmetic sources

Name of fragrance/flavour	Product	Side effect	Refs.
α-amylcinnamic alcohol	topical medicament	allergic contact dermatitis	(28)
anethole	toothpaste	allergic contact cheilitis stomatitis	(224)
benzyl alcohol	topical medicament	allergic contact dermatitis	(28)
Δ3-carene	oil of turpentine	contact allergy	(240)
carvone	toothpaste	allergic contact cheilitis stomatitis	(224)
cassia oil	toothpaste	contact urticaria	(241)
chamomile oil German	topical medicament	allergic contact dermatitis	(228)
cinnamic alcohol	topical medicament	allergic contact dermatitis	(28)
	moist toilet paper	allergic contact dermatitis	(25)
	sanitary napkin	allergic contact dermatitis	(26)
cinnamic aldehyde	toothpaste	allergic contact cheilitis stomatitis	(242)
		cheilitis, burning mouth syndrome, buccal ulcers, perioral dermatitis, angular cheilitis	(220)
	food	contact urticaria	(243)
	mouthwash	depigmentation	(244)
		contact urticaria	(245)
	eyedrops	conjunctival cicatrisation	(246)
	chewing gum	stomatitis	(247)
	sanitary napkin	allergic contact dermatitis	(26)
dipentene	oil of turpentine	contact allergy	(240)
	honing oil	allergic contact dermatitis	(248)
ethyl vanillin	toffee	contact urticaria	(249)
eugenol	toothpaste	allergic contact cheilitis	(224)
	mouthwash	stomatitis	(250)
geraniol	topical medicament	allergic contact dermatitis	(251, 252)
hydroxycitronellal	topical medicament	allergic contact dermatitis	(28)
lavender fragrance	topical medicament	allergic contact dermatitis	(164)
d-limonene	oil of turpentine	contact allergy	(240)
d-limonene in peppermint oil	mouthwash	stomatitis	(145)
l-limonene	oil of turpentine	contact allergy	(240)
l-limonene in peppermint oil	mouthwash	stomatitis	(145)
maltol in strawberry flavor	lip salve	allergic contact cheilitis	(253)
menthol	various	recurrent mouth ulceration	(234, 254)
	toothpaste	allergic contact cheilitis	(224)
	various	orofacial granulomatosis of the lower lip	(254)
	various	burning mouth syndrome	(234)
	various	oral lichenoid lesions	(234)
musk ambrette	incense	airborne (de) pigmented allergic contact dermatitis	(172, 202)
oak moss	topical medicament	allergic contact dermatitis	(28)
oak moss (?)	topical medicament	allergic contact dermatitis	(29)
peppermint oil	various	orofacial granulomatosis of the lower lip	(254)
	various	burning mouth syndrome	(234)
	various	recurrent oral ulcerations	(234)
	various	oral lichenoid reactions	(234)
	toothpaste	stomatitis, allergic contact cheilitis	(255)
phellandrene in peppermint oil	mouthwash	stomatitis	(145)
phenyl salicylate	toothpaste	allergic contact dermatitis	(224)
α-pinene	oil of turpentine	contact allergy	(240)
α-pinene in peppermint oil	mouthwash	stomatitis	(145)
β-pinene	oil of turpentine	contact allergy	(240)
sandalwood oil	incense	allergic airborne depigmented contact dermatitis	(202)
santalol	incense	allergic airborne depigmented contact dermatitis	(202)
spearmint oil	toothpaste	allergic contact stomatitis and cheilitis	(255)
α-terpineol	oil of turpentine	contact allergy	(240)
vanilla	lip salve	allergic contact dermatitis	(256)
not specified	toilet paper	allergic contact dermatitis	(231)

Table 11. Reported cutaneous adverse reactions to (ingredients of) balsam of Peru

Name of ingredient	Test conc/vehicle (209)	Adverse reaction	Refs.
balsam of Peru	25% pet.	contact urticaria	(243)
		ACD	(257)
		photosensitivity	(8)
		systemic contact dermatitis from flavoured foods	(221)
		purpuric vasculitis-like ACD	(258, 259)
		photocontact urticaria	(260)
benzaldehyde	5% pet.	contact urticaria, ACD	(243, 261, 262)
benzoic acid	<5%	contact urticaria, ACD	(261)
benzyl alcohol	5% pet.	ACD	(8)
benzyl benzoate	5% pet.	CA in routine testing	(263)
benzyl cinnamate	5% pet.	CA in routine testing	(263)
benzyl ferulate		weak experimental sensitizer	(257)
benzyl isoferulate	1% pet.	moderate to strong experimental sensitizer	(257)
cinnamic acid	5% pet.	CA in routine testing	(257, 263, 264)
		contact urticaria	(261)
cinnamic alcohol	3%–5% pet.	ACD	
cinnamyl cinnamate	5% pet.	weak experimental sensitizer	(257)
coniferyl alcohol	2% pet.	moderate experimental sensitizer	(257)
		ACD	(262)
coniferyl benzoate	2% pet. (prepare fresh)	moderate to strong experimental sensitizer	(257)
eugenol	3%–5% pet.	ACD	
cis-/trans-farnesol	5% pet.	weak experimental sensitizer	(257)
isoeugenol	3%–5% pet.	ACD	
methyl benzoate	3% pet.	not sensitizing	(257)
methyl cinnamate	5% pet.	CA in routine testing	(264)
cis-/trans-nerolidol	1% pet.	weak experimental sensitizer	(257)
vanillin	10% pet.	CA in routine testing	(263)

ACD: allergic contact dermatitis.
CA: contact allergy.
Other constituents identified in balsam of peru are (257):
amyrin, benzyl ferulate, benzyl *trans*-4-hydroxy cinnamate, benzyl 4-hydroxy-3-methoxybenzoate, coniferyl cinnamate, docosanoic acid, dodecanoic acid, eicosanoic acid, ethylhexanoic acid (?), *trans*-ferulic acid, heptadecanoic acid, hexacosanoic acid, 1-hexacosanol, hexadecanoic acid, hydroconiferyl cinnamate, 4-hydroxy-3-methoxy acetophenone, 4-hydroxy-3-methoxy benzoic acid, 2-hydroxypropanoic acid, methoxyeugenol, 1-octacosanol, octadecanoic acid, 1-phenylethanol, 3-phenyl-1-propanol, terpenoid alcohol, 1-tetracosanol, tetradecanoic acid, 1-undecanol.

