

Fragrances: Contact Allergy and Other Adverse Effects

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This article gives an overview of fragrance allergy. The following subjects are discussed: composition of perfumes, contact with fragrances, diagnosing fragrance allergy, frequency of allergy, clinical picture of allergic contact dermatitis, culprit products, occupational contact dermatitis, and other adverse effects of fragrances. For diagnosing fragrance sensitization, personal products and a fragrance series may need to be tested in addition to the baseline series. In the general adult population, up to 4.5% may be allergic to fragrance materials, and in consecutive patients patch tested for suspected contact dermatitis, the frequency may reach 20% to 25%. More than 150 fragrances have caused contact allergy. The most frequent sensitizers are linalool and limonene hydroperoxides, hydroxyisohexyl 3-cyclohexene carboxaldehyde, treemoss and oakmoss absolute, isoeugenol, cinnamyl alcohol, and cinnamal. Culprit products for induction of sensitization are often deodorants, fine fragrances, and aftershaves. Occupational contact dermatitis from fragrances is seen occasionally. Other adverse effects are all discussed but occur infrequently.

Fragrances are an important and frequent cause of contact allergy and allergic contact dermatitis, notably from their presence in fragranced products such as deodorants, fine fragrances and aftershaves, other cosmetics (both leave-on and rinse-off products), household products, topical pharmaceuticals, essential oils, foods, and, to a lesser degree, industrial products. Other adverse effects such as photosensitivity and immediate contact reactions are rare.

The literature on contact allergy to fragrances and many other aspects of individual fragrance compounds has recently been fully reviewed by the author of this article in the second volume of his book series *Monographs in Contact Allergy*.^{1,2} This article briefly discusses some important aspects of the subject of fragrances: the composition of perfumes, how we come in contact with fragrances, fragrances that have caused contact allergy/allergic contact dermatitis, diagnosing fragrance allergy, how frequent is fragrance allergy, clinical picture of allergic contact dermatitis from fragrances, products responsible for contact allergy to and allergic contact dermatitis from fragrances, occupational contact dermatitis from fragrance allergy, and other adverse effects of fragrances (adapted from the studies by de Groot^{1,3}).

A full review of older literature on fragrance allergy was published in 1997.⁴ Other useful reviews have been published in 2003,⁵ 2012–2013,^{6,7} 2013,⁸ and 2014.⁹

THE COMPOSITION OF PERFUMES

There are thousands of chemical substances that have an odor, and more than 2000, of which 300 to 400 are of natural origin, are used in the fragrance industry. A perfume consists of a few to several hundred fragrance materials.¹⁰ To create a modern perfume, the perfumer carries out a long series of experiments to determine the optimal balance of the ingredients. Because fragrance character evolves over time, the volatility of all raw materials plays a decisive role. The most volatile ingredients are called “top notes,” followed by the bouquet or “heart note” forming the most essential part of the perfume. The long-lasting materials are known as “bottom” or “dry out.”¹⁰ In some cases, substances (fixatives) are added to perfumes to prevent the more volatile components from evaporating too easily. A fixative may be a fragrance material itself or may be odorless. It is characterized by a low vapor pressure. A perfume is developed for one particular purpose, and the composition may have to be changed to retain the same odor if it is incorporated into a different type of product.¹¹

“Proper” perfumes contain approximately 15% to 30% of the fragrance compound. They are expensive and too concentrated. The more diluted products such as eau de parfum, eau de toilette, and colognes are therefore much more popular.³ Approximate concentrations of fragrance materials in cosmetics and some household products are shown in Table 1.

Details of the composition of a particular perfume (both in cosmetics used for their scent and in other cosmetic and household

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TABLE 1. Approximate Concentrations of Perfume in Cosmetics and Household Products^{3,4,11,12}

Product	Concentration
Aerosol freshener	0.5%–2%
Bath product	2%
Bathroom cleaner	≤5%
Body lotion	0.4%
Compressed powder	0.5%
Deodorant/antiperspirant	1%–3%
Dishwashing liquid	0.1%–0.5%
Eau de cologne	3%–5%
Eau de parfum	8%–15%
Eau de toilette	4%–8%
Face cream	0.3%
Facial make-up	1%
Fragranced cream	4%
Hair pomade	0.5%
Hair spray	0.1%–0.5%
Laundry powder	0.1%–0.3%
Lipstick	1%
Liquid detergent	0.1%–1%
Masking perfume	≤0.1%
Perfume (proper)	15%–30%
Shampoo (undiluted)	0.5%
Shower gel	1.2%
Skin care product	0.3%–0.5%
Soap (undiluted)	0.5%–2%

products) are usually closely guarded by industry. However, since 2005, in the European Union (EU), cosmetic products and detergent products are required to be labeled for the presence of 26 fragrance chemicals (of which 2 are mixtures: *Evernia prunastri* extract [oak-moss absolute] and *Evernia furfuracea* extract [treemoss absolute]), if present at greater than 10 ppm (0.001%) in leave-on products and greater than 100 ppm (0.01%) in rinse-off products (Table 2).¹³ Since then, some 15 investigations have studied the presence of these fragrances in certain products by reading the labels.^{14–20} The studies have nearly always been performed in European countries, a few in the United States. The number of products investigated has ranged from 23 to 5588, and the product types varied widely, for example, “cosmetic products in hair dye kits,” “fragranced cosmetic products,” “household detergents,” “emollients,” “pediatric cosmetics,” “deodorants,” “liquid household and cleaning products,” “cosmetic products,” “perfumed cosmetics and household products,” and “popular perfumed deodorants.” It can hardly be surprising that the results have varied widely. Indeed, the studies are difficult to compare because of differing parameters such as country, period of investigation, product types, sample sizes, and methods of selection.

Nevertheless, very generally speaking, it seems that—all products taken together—linalool and limonene are used most frequently, followed by citronellol, geraniol, hexyl cinnamal, butylphenyl methylpropional, and benzyl salicylate. The least frequently used chemicals seem to be cinnamal, *E. prunastri* extract (oakmoss absolute), *E. furfuracea* extract (treemoss absolute), benzyl cinnamate,

anise alcohol, methyl 2-octynoate, and amylcinnamyl alcohol. Most products contain at least 3 of the 26 fragrances that need to be labeled. Undoubtedly, they often contain more but in lower concentrations that need no declaration.

HOW DO WE COME IN CONTACT WITH FRAGRANCES?

Cosmetic products that are used primarily for their scent such as perfume, eau de cologne, eau de toilette, deodorant, and aftershave, although having the highest concentrations, certainly are not the only sources of contact with fragrance materials. All cosmetics and most household products probably contain fragrance materials, unless it is stated otherwise. However, even “unscented” or “fragrance-free” products may sometimes contain a perfume or an essential oil to mask the unpleasant odor of the product or specific ingredients. Examples of products containing fragrances are shown in Table 3.

Virtually, everyone has contact with fragrance materials every day. Contact with fragrances may occur from direct product application to the skin or mucous membranes; by occasional contact with an allergen-contaminated product such as towels and pillows; contact with products used by partners, friends, or coworkers (consort or connubial contact dermatitis); airborne contact; and systemic exposure by inhalation and ingestion (fragrances, flavors, and spices

TABLE 2. Fragrances That Need to Be Labeled in the EU in Cosmetics and Household Products

Amyl cinnamal (α -amylcinnamic aldehyde)
Amylcinnamyl alcohol
Anise alcohol (anisyl alcohol)
Benzyl alcohol
Benzyl benzoate
Benzyl cinnamate
Benzyl salicylate
Butylphenyl methylpropional (Lilial)
Cinnamal (cinnamic aldehyde, cinnamaldehyde)
Cinnamyl alcohol
Citral
Citronellol
Coumarin
Eugenol
<i>E. furfuracea</i> (treemoss) extract
<i>E. prunastri</i> (oakmoss) extract
Farnesol
Geraniol
Hexyl cinnamal (α -hexylcinnamic aldehyde)
Hydroxycitronellal
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall)
Isoeugenol
α -Isomethyl ionone (γ -methylionone)
Limonene
Linalool
Methyl 2-octynoate (methyl heptene carbonate)

Labeling of the fragrances is only mandatory if present at >10 ppm (0.001%) in leave-on products and >100 ppm (0.01%) in rinse-off products.

TABLE 3. Examples of Products Containing Fragrances^{3,4}

Cosmetics including perfumes
Essential oils, eg, tea tree oil and various oils used in aromatherapy
Fabrics and clothes (after they have been laundered or treated with a fabric softener)
Flavors used in oral hygiene products: toothpaste, mouthwash, and dental floss
Household products: detergents, cleaners, softeners, fabric conditioners, deodorizing sprays, polishes, solvents, and waxes
Industrial products: cutting fluids, electroplating fluids, paints, rubber, plastics, insecticides, herbicides, and additives used in air conditioning
Paper and paper products: diapers, facial tissues, moist toilet paper, and sanitary napkins
Products used in dentistry (notably eugenol)
Spices including cinnamon, clove, vanilla and cardamom added to foods, soft drinks, lozenges, chewing gum, candies, ice cream, and tobacco
Topical drugs (especially essential oils)
Ventilating systems and diffusers

in foods and drinks). Indeed, any part of the body may more or less frequently have contact with fragrances.^{3,4}

FRAGRANCES THAT HAVE CAUSED CONTACT ALLERGY/ALLERGIC CONTACT DERMATITIS

The author of this article has found 162 fragrances that have been reported to cause contact allergy/allergic contact dermatitis, from any source. Most are single chemicals, and some are complex mixtures of botanical origin: *E. furfuracea* (treemoss) extract, *E. prunastri* (oakmoss) extract, *Ferula galbaniflua* gum, methyl ionones (mixture of 4 chemicals, not botanical), *Narcissus poeticus* flower extract, and *Viola odorata* leaf extract. Of these 162 fragrance compounds, 15 have been tested (with positive results) in the general population and 65 in groups of consecutive patients suspected of having contact dermatitis (routine testing). Patch tests in groups of *selected* patients (eg, patients known or suspected to be allergic to fragrances, individuals suspected of having cosmetic dermatitis, patients with eyelid/periorbital dermatitis, with allergic contact cheilitis, hairdressers or their clients, patients previously shown to be allergic to *Myroxylon pereirae* resin or tea tree oil and tested with 1 or more of their ingredients) with positive results have been performed with 126 fragrances. Case reports/series were found for 83 compounds.

It should be realized that for a large number of fragrances, (very) few data are available. Forty fragrances have given positive results in a single study only, in which a group of selected patients was tested with a battery of fragrances, leading to a number of positive patch test reactions, but where the authors did not comment on their relevance.^{21–31} With 10 fragrances, patch tests have been performed in the 1970s in Japan, but details are lacking, because the results have been published in Japanese journals only.³²

Generally speaking, in by far most studies performed with fragrances, data on relevance are either completely absent or inadequate. As to case reports and case series, these include the results of retrospective studies in, for example, groups of patients with cosmetic dermatitis, in which it was stated in how many cases specific fragrances were the allergenic ingredient, but without additional supportive data.^{33–40} Well-described case reports (clinical picture, patch test results, culprit products, identification of the allergenic ingredients in these products, improvement or healing after avoiding the allergens) constitute a small minority. In total, only 36 fragrances have shown positive results in routine testing and in testing in selected groups and were reported to be the cause of allergic contact dermatitis in 1 or more case reports.

In Table 4, for every of the 162 fragrances that have caused contact allergy/allergic contact dermatitis and for 3 “indicators” of fragrance allergy (fragrance mix I [FM I], FM II, *M. pereirae* resin [MP; balsam of Peru]), the following data—where available—are provided: results of patch testing in the general population (with percentage of positive reactions), results of routine testing and testing in groups of selected patients (both with [range of] percentages of positive reactions), whether case reports or case series have been documented, and sometimes references (in brackets).

Not included in this Table are 16 chemicals that are not used as fragrances per se but are potentially allergenic ingredients of botanical products, which may be applied in perfumery. These botanicals and their respective ingredients are *E. furfuracea* (treemoss) extract (atranol, atranorin, chloroatranol, fumarprotocetraric acid, physodalic acid, physodic acid), *E. prunastri* (oakmoss) extract (atranol, atranorin, chloroatranol, evernic acid, usnic acid), MP derivatives (benzyl isoferulate, coniferyl alcohol, coniferyl benzoate, isoferulic acid), and *Melaleuca alternifolia* (tea tree) leaf oil (aromadendrene, ascaridole, ledene, 1,2,4-trihydroxymenthane).