projects among dermatologists, toxicologists, cosmetic scientists and the perfumer will ascertain maximum (cutaneous) safety of fragranced products to consumers. There is no doubt that fragrances enrich our lives, which makes these efforts even more worthwhile.

References

1. Fisher A A. Perfume dermatitis in children sensitized to balsam of Peru in topical agents. *Cutis* 1990: *45:* 21–23.
2. Larsen W G. Perfumes. In: Baran R, Maibach H I (eds): *Cosmetic dermatology.* London: Martin Dunitz, 1994: 21–26.
3. Schaller M, Korting H C. Allergic airborne contact dermatitis from essential oils used in aromatherapy. *Clin Exp Dermatol* 1995: *20:* 143–145.
4. Rudzki E, Grzywa Z. Allergy to perfume mixture. *Contact Dermatitis* 1986: *15:* 115–116.
5. Fischer T. Perfumed products. In: Guin J D (ed): *Practical contact dermatitis.* New York: McGraw-Hill, 1995: 355–371.
6. Guin J D. History, manufacture, and cutaneous reactions to perfumes. In: Frost P, Horwitz S W (eds): *Principles of cosmetics for the dermatologist.* St Louis: The CV Mosby Company,1982: 111–129.
7. Scheinman P L. Allergic contact dermatitis to fragrance: A review. *Am J Contact Dermatitis* 1996: *7:* 65–76.
8. De Groot A C, Weyland J W, Nater J P. *Unwanted effects of cosmetics and drugs used in dermatology,* 3rd edition. Amsterdam: Elsevier, 1994: 65, 97, 142–147, 446–451, 475, 502–504, 509, 579–627.
9. Bauer K, Garbe D, Surburg H. *Common fragrance and flavor materials. Preparation, properties and uses.* Weinheim: VCH Verlagsgesellschaft, 1990.
10. Larsen W G. Perfume dermatitis. *J Am Acad Dermàtol* 1985: *12:* 1–9.
11. Muller P M, Lamparsky D. *Perfumes: art, science, and technology.* New York: Elsevier, 1991.
12. Fenn R S. Aroma chemical usage trends in modern perfumery. *Perfumer & Flavorist* 1989: *14:* 3–10.
13. Cooke M A, Cadby P A, Harrison R G. Data generation from perfume ingredient safety evaluation. In: Frosch P J et al. (eds): *Current topics in contact dermatitis. Heidelberg: Springer-Verlag, 1989: 122–126.*
14. Cooke M A. IFRA and the dermatologist. *Contact Dermatitis* 1991: *25:* 209–210.
15. Cooke M A, Cadby P A, Ford R A. Databases in the perfumery industry. *Semin Dermatol* 1989: *8:* 85–87.
16. Eiermann H J. Comments on cosmetic safety and product labeling issues. *Cosm Toiletries* 1988: *103:* 53–56.
17. Opdyke D L J. Inhibition of sensitization reactions induced by certain aldehydes. *Fd Cosmet Toxicol* 1976: *14:* 197–198.

18. Ford R A. Studies on the quenching phenomenon. *Contact Dermatitis* 1992: *27:* 60.
19. Basketter D A, Allenby C F. Studies of the quenching phenomenon in delayed contact hypersensitivity reactions. *Contact Dermatitis* 1991: *25:* 160–171.
20. Basketter D, Allenby F. Studies on the quenching phenomenon. Reply. *Contact Dermatitis* 1992: *27:* 61.
21. Safford R J, Basketter D A, Allenby C F, Goodwin B F J. Immediate contact reactions to chemicals in the fragrance mix and a study of the quenching action of eugenol. *Br J Dermatol* 1990: *123:* 595–606.
22. Rothenborg H W, Hjorth N. Allergy to perfumes from toilet soaps and detergents in patients with dermatitis. *Arch Dermatol* 1968: *97:* 417–421.
23. Panconesi E, Sertoli A, Spallanzani P, Giorgini S. Balsam of Peru sensitivity from a perfumed cutting fluid in a laser factory. *Contact Dermatitis* 1980: *6:* 297–298.
24. Guin J D. Contact dermatitis to perfume in paper products. *J Am Acad Dermatol* 1981: *4:* 733–734.
25. De Groot A C, Baar A J M, Terpstra H, Weyland J W. Contact allergy to moist toilet paper. *Contact Dermatitis* 1991: *24:* 135–136.
26. Larsen W G. Sanitary napkin dermatitis due to perfume. *Arch Dermatol* 1979: *115:* 363.
27. Keith L, Erich W, Bush I M. Toilet paper dermatitis. *JAMA* 1969: *209:* 269.
28. Larsen W G. Allergic contact dermatitis to the perfume in Mycolog cream. *J Am Acad Dermatol* 1979: *1:* 131–133.
29. Garioch J J, Forsyth A, Chapman R S. Allergic contact dermatitis from the perfume in Locan® cream. *Contact Dermatitis* 1989: *20:* 61–62.
30. Larsen W G. How to instruct patients sensitive to fragrances. *J Am Acad Dermatol 1989: 4* (part II): 880–884.
31. Dooms-Goossens A, Dubelloy R, Degreef H. Contact and systemic contact-type dermatitis to spices. In: Adams R M, Nethercott J R (eds): *Dermatologic Clinics. Contact Dermatitis.* Philadelphia: WB Saunders Company, 1990: 89–93.
32. Veien N K, Hattel T, Justesen O, et al. Dietary restrictions in the treatment of adult patients with eczema. *Contact Dermatitis* 1987: *17:* 223–227.
33. Guin J D. Balsam of Peru. In: Guin J D (ed): *Practical contact dermatitis.* New York: McGraw-Hill, 1995: 265–270.
34. Fisher A A. Allergic reactions to feminine hygiene sprays. *Arch Dermatol* 1973: *108:* 801–803.
35. Meynadier J-M, Meynadier J, Peyron J-L, Peyron L. Formes cliniques des manifestations cutanées d'allergie aux parfums. *Ann Dermatol Venereol* 1986: *113:* 31–39.
36. Fisher A A. Consort contact dermatitis due to musk ambrette. *Cutis* 1995: *55:* 199–200.
37. Morren M-A, Rodrigues R, Dooms-Goossens A et al. Connubial contact dermatitis: a review. *Eur J Dermatol* 1992: *2:* 219–223.
38. Leroy D, Dompmartin A. Connubial photosensitivity to musk ambrette. *Photodermatology* 1989: *6:* 137–139.
39. Lorenzi S, Guerra L, Vezzani C, Vinzenzi C. Airborne contact dermatitis from atranorin. *Contact Dermatitis* 1995: *32:* 315–316.
40. Dooms-Goossens A. Cosmetics as causes of allergic contact dermatitis. *Cutis* 1993: *52:* 316–320.
41. Dooms-Goossens A, Deleu H. Airborne contact dermatitis: an update. *Contact Dermatitis* 1991: *25:* 211–217.
42. Angelini G, Vena G A. Airborne contact dermatitis. *Clin Dermatol* 1992: *10:* 123–131.
43. Shall L, Reynolds A J, Holt P J A. Photosensitivity to musk ambrette in a toilet soap and hair gel. *Contact Dermatitis* 1986: *14:* 324.
44. De Groot A C. *Adverse reactions to cosmetics.* Thesis, State University of Groningen, 1988.
45. Dahlquist I, Fregert S. Atranorin and oak moss contact allergy. *Contact Dermatitis* 1981: *7:* 168–169.
46. Burry J N. Colophony, perfumes and paper handkerchiefs. *Contact Dermatitis* 1986: *15:* 304–305.
47. 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.
48. Schorr W F. Lip gloss and gloss type cosmetics. *Contact Dermatitis Newsletter* 1973: *14:* 408.
49. Maibach H I. Cheilitis: occult allergy to cinnamic aldehyde. *Contact Dermatitis* 1986: *15:* 106–107.
50. Calnan C D, Cronin E, Rycroft R J G. Allergy to phenyl salicylate. *Contact Dermatitis* 1981: *7:* 208–210.
51. Van Ketel W G. Sensitization to cis-3-hexenyl salicylate. *Contact Dermatitis* 1983: *9:* 154–155.
52. Larsen W G. Allergic contact dermatitis to the fragrance material lilial. *Contact Dermatitis* 1983: *9:* 158–159.
53. Dahlquist I, Fregert S. Contact allergy to atranorin in lichens and perfumes. *Contact Dermatitis* 1980: *6:* 111–119.
54. Heine A. Allergisches Kontaktekzem durch Usninsäure in Deodorant Sprays. *Derm Monatsschr* 1987: *173:* 221–225.
55. Thune P, Salberg Y, McFadden N, Staerfelt F, Sandberg M. Perfume allergy due to oak moss and other lichens. *Contact Dermatitis* 1982: *8:* 396–400.
56. Lewis F M, Harrington C I, Gawkrodger D J. Contact sensitivity in pruritus vulvae: a common and manageable problem. *Contact Dermatitis* 1994: *31:* 264–265.
57. Burry J N. Environmental dermatitis. Contact dermatitis from perfumes in soap. *Med J Austral* 1986: *145:* 160–161.
58. De Groot A C, Beverdam E, Tjong Ayong C, Coenraads P J, Nater J P. The role of contact allergy in the spectrum of adverse effects caused by cosmetics and toiletries. *Contact Dermatitis 1988: 19:* 195–201.
59. Westat Inc. *An investigation of consumers' perceptions of adverse reactions to cosmetic products.* Washington: National Technical Information Service, US Department of Commerce, 1975.
60. Berne B, Lundin Å, Malmros P E. Side effects of cosmetics and toiletries in relation to use. A retrospective study in a Swedish population. *Eur J Dermatol* 1994: *4:* 189–193.
61. Adams R M, Maibach H I. A five-year study of cosmetic reactions. *J Am Acad Dermatol* 1985: *13:* 1062–1069.
62. De Groot A C. Contact allergy to cosmetics: causative ingredients. *Contact Dermatitis* 1987: *17:* 26–34.
63. De Groot A C, Bruynzeel D P, Bos J D et al. The allergens in cosmetics. *Arch Dermatol* 1988: *124:* 1525–1529.
64. Broeckx W, Blondeel A, Dooms-Goossens A, Achten G. Cosmetic intolerance. *Contact Dermatitis* 1987: *16:* 189–194.
65. Dooms-Goossens A, Kerre S, Drieghe J, Bossuyt L, Degreef H. Cosmetic products and their allergens. *Eur J Dermatol* 1992: *2:* 465–468.
66. Nielsen N H, Menné T. Allergic contact sensitization in an unselected Danish population. Acta Dermato-venereologica 1992: *72:* 456–460.
67. Nielsen B H, Menné T. Sensibilisation de contact aux constituants des cosmetiques dans une population Danoise non sélectionnée. La Glostrup allergy study, Danemark. *Ann Dermatol Venereol 1993: 120:* 33–36.
68. Guin J D, Berry V K. Perfume sensitivity in adults females. A study of contact sensitivity to a perfume mix in two groups of student nurses. *J Am Acad Dermatol* 1980: *3:* 299–302.
69. De Groot A C, Nater J P, Van der Lende R, Rijcken B. Adverse effects of cosmetics: A retrospective study in the

general population. *Int J Cosmetic Science* 1987: *9:* 255–259.
70. Edman B. The influence of shaving method on perfume allergy. *Contact Dermatitis* 1994: *31:* 291–292.
71. De Groot A C, Bruynzeel D P, Bos J D et al. The allergens in cosmetics. *Arch Dermatol* 1988: *124:* 1525–1529.
72. Schorr W F. Cosmetic allergy. Diagnosis, incidence, and management. *Cutis* 1974: *14:* 844–850.
73. Skog E. Incidence of cosmetic dermatitis. *Contact Dermatitis* 1980: *6:* 449–451.
74. Romaguera C, Camarasa J M G, Alomar A, Grimalt F. Patch tests with allergens related to cosmetics. *Contact Dermatitis* 1983: *9:* 167–168.
75. Ngangu Z, Samsoen M, Foussereau J. Einige Aspekte zur Kosmetika-Allergie in Strassburg. *Dermatosen* 1983: *31:* 126–129.
76. Christophersen J, Menné T, Tanghøj P et al. Clinical patch test data evaluated by multivariate analysis. *Contact Dermatitis* 1989: *21:* 291–299.
77. Edman B. Sites of contact dermatitis in relationship to particular allergens. *Contact Dermatitis* 1985: *13:* 129–135.
78. Larsen W, Nakayama H, Lindberg M et al. Fragrance contact dermatitis. A worldwide multicenter investigation (Part I). *Am J Contact Dermatitis* 1996: *7:* 77–83.
79. Fisher A A. Perfume dermatitis. Part 1. General considerations and testing procedures. *Cutis* 1980: *26:* 458–463,477.
80. De Groot A C, Liem D H. Facial psoriasis caused by contact allergy to linalool and hydroxy-citronellal in an aftershave. *Contact Dermatitis* 1983: *9:* 230–232.