Details for all fragrances and other nonfragrance allergens in botanical products used as fragrances have been published recently.¹

DIAGNOSING FRAGRANCE ALLERGY

This section was adapted from the study by de Groot.³ Many individuals with contact allergy to fragrance ingredients are aware that they cannot tolerate scented products on their skin and are often able to specifically name product categories that initiated their disease, notably colognes, eau de toilette, deodorants, and lotions.⁵⁹ However, in a recent study from the United Kingdom, 75% of patients, who proved to be fragrance allergic by patch testing, were not aware of this before.⁶⁰ Indeed, many hypersensitive individuals have never experienced fragrance-allergic contact dermatitis and seem to tolerate perfumes and fragranced products without problems. This may be explained by irritant (false-positive) patch test reactions to fragrances, the absence of relevant allergens in the products used, or their concentration being too low to elicit clinically visible allergic contact reactions. In addition, some allergic individuals who are exposed will not necessarily develop a clinical hypersensitivity reaction.³¹ Conversely, many more people complain about

TABLE 4. Fragrances That Have Caused Contact Allergy/Allergic Contact Dermatitis

Fragrance	Nature of Reports of Contact Allergy/Allergic Contact Dermatitis			
	General Pop.	Routine Testing	Selected Groups*	Case Rep.
Fragrance allergy indicators				
FM I	3.5% (pooled) ⁴¹	4.5%–22.2%	4.5%–57%	
FM II	1.9%	1.4%–8.0%	1.7%–19%	
<i>M. pereirae</i> resin	1.8% (pooled) ⁴¹	2.4%–13.7%	1.7%–50%	
Fragrances				
Acetylcedrene (Vertofix)		0.2%–1%		+
Acetyl hexamethyl indan (Phantolide)			n = 1 (5%) ²⁶	
Acetyl hexamethyl tetralin			n = 2 (10%) ²⁶	
Allylanisole				+
Allyl cyclohexylpropionate			No specific data ³²	+
Ambrettolide			n = 6 (3.4%) ²³	
Amyl cinnamal (α -amylcinnamic aldehyde)	0.1% ⁴²	0.08%–1.4%	0.3%–15%	+
Amyl cinnamate				+
Amylcinnamyl alcohol		0.1%–0.5%	0.5%–4%	+
Amyl salicylate		0.2%–1%	n = 1 (5%) ²⁵	
Anethole			0.6%–33%	+
Anise alcohol (anisyl alcohol)		0.03%–0.2%	0.1%–20%	
Anisylidene acetone			n = 2 (1.1%) ²¹	
Benzaldehyde			0.2%–0.5%	+
Benzyl acetate			0%–5.7%	
Benzyl alcohol		0.1%–1%	0.2%–15%	+
Benzyl benzoate		<0.1%–0.3%	0.1%–13%	+
Benzyl cinnamate		0.02%–0.3%	0.1%–19.1%	+
Benzylidene acetone				+
Benzyl isoeugenol		0.09% ⁴³		
Benzyl propionate			No specific data ³²	
Benzyl salicylate		3.3%–8.0%	0.04%–22%	+
Butyl acetate				+
Butylphenyl methylpropional (Lilial)		0.2%–1%	0.4%–4%	+
Camphor			n = 1 (5%) ²⁵	+
Camphylcyclohexanol			1.3%–2.5%	
Caprylic alcohol†				+ ^{44,45}
3-Carene			18%–27%	+
Carvacrol			2.1%–19%	
Carvone		0.6%–2.8%	4.6%–40%	+
β -Caryophyllene		0.5%–1.1%		+
Caryophyllene oxide		0.1%–0.4%		
Cedrol methyl ether (cedramber)			No specific data ³²	
Cinnamal (cinnamic aldehyde)	0.8% ⁴²	0.3%–9%	1.4%–30%	+
Cinnamic acid		1.5% ⁴⁶	13%–44%	+
Cinnamyl alcohol	0.3% ⁴²	0.14%–11.2%	1.5%–75%	+
Cinnamyl benzoate				+
Cinnamyl cinnamate			20%–25%	+
Citral	0.3% ⁴²	0.3%–3.2%	0.4%–25%	+
Citral diethyl acetal			No specific data ³²	
Citronellal				+
Citronellol	0.1% ⁴²	0.07%–1%	0.3%–35%	+
Coumarin	0.1% ⁴²	0.05%–0.7%		
Cuminaldehyde				
5-Cyclohexadecenone			No specific data ³²	
Cyclohexyl acetate			n = 1 (0.5%) ²⁴	

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TABLE 4. (Continued)

Fragrance	Nature of Reports of Contact Allergy/Allergic Contact Dermatitis			
	General Pop.	Routine Testing	Selected Groups*	Case Rep.
Cyclopentadecanone			n = 3 (1.7%) ²³	
<i>p</i> -Cymene			n = 1 (14%) ⁴⁷	
α -Damascone		0.5% ⁴⁸		+
β -Damascone		0.5% ⁴⁸		
Dehydrodiisoeugenol			No specific data	
Diethyl maleate			n = 6 (3.3%) ²¹	
Dihydrocarveol			n = 1 (10%) ²⁷	
Dihydrocitronellol				+
Dihydrocoumarin			3.7%–21%	+
Dihydro pentamethylindanone (Cashmeran)			n = 1 (0.6%) ²²	
Dimethylbenzyl carbinyl acetate		0.2%–0.3%		
Dimethyl citraconate			n = 7 (3.8%) ²¹⁺	
2,4-Dimethyl-3-cyclohexene carboxaldehyde (Ligustral)			n = 1 (0.6%) ²²	
Dimethyl tetrahydro benzaldehyde			n = 4 (2.3%) ²³	
Ethyl anisate				+
Ethylene dodecanedioate			n = 2 (0.9%) ²⁴	
Ethyl vanillin			n = 9 (14%) ⁴⁹	
Eucalyptol (1,8-cineole)				+
Eugenol	0.2% ⁴²	0.3%–3.4%	1.3%–56%	+
<i>E. furfuracea</i> (treemoss) extract		1.5%–3.3%	2.5%–30%	+
<i>E. prunastri</i> (oakmoss) extract	1.0% ⁴²	0.7%–3.1%	1.9%–64%	+
Farnesol	0.4% ⁴²	0.2%–2.5%	0.2%–2.5%	+
<i>F. galbaniflua</i> gum (galbanum resin)			n = 8 (4.8%) ²²	
Geranial		0.4%–2.0%		+
Geraniol	0.4% ⁴²	0.2%–2.6%	0.6%–30%	+
Geranyl acetate				+
Heliotropine (piperonal)		0.4%–1.0%	n = 1 (5%) ²⁵	+
Heptanalt				+ ^{44,45}
Hexadecanolactone (hexadecanolide)			0.6%–1.4%	
Hexamethylindanopyran (Galaxolide)		0.2% ⁵⁰	0.3%–3.4%	
<i>cis</i> -3-Hexenyl salicylate			No specific data ³²	+
Hexyl cinnamal (α -hexylcinnamic aldehyde)	0.3% ⁴²	0.06%–0.6%	0.5%–7%	+
Hexyl salicylate				+
Hydroxycitronellal	0.5% ⁴²	0.4%–3.8%	1.0%–45%	+
Hydroxycitronellol			n = 13 (6.0%) ²⁴	
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall)	1.5% ⁴²	0.4%–4.8%	0.9%–40%	+
Ionone (α -Irisone)		0.5% ⁵¹	n = 2 (1.1%) ²⁹	+
Isoamyl salicylate		3.7%	n = 1 (0.6%) ²⁹	
Isoeugenol	0.7% ⁴²	1.0%–4.5%	1.3%–33%	+
Isoeugenyl acetate		0.8%–3.9%		
Isoeugenyl benzoate		0.2% ⁴³		
Isoeugenyl phenylacetate		0.7% ⁴³		
Isolongifolanone			n = 1 (0.6%) ²³	
α -Isomethyl ionone (γ -methylionone)		0.03%–0.1%	0.4%–2.1%	+
Isopulegol			n = 2 (10%) ²⁵	
Isosafrole			n = 1 (2.3%) ⁴⁹	
Limonene			0.3%–86%	+
Linalool			0.2%–20%	+
Linalyl acetate		0.2%–2.2%		+
Maltol				+