81. Santucci B, Cristaudo A, Cannistraci C, Picardo M. Contact dermatitis to fragrances. *Contact Dermatitis* 1987: *16:* 93–95.
82. Malten K E, van Ketel W G, Nater J P, Liem D H. Reactions in selected patients to 22 fragrance materials. *Contact Dermatitis* 1984: *11:* 1–10.
83. Audicana M, Bernaola G. Occupational contact dermatitis from citrus fruits: lemon essential oils. *Contact Dermatitis* 1994: *31:* 181–183.
84. Marren P, Wojnarowska F, Powell S. Allergic contact dermatitis and vulvar dermatoses. *Br J Dermatol* 1992: *126:* 52–56.
85. Fisher A A. Perfume dermatitis. Part 1. General considerations and testing procedures. *Cutis* 1980: *26:* 458–478.
86. Larsen W G. Perfume dermatitis. A study of 20 patients. *Arch Dermatol* 1977: *113:* 623–626.
87. Frosch P J, Pilz B, Andersen K E 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.
88. Frosch P J, Pilz B, Burrows D et al. Testing with the fragrance mix – is the addition of sorbitan sesquioleate to the constituents useful? *Contact Dermatitis* 1995: *32:* 266–272.
89. De Groot A C, Van der Kley A M J, Bruynzeel D P et al. Frequency of false-negative reactions to the fragrance mix. *Contact Dermatitis* 1993: *28:* 139–140.
90. De Groot A C, Liem D H, Nater J P, van Ketel W G. Patch tests with fragrance materials and preservatives. *Contact Dermatitis* 1985: *12:* 87–92.
91. Schnuch A, Uter W, Lehmacher W et al. Epikutantestung mit der Standardserie. Erste Ergebnisse des Projektes "Informationsverbund Dermatologischer Kliniken" (IVDK). *Dermatosen* 1993: *41:* 60–70.
92. Pilz B, Frosch P J. Kontaktallergene 1994. In: Plewig G, Korting H C (eds): *Fortschritte der praktischen Dermatologie und Venereologie.* Heidelberg: Springer-Verlag, 1995: 7–14.
93. Johansen J D, Menné T. The fragrance mix and its constituents: a 14-year material. *Contact Dermatitis* 1995: *32:* 18–23.
94. Edman B, Möller H. Contact allergy and contact allergens in atopic skin disease. *Am J Contact Dermatitis* 1992: *3:* 27–29,90.
95. Becker K, Temesvari E, Nemeth I. Patch testing with fragrance mix and its constituents in a Hungarian population. *Contact Dermatitis* 1994: *30:* 185–186.
96. Wilkinson J D, Andersen K E, Camarasa J G et al. Preliminary results of effectiveness of two forms of fragrance mix as screening agents for fragrance sensitivity. In: Frosch PJ et al. (eds): *Current topics in contact dermatitis.* Heidelberg: Springer-Verlag, 1989: 127–131.
97. Marks J G, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group standard tray patch test results (1992 to 1994). *Am J Contact Dermatitis* 1995: *6:* 160–165.
98. Freeman S. Fragrance and nickel: old allergens in new guises. *Am J Contact Dermatitis* 1990: *1:* 47–52.
99. Shehade S A, Beck M H, Hillier V F. Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings. *Contact Dermatitis* 1991: *24:* 119–122.
100. Kintziou H, Papaioannou G, Rallis M. Sensitivity to perfumes and preservatives in patients with contact dermatitis. *Int J Cosm Science* 1990: *12:* 115–120.
101. Lim J T E, Goh C L, Ng S K, Wong W K. Changing trends in the epidemiology of contact dermatitis in Singapore. *Contact Dermatitis* 1992: *26:* 321–326.
102. Gonçalo S, Cabral F, Gonçalo M. Contact sensitivity to oak moss. *Contact Dermatitis* 1988: *19:* 355–357.
103. Enders F, Przybilla B, Ring J. Patch testing with fragrance mix at 16% and 8%, and its individual constituents. *Contact Dermatitis* 1989: *20:* 237–238.
104. Johansen J D, Andersen K E, Rastogi S C, Menné T. Threshold responses in cinnamic aldehyde-sensitive subjects. Results and methodological aspects. *Contact Dermatitis* 1996: *34:* 165–171.
105. Nethercott J R, Holness D L, Adams R M et al. Patch testing with a routine screening tray in North America, 1985 through 1989 (I). Frequency of response. *Am J Contact Dermatitis* 1991: *2:* 122–129.
106. Swinyer L J. Connubial contact dermatitis to atranorin in lichens. *Contact Dermatitis* 1980: *6:* 226.
107. Fregert S, Dahlquist I. Patch testing with oak moss extract. *Contact Dermatitis* 1983: *9:* 227.
108. Fisher A A, Dooms-Goossens A. The effect of perfume "ageing" on the allergenicity of individual perfume ingredients. *Contact Dermatitis* 1976: *2:* 155–159.
109. Hannuksela M. The repeated open application test (ROAT). *Contact Dermatitis* 1986: *14:* 221–227.
110. Hannuksela M. Sensitivity of various skin sites in the repeated open application test. *Amer J Contact Dermatitis* 1991: *2:* 102–104.
111. Peter C, Hoting E. Anwendungstest mit parfümierten Kosmetika bei Patienten mit positivem Epikutantest auf Duftstoff-Mischung. *Dermatosen* 1993: *41:* 237–241.
112. Malanin G, Ohela K. Allergic reactions to fragrance mix and its components. *Contact Dermatitis* 1989: *21:* 62–63.
113. McLelland J, Shuster S. Contact dermatitis with negative patch tests: the additive effect of allergens in combination. *Br J Dermatol* 1990: *122:* 623–630.
114. Enders F, Przybilla B, Ring J. Patch testing with fragrance-mix and its constituents: discrepancies are largely due to the presence or absence of sorbitan sesquioleate. *Contact Dermatitis* 1991: *24:* 238–239.
115. Announcements. *Contact Dermatitis* 1991: *24:* 240.
116. Sugawara M, Nakayama H, Watanabe S. Contact hyper-

sensitivity to ylang-ylang oil. *Contact Dermatitis* 1990: *23:* 248–249.