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TABLE 4. (Continued)

Fragrance	Nature of Reports of Contact Allergy/Allergic Contact Dermatitis			
	General Pop.	Routine Testing	Selected Groups*	Case Rep.
Menthol		0.1% ⁵²	0.1%–40%	+
Menthyl acetate			n = 1 (10%) ²⁷	
Methoxycinnamal				+
Methoxycitronellal			n = 12 (9%) ⁵³	
2-Methoxyphenol/2,2-dimethyl-3-methylene bicycloheptane hydrogenated (Sandela)			n = 11 (6.6%) ^{22‡}	
Methoxytrimethylheptanol			n = 2 (0.9%) ²⁴	
Methyl <i>p</i> -anisate			n = 1 (0.5%) ²⁴	+
Methyl anthranilate			1%–1.9%	
Methyl cinnamate			3%–4.2%	
6-Methyl coumarin			0.3%–11.9%	
Methyl dihydrojasmonate (Hedione)		0.2% ⁴⁸	+ (Ph)	+ (Ph)
Methylenedioxyphenyl methylpropanal (Helional)			n = 4 (2.4%) ²²	
Methyl eugenol			n = 4 (1.8%) ²⁴	
Methyl ionones				+
5-Methyl- α -ionone (α -Irone)		0.3% ⁴⁸	No specific data ³²	
Methyl isoeugenol		0.3% ⁴³	n = 16 (7.3%) ²⁴	
Methyl octine carbonate				+
Methyl 2-octynoate (methyl heptene carbonate)		0.1%–0.9%	0.1%–5%	
Methyl salicylate		0.1%–0.5%	1.3%–1.6%	+
3-Methyl-5-(2,2,3-trimethyl-3-cyclopentenyl)pent-4-en-2-ol (Ebanol)			0.6%–2.8%	
Musk [†]				+ ^{44,45}
Musk ambrette		0.3%–0.4%	0.2%–10%	+
		0.8% (Ph)	+ (Ph)	+ (Ph)
Musk ketone		0.3% ⁵⁴	1%–2%	+ (& Ph)
Musk moskene		1.4% ⁵⁴		+
Musk tibetene			+ (Ph)§	
Musk xylene		0.7% ⁵⁴	n = 2 (2%) ⁵⁵	+
Myrcene		0.1% ⁵⁶	10%–35%	+
<i>N. poeticus</i> flower extract		0.5%–1.3%	0.5%–1.3%	
Neral		0.1%–0.9%	n = 5 (2.7%) ²¹	
Nerol			n = 13 (6.0%) ²⁴	
Nerolidol		3.5% ⁴⁶	3%–6%	
Nonanal [†]				+ ^{44,45}
Nonyl alcohol [†]				+ ^{44,45}
Nopyl acetate			n = 2 (1.1%) ^{29‡}	
Pentamethylcyclopent-3-ene-butanol (Sandalore)			n = 5 (3.0%) ²²	
α -Phellandrene			14%–63%	+
Phenethyl alcohol			1.1%–5%	
Phenylacetaldehyde		1.5% ⁵⁷	n = 4 (1.1%) ²¹	+
Phenylpropanol			n = 2 (0.9%) ²⁴	
α -Pinene			50%–77%	+
β -Pinenes		0.2% ⁵²	9%–37%	+
Piperitone			n = 4 (40%) ²⁷	
Propylidene phthalide			n = 5 (2.7%) ²¹	
D-Pulegone			n = 3 (30%) ²⁷	
Rhodinol			1–5%	
Rose ketone-4			No specific data ³²	
Sabinene			n = 2 (10%) ³⁰	
Safrole			2%–7%	

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TABLE 4. (Continued)

Fragrance	Nature of Reports of Contact Allergy/Allergic Contact Dermatitis			
	General Pop.	Routine Testing	Selected Groups*	Case Rep.
Salicylaldehyde			0.1%–2.5%	+
Santalol		No specific data	0.6%–1.5%	+
Styryl acetate			n = 2 (10%) ³¹	
α-Terpinene			69%–100%	+
4-Terpineol			5%–29%	+
α-Terpineol		0.1%–0.2%	1.3%–14%	+
Terpinolene			85%–100%	+
Terpinyl acetate			n = 1 (5%) ²⁵	
Tetrahydro-dimethylbenzofuran			n = 2 (20%) ²⁷	
Tetramethyl acetyloctahydronaphthalene (Iso E Super)		0.2%–0.3%	n = 3 (1.7%) ²³	
Thymol			1.2%–5%	+
Trimethylbenzenepropanol (Majantol)		0.2%–1.4%	0.8%–5.4%	+
5,5,6-Trimethylbicyclohept-2-ylcyclohexanol (isobornyl cyclohexanol) [†]			No specific data ⁵³	
2,4,6-Trimethyl-4-phenyl-1,3-dioxane (Floropal)			n = 2 (1.2%) ²²	
Vanillin		0.3% ⁵⁴	0.1–17%	+
Verdyl acetate (Cyclacet)		0.1%–0.3%		
Vetiveryl acetate			No specific data ³²	
<i>V. odorata</i> leaf extract			n = 2 (1.2%) ²²	

*When only one single study on allergy to a fragrance is available, in a group of selected patients with one or more positive reactions to the fragrance, the number of positive reactions (*n*), percentage of positive reactions (in brackets), and the reference (in brackets) are shown. In case of more studies identifying the fragrance as allergen, the range of positives is shown. It should be appreciated that the percentages vary considerably for individual fragrances and are strongly dependent on the mode of selecting the patients. Sometimes, data are missing or incomplete, notably from studies that have been published in Japanese journals only.

[†]Contact allergy not established with certainty; one case report, at retesting negative.^{44,45}

[‡]Probably includes a number of false-positive reactions.

[§]Only photo cross-reaction to musk ambrette.

^{||}Formerly stated to be an important allergen in ylang-ylang oil in Japan, but ylang-ylang oil seems not to contain this chemical.⁵⁸

Case Rep, case reports; General Pop., general population; Ph, photosensitivity.

intolerance to or rash caused by perfumes or perfumed products than are shown to be allergic by patch testing. This may be attributable to irritant effects of or immediate-type effects to the fragrances or fragranced products or to inadequate diagnostic (patch testing) procedures.^{8,59}

Full and adequate testing can be complicated, because a perfume may contain more than 250 individual ingredients. The European baseline series, which is routinely tested in all patients suspected of having contact dermatitis, contains the fragrance hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyril, HICC) and the following 3 “markers” or “indicators” of fragrance allergy: FM I, FM II, and MP (balsam of Peru). Colophonium (rosin) was traditionally considered to be a marker for fragrance allergy, but it identifies very

few cases not detected by the other markers and is hardly, if at all, viewed as a fragrance allergy marker anymore.⁶⁰

Fragrance mix I has been part of most routine series since the late 1970s and contains the following 8 fragrance chemicals in a concentration of 1% each: amyl cinnamal, cinnamal, cinnamyl alcohol, eugenol, *E. prunastri* (oakmoss) extract, geraniol, isoeugenol, and hydroxycitronellal. The petrolatum vehicle contains 5% sorbitan sesquioleate (SSO) as emulsifier to ensure even dispersion of the ingredients. Fragrance mix I is very useful but has certain imperfections, which are shown in Table 5.

When patients allergic to FM I were (concurrently or later) tested with the 8 ingredients (“breakdown testing”), on average one-third of the patients did not react to any ingredient. Possible explanations include (a) false-positive (irritant) reactions to the mix and (b) false-negative reactions to the individual constituents. In most studies, these have been tested at 1% in petrolatum, which is the same as in the mix. That the FM *does* react despite having the same concentration as the constituents that are negative separately may be related to the following: (a) enhancement of elicitation of contact allergic reactions by allergen mixtures⁶¹ or irritants, (b) increased skin penetration caused by the (combined) irritancy of other constituents of the mix including SSO, or (c) the formation of new allergens in the mix (compound allergy). No evidence for this latter scenario is as

TABLE 5. Imperfections of FM I

May cause irritant reactions interpreted as positive (false-positive)
May cause false-negative reactions (negative reaction to the mix, positive reaction to ≥ 1 ingredients)
Leaves up to 65% of fragrance sensitivities undetected
Sorbitan sesquioleate may cause an allergic reaction; risk of wrong interpretation as fragrance allergy
Occasional cases of patch test sensitization

TABLE 6. Fragrances and Fragrance Markers Commercially Available for Patch Testing

Patch Test Allergen	Chemotechnique	SmartPractice
Amyl cinnamal (α -amylcinnamic aldehyde)	2%	1%
Amylcinnamyl alcohol	5%	1%
Anethole (<i>E</i> -)	5%	
Anise alcohol (anisyl alcohol)	10% Softisan	1%
Atranorin*	0.1%	0.1%
Benzaldehyde		5%
Benzyl alcohol	10% Softisan	1% and 5%
Benzyl benzoate	10%	1%
Benzyl cinnamate	10%	5%
Benzyl salicylate	10%	1%
Butylphenyl methylpropional (Lilial, <i>p</i> - <i>tert</i> -butyl- α -methyl-hydrocinnamic aldehyde)	10%	10% [†]
Carvone	5%	5% [‡]
Cinnamal (cinnamic aldehyde, cinnamaldehyde)	1%	1%
Cinnamyl alcohol	2%	1%
Citral	2%	2%
Citronellal		2%
Citronellol	1%	1%
Colophonium (colophony, rosin) [§]	20%	20%
Coumarin	5%	5%
Dipentene (DL-limonene)		2% [‡]
Eugenol	2%	1%
<i>E. furfuracea</i> extract (treemoss absolute)	1%	1%
<i>E. prunastri</i> extract (oakmoss absolute)	2%	1%
Evermic acid*	0.1%	
Farnesol	5%	5%
FM I [§]	8%	8%
Amyl cinnamal 1%		
Cinnamal 1%		
Cinnamyl alcohol 1%		
Eugenol 1%		
Geraniol 1%		
Hydroxycitronellal 1%		
Isoeugenol 1%		
Oakmoss absolute 1%		
Fragrance mix A [§] (as FM I, oakmoss absolute replaced with sandalwood oil 1%)		8%
FM II [§]	14%	14%
Citral 1%		
Citronellol 0.5%		
Coumarin 2.5%		
Farnesol 2.5%		
Hexyl cinnamal 5%		
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyril) 2.5%		
Geraniol	2%	1%
Hexyl cinnamal	10%	10%
Hydroxycitronellal	2%	1%
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyril)	5%	5%
Isoeugenol	2%	1%
α -Isomethyl ionone (γ -methylionone)	10%	1%
Lichen acid mix* [§] (atranorin, evermic acid, usnic acid, each 0.1%)	0.3%	0.3%
D-Limonene	10%	2% and 3% [¶]
Limonene hydroperoxides	0.2% and 0.3%	
Linalool	10%	10%
Linalool hydroperoxides	0.5% and 1%	