117. Sugai T. Group Study IV – farnesol and lily aldehyde. *Environ Dermatol* 1994: *1:* 213–214.
118. Utsumi M, Sugai T, Shoji A, Watanabe K, Asoh S, Hashimoto Y. Incidence of positive reactions to sandalwood oil and its related fragrance materials in patch tests and a case of contact allergy to natural and synthetic sandalwood oil in a museum worker. *Skin Res* 1992: *34* (suppl 14): 209–213.
119. Paulsen E, Andersen K E, Carlsen L, Egsgaard H. Carvone: an overlooked contact allergen cross-reacting with sesquiterpene lactones? *Contact Dermatitis* 1993: *29:* 138–143.
120. Rudner E A. North American Group results. *Contact Dermatitis* 1977: *3:* 208–209.
121. Mitchell J C, Adams R M, Glendenning W E et al. Results of standard patch tests with substances abandoned. *Contact Dermatitis* 1982: *8:* 336–337.
122. Handley J, Burrows D. Allergic contact dermatitis from the synthetic fragrances Lyral and acetyl cedrene in separate underarm deodorant preparations. *Contact Dermatitis* 1994: *31:* 288–290.
123. Malten K E. Four bakers showing positive patch-tests to a number of fragrance materials, which can also be used as flavors. *Acta Dermato-venereologica* 1979: suppl *85:* 117–121.
124. Guin J D, Haffley P. Sensitization to alpha amyl cinnamic aldehyde and alpha amyl cinnamic alcohol. *J Am Acad Dermatol* 1983: *8:* 76–80.
125. Lorenzi S, Guerra L, Vezzani C, Vincenzi C. Airborne contact dermatitis from atranorin. *Contact Dermatitis* 1995: *32:* 315–316.
126. Meneghini C L. Cosmetic constituents. *Contact Dermatitis Newsletter* 1970: *8:* 182.
127. Sousa Basto A, Azenha A. Contact dermatitis due to incense. *Contact Dermatitis* 1991: *24:* 312–313.
128. Nakayama H. Pigmented contact dermatitis and chemical depigmentation. In: Rycroft R J G, Menné T, Frosch P J (eds): *Textbook of contact dermatitis,* 2nd edition. Berlin: Springer-Verlag, 1995: 637–659.
129. Keil H. Contact dermatitis due to oil of citronellal. *J Invest Dermatol* 1947: *8:* 327.
130. Johansen J D, Rastogi S C, Jemec G B E. Dipropylene glycol allergy: a hidden cause of perfume contact dermatitis. *Am J Contact Dermatitis* 1994: *5:* 98–101.
131. Toyoda T, Watanabe S, Kawasaki M, Nakayama H, Sugawara M. Dehydro-eugenol found in ylang-ylang oil. *Skin Res* 1989: *31* (suppl 7): 35–43.
132. Malten K E. Sensitization to solcoseryl and methylanisate (fragrance ingredient). *Contact Dermatitis* 1977: *3:* 219.
133. De Groot A C, Weyland J W. Systemic contact dermatitis from tea tree oil. *Contact Dermatitis* 1992: *27:* 279–280.
134. Nakayama H, Hanaoka H, Oshiro A. *Allergen controlled system* (ACS). Tokyo: Kanehara Shuppan Co, 1974.
135. Benke G M, Larsen W G. Safety evaluation of perfumed shampoos: dose/response relationships for product use testing by presensitized subjects. *J Toxicol Cut Ocular Toxicol* 1984: *3:* 65–67.
136. Bernaola G, Escayol P, Fernández E, Fernández de Corrés L. Contact dermatitis from methylionone fragrance. *Contact Dermatitis* 1989: *20:* 71–72.
137. Sugai T. Historical data of the JSCD. Group study III – Fragrance materials. *Environ Dermatol* 1994: *1:* 209–212.
138. Karlberg A-T, Magnusson K, Nilsson U. Air oxidation of d-limonene (the citrus solvent) creates potent allergens. *Contact Dermatitis* 1992: *26:* 332–340.
139. Nakayama H, Matsuo S, Hayakawa K et al. Pigmented cosmetic dermatitis. *Int J Dermatol* 1984: *23:* 299–305.
140. English J S C, Rycroft R J G. Allergic contact dermatitis from methyl heptine and methyl octine carbonate. *Contact Dermatitis* 1988: *18:* 174–175.
141. Van Ketel W G. Dermatitis from an aftershave. *Contact Dermatitis* 1978: *4:* 117.
142. Romaguera C, Camarasa J M G, Alomar A, Grimalt F. Patch tests with allergens related to cosmetics. *Contact Dermatitis* 1983: *9:* 167–168.
143. Cronin E. Photosensitivity to musk ambrette. *Contact Dermatitis* 1984: *11:* 88–92.
144. Hausen B M, Kunze B. Kontaktallergie auf Patchouli-Öl. *Akt Dermatol* 1991: *17:* 199–202.
145. Dooms-Goossens A, Degreef H, Holvoet C, Maertens M. Turpentine-induced hyper-sensitivity to peppermint oil. *Contact Dermatitis* 1977: *3:* 304–308.
146. Vilaplana J, Romaguera C, Grimalt F. Contact dermatitis from geraniol in Bulgarian rose oil. *Contact Dermatitis* 1991: *24:* 301.
147. Kanerva L, Estlander T, Jolanki R. Occupational allergic contact dermatitis caused by ylang-ylang oil. *Contact Dermatitis* 1995: *33:* 198–199.
148. Bonnevie P. Some experiences of war-time industrial dermatoses. *Acta Dermato-venereologica* 1948: *28:* 231–237.
149. Holness D L, Nethercott J R. Epicutaneous testing results in hairdressers. *Am J Contact Dermatitis* 1990: *2:* 224–234.
150. Guerra L, Tosti A, Bardazzi F et al. Contact dermatitis in hairdressers: the Italian experience. *Contact Dermatitis* 1992: *26:* 101–107.
151. Van der Walle H B, Brunsveld V M. Dermatitis in hairdressers (I). The experience of the past 4 years. *Contact Dermatitis* 1994: *30:* 217–221.
152. Gola M, Sertoli A, Angelini G et al. GIRDCA data bank for occupational and environmental contact dermatitis. *Am J Contact Dermatitis* 1992: *3:* 179–188.
153. Holness D L, Nethercott J R. Patch testing in an occupational health clinic. *Am J Contact Dermatitis* 1994: *5:* 150–155.
154. Wall L M, Gebauer K A. Occupational skin disease in Western Australia. *Contact Dermatitis* 1991: *24:* 101–109.
155. Sun C-C, Guo Y-L, Lin R-S. Occupational hand dermatitis in a tertiary referral dermatology clinic in Taipei. *Contact Dermatitis* 1995: *33:* 414–418.