(Continued on next page)

TABLE 6. (Continued)

Patch Test Allergen	Chemotechnique	SmartPractice
Menthol	2%	1%
Methyl anthranilate	5%	5% [†]
6-Methylcoumarin	1% and 1% alcohol	
Methyl-2-octynoate (methyl heptene carbonate)	0.2%	
Methyl salicylate		2%
Musk ambrette		5%
Musk ketone	1%	
Musk mix (musk xylene, moskene, ketone, each 1%) [§]	3%	
Musk moskene	1%	
Musk xylene	1%	
<i>M. pereirae</i> resin (balsam of Peru) [§]	25%	25%
<i>N. poeticus</i> absolute	2%	2%
Perfume mix [§] (as FM I, without amyl cinnamal and oakmoss absolute)	6%	
α -Pinene		15%
Salicylaldehyde		2%
Thymol		1%
Trimethylbenzenepropanol (Majantol)	5%	5%
Usnic acid*	0.1%	0.1%
Vanillin	10%	10%

*Lichen acid.

[†]Only available at SmartPractice Europe.

[‡]Only available at SmartPractice Canada.

[§]Not a fragrance ingredient per se, but an indicator of fragrance allergy.

^{||}Patch testing should be performed with the hydroperoxides of limonene and linalool.

[¶]SmartPractice Europe only 2%.

Available at Chemotechnique: Chemotechnique Diagnostics (<http://www.chemotechnique.se>), SmartPractice: SmartPractice Europe (<http://www.smartpracticeeurope.com>), and SmartPractice Canada (<http://www.smartpracticecanada.com>).

yet available. Because the emulsifier SSO may cause contact allergic reactions in up to 5% to 10% of patients tested with FM I (and can wrongly be interpreted as fragrance allergy), SSO needs always to be tested separately when breakdown testing is performed.⁶² Addition of SSO to the baseline series would be preferable. Of the ingredients of FM I, oakmoss absolute is the most frequent sensitizer, followed by isoeugenol, with geraniol and amyl cinnamal by far causing positive reactions least frequently.¹

Fragrance mix II was added to the European baseline series in 2008. It consists of 6 ingredients with a total concentration of 14% in petrolatum: citral (1%), citronellol (0.5%), coumarin (2.5%), farnesol (2.5%), hexyl cinnamal (5%), and HICC (2.5%). It has proven its value, as 35% to 50% of the patients with a positive reaction to FM II do not react to FM I.⁶³ Approximately one-third of the patients reacting to FM II have a negative breakdown, with no positive reactions to any of its ingredients.⁶³ By far, the most frequent sensitizer in the mix is HICC. This fragrance is also part of the baseline series as a single chemical in a concentration of 5%, and its rate of positive reactions is one of the higher one in the baseline series. However, most reactions to HICC are already picked up by FM II, and the single chemical detects only an additional 0.2% to 0.3% positive reactions, which led Swedish researchers to delete it from their national baseline series.⁶⁴

The indicators MP¹¹ and especially colophonium detect relatively few fragrance sensitivities that are not already identified by reactions to one or both fragrance mixes.

Although extremely useful, the 3 indicators + HICC together leave a considerable number of sensitizations to fragrances (up to 59%⁶⁰) undetected, and testing with additional fragrances and/or essential oils may reveal many additional cases of fragrance contact allergy. Nearly 60 fragrance allergens (including indicators and lichen acids, which are themselves not used as fragrances but may be present in treemoss and/or oakmoss extract) are commercially available for patch testing (Table 6; all fragrances in petrolatum, unless otherwise indicated).

When fragrance allergy is suspected on the basis of the patient's history or the clinical presentation, testing a "fragrance series" is strongly recommended. When this is omitted, this may have to be performed in a second session yet, when fragrance sensitivity is strongly suspected, but the fragrance test substances in the baseline series remain negative.³ In the case of a positive reaction to FM I and/or FM II, subsequently, breakdown tests must be performed to identify the specific sensitizer(s). In the EU, these must be labeled on cosmetics and detergent products, if present at greater than 10 ppm (0.001%) in leave-on products and greater than 100 ppm (0.01%) in rinse-off products, and contact with them can therefore largely be avoided. It

is also imperative that all products used by the patients and suspected to cause reactions are patch tested. It has been shown, for example, that relevant allergic reactions to perfumes, deodorants, and shaving lotions in approximately half of the cases are not identified by any fragrance indicator reacting in the baseline series.⁶⁵

Most recently, the European Society of Contact Dermatitis has advised to test linalool hydroperoxides 1% and 0.5% and limonene hydroperoxides 0.3% and 0.2% petrolatum as an addition to the European baseline series.²⁸ It was highlighted that frequent irritant and doubtful patch test reactions to these haptens have been observed and that, to aid in interpretation, 2 dilutions of each should be tested if these haptens are tested routinely.²⁸

In case of dubious (?+) or weak-positive (+) reactions to fragrances, fragrance markers, or products used by the patient, repeat testing, use tests, or repeated open application tests are helpful to confirm the allergic nature of the patch test reaction and aid in establishing the relevance.

Patch test concentrations and vehicles for fragrance materials, which are not commercially available for patch testing and for all cosmetic products, can be found in *Patch Testing*, fourth edition.⁶⁶

HOW FREQUENT IS FRAGRANCE ALLERGY?

Although fragrances are mostly moderate sensitizers,⁶⁷ they are among the most frequent causes of contact allergy, presumably from their extremely widespread use. Some fragrances are themselves nonsensitizing or low sensitizing but are transformed into a—far stronger sensitizing—haptens outside the skin by chemical transformation from air oxidation or photoactivation (a prehapten) or are transformed into a hapten in the skin (bioactivation), usually via enzymatic catalysis (a prohaptens).^{68,69} Eugenol and isoeugenol are prohaptens; geraniol, limonene, linalool, and linalyl acetate are prehaptens; and cinnamyl alcohol, geraniol, and α -terpinene act both as prohaptens and prehaptens. In recent years, it has been shown that autooxidation of linalool, limonene, and linalyl acetate forms potentially allergenic hydroperoxides. Indeed, linalool and limonene, by patch testing with their hydroperoxides, were identified as very frequent causes of fragrance allergy. When tested with the pure compounds, these chemicals rarely give positive reactions.