156. Goodfield M J D, Saihan E M. Fragrance sensitivity in coal miners. *Contact Dermatitis* 1988: *18:* 81–83.
157. Dugué P, Bel J, Gomez-Figueredo M. Allergie professionnelle à l'ambrette. Cinq observations dans l'industrie de la parfumerie. *Rev fr Allergol* 1990: *30:* 29–31.
158. Zacher K D, Ippen H. Kontaktekzem durch Bergamottöl. *Derm Beruf Umwelt* 1984: *32:* 95–97.
159. Calnan C D. Lovage sensitivity. *Contact Dermatitis Newsletter* 1969: *5:* 99.
160. Gutman S G, Somov B A. Allergic reactions caused by components of perfumery prepa-rations. *Vestn Dermatol Venereol* 1968: *12:* 62–66.
161. Rudzki E, Rebandel P, Grzywa Z. Occupational dermatitis from cosmetic creams. *Contact Dermatitis* 1993: *29:* 210.
162. Brandão F M. Occupational allergy to lavender oil. *Contact Dermatitis* 1986: *15:* 249–250.
163. Nethercott J R, Pilger C, O'Blenis L, Roy A-M. Contact dermatitis due to cinnamic aldehyde induced in a deodorant manufacturing process. *Contact Dermatitis* 1983: *9:* 241–242.
164. Rademaker M. Allergic contact dermatitis from lavender fragrance in Difflam® gel. *Contact Dermatitis* 1994: *31:* 58–59.
165. Rothenborg H W, Menné T, Sjølin K-E. Temperature dependent primary irritant dermatitis from lemon perfume. *Contact Dermatitis* 1977: *3:* 37–48.

166. Raugi G J, Storrs F J, Larsen W G. Photoallergic contact dermatitis to men's perfumes. *Contact Dermatitis* 1979: *5:* 251–260.
167. Wennersten G, Thune P, Brodthagen H, Jansen C, Rystedt I. The Scandinavian multicenter photopatch study. Preliminary results. *Contact Dermatitis* 1984: *10:* 305–309.
168. Leow Y H, Wong W K, Ng S K, Goh C L. 2 Years experience of photopatch testing in Singapore. *Contact Dermatitis* 1994: *31:* 181–182.
169. Gonçalo S, Gil J, Gonçalo M, Baptista A P. Pigmented photoallergic contact dermatitis from musk ambrette. *Contact Dermatitis* 1991: *24:* 229–230.
170. Hayakawa R, Matsunaga K, Arima Y. Airborne pigmented contact dermatitis due to musk ambrette in incense. *Contact Dermatitis* 1987: *16:* 96–98.
171. Parodi G, Guerrera M, Rebora A. Lichenoid photocontact dermatitis to musk ambrette. *Contact Dermatitis* 1987: *16:* 136–138.
172. Giovinazzo V J, Harber L C, Bickers D R, Armstrong R B, Silvers D. Photoallergic contact dermatitis to musk ambrette. Histopathological features of photobiologic reactions observed in a persistent light reactor. *Arch Dermatol* 1981: *117:* 344–348.
173. Ducombs G, Abbadie D, Maleville J. Persistent light reaction from musk ambrette. *Contact Dermatitis* 1986: *14:* 129–130.
174. Cirne de Castro J L, Pereira M A, Nunes F P, Pereira dos Santos A. Musk ambrette and chronic actinic dermatitis. *Contact Dermatitis* 1985: *13:* 302–306.
175. Lan L R, Lee J Y Y, Kao H F, Wang B J, Chen H C. Persistent light reaction with erythroderma caused by musk ambrette. A case report. *Cutis* 1994: *54:* 167–170.
176. Megahed M, Holzle E, Plewig G. Persistent light reaction associated with photoallergic contact dermatitis to musk ambrette and allergic contact dermatitis to fragrance mix. *Dermatologica* 1991: *182:* 199–202.
177. Addo H A, Ferguson J, Johnson B E, Frain-Bell W. The relationship between exposure to fragrance materials and persistent light reactions in the photosensitivity dermatitis. *Brit J Dermatol* 1982: *107:* 261–274.
178. Kaidbey K H, Kligman A M. Photocontact allergy to 6–methylcoumarin. *Contact Dermatitis* 1978: *4:* 277–282.
179. Kaidbey K H, Kligman A M. Photomaximization test for identifying photoallergic contact sensitizers. *Contact Dermatitis* 1980: *6:* 161–169.
180. Kaidbey K H, Kligman A M. Photosensitization to coumarin derivatives. *Arch Dermatol* 1981: *117:* 258–265.
181. Jackson R T, Nesbitt L T, DeLeo V A. 6-Methylcoumarin photocontact dermatitis. *J Am Acad Dermatol* 1980: *2:* 124–127.
182. Kaidbey K H, Kligman A M. Contact photoallergy to 6–methylcoumarin in proprietary sunscreens. *Arch Dermatol* 1978: *114:* 1709–1710.
183. Eiermann H J. Regulatory issues concerning AETT and 6-MC. *Contact Dermatitis* 1980: *6:* 120–122.
184. Szczurko C, Dompmartin A, Michel M, Moreau A, Leroy D. Photocontact allergy to oxybenzone: ten years of experience. *Photodermatol Photoimmunol Photomed* 1994: *10:* 144– 147.
185. Leonard F, Kalis B, Journe F. The standard battery for photopatch tests in France. Prospective study by the French Society for Photodermatology. *Nouv Dermatol* 1994: *13:* 305–314.
186. Fernández de Corres L, Muñoz D, Leaniz-Barrutia I, Corrales JL. Photocontact dermatitis from oak moss. *Contact Dermatitis* 1983: *9:* 528–529.
187. Menagé H du P, Ross J S, Norris P G, Hawk J L M, White I R. Contact and photocontact sensitization in chronic actinic dermatitis; sesquiterpene lactone mix is an important allergen. *Brit J Dermatol* 1995: *132:* 543–547.
188. Abifadel R, Mortureux P, Perromat M, Ducombs G, Taieb A. Contact sensitivity to flavourings and perfumes in atopic dermatitis. *Contact Dermatitis* 1992: *27:* 43–46.
189. Emmons W W, Marks J G Jr. Immediate and delayed reactions to cosmetic ingredients. *Contact Dermatitis* 1985: *13:* 258–265.
190. De Groot A C, Liem D H. Contact urticaria to rouge. *Contact Dermatitis* 1983: *9:* 322.
191. McDaniel W R, Marks J G. Contact urticaria due to sensitivity to spray starch. *Arch Dermatol* 1979: *115:* 628.
192. Temesvári E, Soos G, Podányi, Kovács I, Nemeth I. Contact urticaria provoked by balsam of Peru. *Contact Dermatitis* 1978: *4:* 65–68.
193. Rudzki E, Grzywa Z. Immediate reactions to balsam of Peru, cassia oil and ethyl vanillin. *Contact Dermatitis* 1976: *2:* 360.
194. Nakayama H, Harada R, Toda M. Pigmented cosmetic dermatitis. *Int J Dermatol* 1976: *15:* 673–675.
195. Saito F. Relationship between cosmetics and Riehl's melanosis. *Hifuka Rinsho* 1964: *6:* 333.
196. Nagareda T, Sugai T, Shouji A et al. Incidence of positive reactions to cosmetic products and their ingredients in patch tests and representative cases with cosmetic dermatitis in 1991. *Skin Res* 1992: *34* (suppl 14): 176–182.
197. Romaguera C, Vilaplana J. Grimalt F. Contact dermatitis from oak moss. *Contact Dermatitis* 1991: *24:* 224–225.
198. Hayakawa R, Hirose O, Arima Y. Pigmented contact dermatitis due to musk moskene. *J Dermatol* 1991: *18:* 420–421.
199. Serrano G, Pujol C, Cuadra J, Gallo S, Aliaga A. Riehl's melanosis. Pigmented contact dermatitis caused by fragrances. *J Am Acad Dermatol* 1989: *21:* 1057–1060.
200. Zaynoun S T, Aftimas B A, Tenekjian K K, Kurban A K. Berloque dermatitis. A continuing cosmetic problem. *Contact Dermatitis* 1981: *7:* 111–116.
201. Katsambas A, Antoniou Ch. Melasma. Classification and treatment. *J Eur Acad Derm Venereol* 1995: *4:* 217–223.
202. Hayakawa R, Matsunaga K, Arima Y. Depigmented contact dermatitis due to incense. *Contact Dermatitis* 1987: *16:* 272–274.
203. Goh C L, Ng S K. Bullous contact allergy from cinnamon. *Dermatosen* 1988: *36:* 186–187.
204. Alomar A, Pujol R M, Esquius J. Erythema multiforme-like contact dermatitis. *Am J Contact Dermatitis* 1990: *1:* 177–179.
205. Thompson J A Jr, Wansker B A. A case of contact dermatitis, erythema multiforme, and toxic epidermal necrolysis. *J Am Acad Dermatol* 1981: *5:* 666–669.
206. Seidenari S, Di Nardo A, Motolese A, Pincelli C. Erythema multiforme associated with contact sensitization. Report of 6 cases. *G Ital Dermatol Venereol* 1990: *125:* 35–40.
207. Schleuter D P. Airway reponse to hair spray in normal subjects and subjects with hyper-reactive airways. *Chest* 1978: *75:* 544–547.
208. Zuskin E, Bouhuys A, Beck G. Hair sprays and lung function. *Lancet* 1978: *2:* 1203.
209. De Groot A C. *Patch testing,* 2nd edition. Amsterdam: Elsevier Science, 1994.
210. Fisher A A. Patch testing with perfume ingredients. *Contact Dermatitis* 1975: *1:* 166–168.
211. McFarlane D F, DeLeo V A. Photopatch testing. In: Guin J D (ed): *Practical contact dermatitis.* New York: McGraw-Hill, 1995: 93–96.
212. White I R. Photopatch testing. In: Rycroft R J G, Menné T, Frosch P J (eds): *Textbook of contact dermatitis,* 2nd edition. Berlin: Springer-Verlag, 1995: 293–305.

213. Lahti A, Maibach H I. Immediate contact reactions. In: Menné T, Maibach H I (eds): *Exogenous dermatoses, environmental contact dermatitis.* Boca Raton: CRC Press, 1990: 21–35.
214. Katchen B R, Maibach H I. Immediate-type contact reactions: immunologic contact urticaria. In: Menné T, Maibach H I (eds): *Exogenous dermatoses, environmental contact dermatitis.* Boca Raton: CRC Press, 1990: 51–64.
215. Harvell J, Bason M, Maibach H I. Contact urticaria (Immediate reaction syndrome). *Clin Rev Allergy* 1992: *10:* 303–323.
216. Harvell J, Bason M, Maibach H I. Contact urticaria and its mechanisms. *Fd Chem Toxicol* 1994: *32:* 103–112.
217. Lahti A. Immediate contact reactions. In: Surber C, Elsner P, Bircher AJ, eds. *Exogenous Dermatology. Curr Probl Dermatol.* Basel: Karger, 1993: *22:* 17–23.
218. Zajonz C, Frosch P J. Ursachen von Kontakturtikaria unter besonderer Berücksichtigung von Arbeitsstoffen. *Hautarzt* 1994: *45:* 65–73.
219. Fisher A A. Reactions of the mucous membranes to contactants. *Clin Dermatol* 1987: *5:* 123–136.
220. Guin J D. Cinnamic aldehyde. In: Guin J D (ed): *Practical contact dermatitis.* New York: McGraw-Hill, 1995: 141–151.
221. Niinimäki A. Double-blind placebo-controlled peroral challenges in patients with delayed-type allergy to balsam of Peru. *Contact Dermatitis* 1995: *33:* 78–83.
222. Veien N K, Hattel T, Laurberg G. Can oral challenge with balsam of Peru predict possible benefit from a low-balsam diet? *Am J Contact Dermatitis* 1996: *7:* 84–87.
223. Rudzki E, Grzywa Z, Bruo W S. Sensitivity to 35 essential oils. *Contact Dermatitis* 1976: *2:* 196–200.
224. Sainio E-L, Kanerva L. Contact allergens in toothpastes and a review of their hypersensitivity. *Contact Dermatitis* 1995: *33:* 100–105.
225. Knight T E, Hausen B M. Melaleuca oil (tea tree oil) dermatitis. *J Am Acad Dermatol* 1994: *30:* 423–427.
226. Selvaag E, Holm J-Ø, Thune P. Allergic contact dermatitis in an aroma therapist with multiple sensitizations to essential oils. *Contact Dermatitis* 1995: *33:* 354–355.
227. Rudzki E, Grzywa Z. The value of a mixture of cassia and citronella oils for detection of hypersensitivity to essential oils. *Dermatosen* 1985: *33:* 59–62.