Fragrance sensitization is seen more often in female patients and its prevalence increases with age rising above 40 years.^{70,71}

General Population

Fragrance Mixes and MP Resin

In a 2018 meta-analysis of 19 studies covering 19,440 patch-tested individuals from the general population, the pooled prevalence for sensitization to FM I was 3.5% (women 3.4%, men 2.9%).⁴¹ For MP (12 studies covering 8002 patch-tested individuals), the pooled prevalence of sensitization was 1.8% (women 1.7%, men 1.6%).⁴¹ In 2008–2011, in 5 European countries (Sweden, Germany, the Netherlands, Portugal, and Italy), a random sample of the general population of 3119 individuals aged 18 to 74 years was patch tested

with FM II. There were 60 reactions (1.9%) to FM II, tested 14% in petrolatum.^{42,72}

Individual Fragrances

In 2008–2011, in 5 European countries (Sweden, Germany, the Netherlands, Portugal, and Italy), a random sample of the general population of 3119 individuals aged 18 to 74 years was patch tested with the 14 ingredients of FM I and FM II.⁴² The percentages of positive reactions (in descending order) were as follows: HICC (1.5%), *E. prunastri* (oakmoss) extract (1.0%), cinnamal (0.8%), isoeugenol (0.7%), hydroxycitronellal (0.5%), farnesol (0.4%), geraniol (0.4%), cinnamyl alcohol (0.3%), citral (0.3%), hexyl cinnamal (0.3%), eugenol (0.2%), amyl cinnamal (0.1%), citronellol (0.1%), and coumarin (0.1%) (42). Approximately half of all positive reactions to fragrances and indicators were considered to be relevant based on standardized criteria. Women were affected twice as often (2.5%) as men (1.3%).⁴²

From these data, the fact that the indicators of fragrance allergy miss a large number of fragrance sensitizations and the recent high frequencies of sensitization to limonene and linalool (in routine testing), it can be concluded that possibly up to 4.5% of the adult general population has contact allergy to 1 or more fragrances. However, many of them can tolerate perfumes and scented products and do not experience or have a history of allergic reactions. Even continuous exposure to fragrances to which contact allergy has been established will not necessarily lead to allergic contact dermatitis.³¹ Indeed, the prevalence of *clinically relevant* fragrance contact allergy has—conservatively—been estimated as 1.9%.⁴²

Patients Patch Tested Because of Suspected Contact Dermatitis

In a study in 12 European countries performed in 2009–2012, 12.7% of a group of more than 50,000 consecutive patients patch tested for suspected contact dermatitis (routine testing) had positive reactions to FM I, FM II, HICC, MP, oil of turpentine (a weak marker for fragrance allergy), or a combination of these.⁷³ In similar 2016 Informationsverbund Dermatologischer Kliniken (IVDK) data, the percentage was nearly 17%.⁷⁰ However, the actual prevalence of fragrance sensitivity may be considerably higher because these markers fail to detect a large number of fragrance-allergic individuals: 58% to 70% of the many individuals reacting to oxidized limonene or linalool^{60,74–76} and 40% to 60% of the reactions to the 26 fragrances that need to be labeled in the EU.^{61,77} In a 2015 to 2016 study performed in the United Kingdom, of 2084 patients who were tested with the baseline series, the 26 fragrances that need to be labeled including oxidized linalool and oxidized limonene, and trimethylbenzenepropanol, 359 individuals (17.2%) reacted to at least 1 fragrance.⁶⁰ Although the latter would not seem to point at an increased frequency by cotesting additional fragrances including oxidized linalool and limonene, it should be appreciated that fragrance allergy as identified by FM I, FM II, and MP in the United Kingdom generally has a lower frequency than in several other European countries.⁶⁰ This means that the actual rate of sensitization in routine testing in some countries, and notably in the

IVDK area (Germany, Switzerland, Austria), may well be more than 20% and possibly reach 25%!

In Thailand, 22.1% of a very small group of 312 consecutive patients reacted to FM I, FM II, MP, or combinations.⁷⁸ Such combined data are unavailable from the United States, but because the rates of reactions in the North American Contact Dermatitis Group (NACDG) studies for FM I, FM II, and MP separately are generally higher than those in Europe,¹ it may be expected that at least 20% of patients patch tested for suspected allergic contact dermatitis in the United States are allergic to fragrances.

Frequencies of Sensitization to Individual Fragrance Markers in Routine Testing

Generally speaking, in Europe, since 2000, frequencies of sensitization to FM I mostly have ranged from 5% to 9%.¹ This is lower than that in the United States, where rates have varied between 9% and 12%. Frequencies of sensitization for MP in the United States have ranged from 6.6% to 13.7%. These rates seem to have decreased somewhat in the last decade, ranging in all NACDG studies between 7% and 8%. In multinational multicenter studies performed in Europe, frequencies of sensitization to MP have ranged in a very narrow band of 5.3% to 6.4%.¹ As to FM II, most studies scored between 3% and 5.2% positive reactions.¹ In multicenter studies, the rates per center have shown significant variability for all fragrance markers, with a range between 0% and 16% for reactions to FM I in the 2013–2014 study of the European Surveillance System on Contact Allergies.⁷⁹ Colophonium, which is a weaker marker for fragrance sensitization, currently has the lowest prevalence scores, 2.6% to 2.9% in Europe^{73,79} and 1.9% to 2.5% in the United States.^{80–82}

Frequencies of Sensitization to Individual Fragrances in Routine Testing

Contact allergy to limonene and linalool was long considered to be rare. In recent years, however, limonene hydroperoxides and linalool hydroperoxides (in oxidized limonene and linalool) have gained much attention and have been patch tested in several studies in consecutive patients in European and some other countries. Patch testing with limonene hydroperoxides 0.3% pet. has shown frequencies of sensitization ranging from 2.5% to 9.4%.^{74,76,83–87} For linalool hydroperoxides 1% pet., the range was even 3.9% to 11.7%.^{74,76,83–87} The author of this article thinks it very likely that a number of these reactions have been false-positive. Nevertheless, linalool and limonene, which are both the fragrances most often used in cosmetics and household detergents, seem to be the most frequent fragrance sensitizers at this moment. Hydroxyisohexyl 3-cyclohexene carboxaldehyde probably is the third most frequent fragrance allergen with frequencies of sensitization generally between 1.2% and 2.5%, but rates up to 4.8% have recently been observed. Hydroxyisohexyl 3-cyclohexene carboxaldehyde will be totally banned from cosmetic products in the EU from August 23, 2021, onward, and the rates are at this moment (2018) already declining.