228. McGeorge B C L, Steele M C. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis* 1991: *24:* 139–140.
229. Isaacs G. Permanent local anaesthesia and anhidrosis after clove oil spillage. *Lancet* 1983: *1:* 882.
230. Selvaag E, Eriksen B, Thune P. Contact allergy to tea tree oil and cross-sensitization to colophony. *Contact Dermatitis* 1994: *31:* 124–125.
231. Leow Y-H, Ng S-K, Wong W-K, Goh C-L. Contact allergic potential of topical traditional Chinese medicaments in Singapore. *Am J Contact Dermatitis* 1995: *6:* 4–8.
232. Escande J P, Foussereau J, Lantz J P, Basset A. Le problème des fausses sensibilisations croisées dans les allergies de groupe aux allergènes végétaux. *Rev Fr Allergol* 1973: *13:* 70–75.
233. El-Rab M O G, Al-Sheikh O A. Is the European standard series suitable for patch testing in Riyadh, Saudi Arabia? *Contact Dermatitis* 1995: *33:* 310–314.
234. Morton C A, Garioch J, Todd P, Lamey P J, Forsyth A. Contact sensitivity to menthol and peppermint in patients with intra-oral symptoms. *Contact Dermatitis* 1995: *32:* 281–284.
235. Rudzki E, Grzywa Z. Sensitizing and irritating properties of star anise oil. *Contact Dermatitis* 1976: *2:* 305–308.
236. Starke J C. Photoallergy to sandalwood oil. *Arch Dermatol* 1967: *96:* 62–63.
237. Li L-F. A clinical and patch test study of contact dermatitis from traditional Chinese medicinal materials. *Contact Dermatitis* 1995: *33:* 392–395.
238. Bilsland D, Strong A. Allergic contact dermatitis from the essential oil of French marigold (Tagetes patula) in an aromatherapist. *Contact Dermatitis* 1990: *23:* 55–56.
239. Puig L, Alomar A, Randazzo L, Cuatrecasas M. Erythema multiforme-like reaction caused by topical application of thuja essential oil. *Am J Contact Dermatitis* 1994: *5:* 94–97.
240. Cachão P, Menezes Brandão F, Carmo M, Frazão S, Silva M. Allergy to oil of turpentine in Portugal. *Contact Dermatitis* 1986: *14:* 205–208.
241. Rietschel R L. Contact urticaria from synthetic casssia oil and sorbic acid limited to the face. *Contact Dermatitis* 1978: *4:* 347–349.
242. Romaguera C, Grimalt F. Sensitization to cinnamic aldehyde in toothpaste. *Contact Dermatitis* 1978: *4:* 377–378.
243. Seite-Bellezza D, El Sayed F, Bazex J. Contact urticaria from cinnamic aldehyde and benzaldehyde in a confectioner. *Contact Dermatitis* 1994: *31:* 272–273.
244. Mathias C G T, Maibach H I, Conant M A. Perioral leukoderma simulating vitiligo from use of a tooth-paste containing cinnamic aldehyde. *Arch Dermatol* 1980: *116:* 1172–1173.
245. Mathias C G T, Chapler R R, Maibach H I. Contact urticaria from cinnamic aldehyde. *Arch Dermatol* 1980: *116:* 74–76.
246. Ostler H B, Okumoto M, Daniels T, Conant M A. Drug-induced cicatrisation of the conjunctiva. *Contact Dermatitis* 1983: *9:* 155.
247. Allen C M, Blozis G C. Oral mucosal reactions to cinnamon-flavored chewing gum. *JADA* 1988: *116:* 664–667.
248. Rycroft R J G. Allergic contact dermatitis from dipentene in honing oil. *Contact Dermatitis* 1980: *6:* 325–329.
249. Rudzki E, Grzywa Z. Immediate reactions to balsam of Peru, cassia oil and ethyl vanillin. *Contact Dermatitis* 1976: *2:* 360–361.
250. Vilaplana J, Grimalt F, Romaguera C, Conellana F. Contact dermatitis from eugenol in mouth-wash. *Contact Dermatitis* 1991: *24:* 223–224.
251. Guerra P, Aguilar A, Urbina F, Cristóbal MC, García-Pérez A. Contact dermatitis to geraniol in a leg ulcer. *Contact Dermatitis* 1987: *16:* 298–299.
252. Romaguera C, Grimalt F, Vilaplana J. Geraniol dermatitis. *Contact Dermatitis* 1986: *14:* 185–186.
253. Taylor A E M, Lever L, Lawrence C M. Allergic contact dermatitis from strawberry lipsalve. *Contact Dermatitis* 1996: *34:* 142.
254. Lewis F M, Shah M, Gawkrodger D J. Contact sensitivity to food additives can cause oral and perioral symptoms. *Contact Dermatitis* 1995: *33:* 429–430.
255. Andersen K E. Contact allergy to toothpaste flavors. *Contact Dermatitis* 1978: *4:* 195–198.
256. Ferguson J E, Beck M H. Contact sensitivity to vanilla in a lip salve. *Contact Dermatitis* 1995: *33:* 352.
257. Hausen B M, Simatupang T, Bruhn G, Evers P, Koenig W A. Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in Balsam of Peru. *Am J Contact Dermatitis* 1995: *6:* 199–208.
258. Meneghini C L, Angelini G. Secondary polymorphic eruptions in allergic contact dermatitis. *Dermatologica* 1981: *163:* 63–66.
259. Bruynzeel D P, van den Hoogenband H M, Koedijk F. Purpuric vasculitis-like eruption in a patient sensitive to balsam of Peru. *Contact Dermatitis* 1984: *11:* 207–209.

260. Thune P. Photosensitivity and allergy to cosmetics. *Contact Dermatitis* 1981: *7:* 54–55.
261. Forsbeck M, Skog E. Immediate reaction to patch tests with balsam of Peru. *Contact Dermatitis* 1977: *3:* 201–205.
262. Hjorth N. Eczematous allergy to balsams, allied perfumes and flavouring agents. *Acta Dermato-venereologica* 1961: *41:* suppl 46.
263. Mitchell J C, Calnan C D, Clendenning W E et al. Patch testing with some components of Balsam of Peru. *Contact Dermatitis* 1976: *2:* 57–58.
264. Oxholm A, Heidenheim M, Larsen E, Batsberg W, Menné T. Extraction and patch testing of methylcinnamate, a newly recognized fraction of Balsam of Peru. *Am J Contact Dermatitis* 1990: *1:* 43–46.

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