In 6 recent studies, the 26 fragrances that need to be labeled in the EU have been patch tested in consecutive patients suspected of

having contact dermatitis.^{60,77,83,84,88,89} These include the 8 ingredients of FM I (indicated with ‡) and the 6 constituents of FM II (indicated with †). The results are shown in Table 7. *Evernia furfuracea* extract (treemoss absolute) is the most frequently reacting fragrance, with prevalence rate of 1.5% to 3.3%. It is followed by HICC and the following 5 components of FM I: *E. prunastri* extract (oakmoss absolute) (1.2%–2.1%), isoeugenol (0.9%–2.6%), cinnamyl alcohol (0.6%–2.5%), cinnamal (1.2%–1.9%), and hydroxycitronellal (0.6%–2.2%). All other fragrances score an average frequency of less than 1%, with the lowest rates for α -isomethyl ionone (0.16%), methyl 2-octynoate (0.16%), amyl cinnamal (0.14%), anise alcohol (0.10%), benzyl cinnamate (0.08%), limonene (not oxidized) (0.06%), and benzyl benzoate (0.04%) (Table 7).

Trimethylbenzenepropanol (Majantol) was positive in 0.2% to 1.4% of routinely tested patients,^{60,73,77,81,90,91} and oxidized linalyl acetate scored 2.2% positive reactions in Sweden, with only 0.2% for the unoxidized test material.^{92,93} In the United States, cinnamal

TABLE 7. Prevalence of Sensitization to 26 Fragrances Labeled in the EU in Routine Testing^{60,77,83,84,88,89}

Fragrance	Range + Reactions	Average + Reactions*
<i>E. furfuracea</i> extract	1.5%–3.3%	2.45%
HICC [†]	1.3%–4.8%	2.39%
<i>E. prunastri</i> extract [‡]	1.2%–2.1%	1.65%
Isoeugenol [‡]	0.9%–2.6%	1.58%
Cinnamyl alcohol [‡]	0.6%–2.5%	1.49%
Cinnamal [‡]	1.2%–1.9%	1.47%
Hydroxycitronellal [‡]	0.6%–2.2%	1.25%
Citral [†]	0.3%–1.6%	0.84%
Eugenol [‡]	0.3%–1.3%	0.68%
Farnesol [†]	0.3%–0.9%	0.53%
Hexyl cinnamal [†]	0.3%–0.6%	0.48%
Geraniol [‡]	0%–1.0%	0.48%
Butylphenyl methyl propional	0.3%–0.7%	0.45%
Coumarin [†]	0.05%–0.6%	0.31%
Amycinnamyl alcohol	0.1%–0.6%	0.30%
Citronellol [†]	0.1%–0.9%	0.29%
Linalool (not oxidized) [§]	0.1%–0.6%	0.28%
Benzyl alcohol	0.1%–0.4%	0.20%
Benzyl salicylate	0.1%–0.3%	0.19%
α -Isomethyl ionone	0%–0.6%	0.16%
Methyl 2-octynoate	0%–0.3%	0.16%
Amyl cinnamal [‡]	0%–0.2%	0.14%
Anise alcohol	0%–0.2%	0.10%
Benzyl cinnamate	0%–0.2%	0.08%
Limonene (unoxidized) [§]	0%–0.2%	0.06%
Benzyl benzoate	0%–0.1%	0.04%

*Not adjusted for sample size.

[†]Present in FM II.

[‡]Present in FM I.

[§]Tested in 5 studies.

+, positive.

seems to be an important fragrance allergen with approximately 4% positive reactions in the studies of the NACDG.^{80–82}

Frequencies of Sensitization in Patients With Cosmetic Dermatitis

In patients experiencing allergic contact dermatitis to cosmetics, in studies published 30 years ago, 30% to 45% of the reactions have been caused by fragrances.^{33,34,94} It is very likely that the percentage would currently be considerably higher.

CLINICAL PICTURE OF ALLERGIC CONTACT DERMATITIS FROM FRAGRANCES

Contact allergy to fragrances most often causes (aggravation of) dermatitis of the hands, the face⁹⁵ and neck,^{96,97} and the axillae. Patches of eczema may also be observed in areas where perfumes are dabbed, such as behind the ears, upper chest, elbow flexures, and wrists.^{1,4} Women are more often affected than men and will typically give a history of a previous rash from a perfume (fine fragrance) or scented deodorant in the axillae.⁵ Indeed, the fragrances used in deodorants are an important, if not the most important, cause of induction and elicitation of fragrance allergy.^{5,98–100} It is recognized that the axillary skin is a problematic area because it is moist, occluded, and easily irritated. Men are primarily sensitized by deodorants and aftershaves. Microtrauma from shaving facilitates contact allergy to aftershave fragrances.^{3,4} After sensitization by products containing high percentages of fragrances, eczema may appear or be worsened by the use of a variety of product types with lower fragrance levels, including other cosmetics, household products, industrial products, and flavors.

The severity of dermatitis may range from mild to severe with dissemination. Most allergic reactions caused by fragrances are erythematous; more acute lesions with vesicles, oozing, and papules may sometimes be observed. Some cases resemble nummular eczema, seborrheic dermatitis, sycosis barbae, or lupus erythematosus. Pustular allergic contact dermatitis has rarely been described,¹⁰¹ as have erythema multiforme-like eruptions.^{102,103} Lesions in the skin folds may be mistaken for atopic dermatitis.

Hand eczema is common in fragrance-sensitive patients, and there is often a possible but not certain association between the dermatitis and fragrance sensitization.^{104–106} Patients may first have irritant dermatitis or atopic dermatitis, which is later complicated by contact allergy to products used for treatment or prevention (hand creams and lotions) of hand dermatitis or to other perfumed products in the household, hobby, or work environment.

Dyshidrotic eruptions and widespread eruptions are ascribed to ingestion of spices, notably in patients reacting to MP (systemic contact dermatitis, hematogenic contact dermatitis). Inhalation of high concentrations of fragrance contact allergens may also manifest hematogenic contact dermatitis in some individuals.¹⁰⁷ Atopic dermatitis located at other body sites, perianal dermatitis, and vulvar dermatitis may also be complicated by fragrance allergy. Allergic contact dermatitis in patients with psoriasis may present with a

mixed dermatitis—psoriasis picture from the Köbner phenomenon.¹⁰⁸ Fragrances present in topical pharmaceutical preparations, such as corticosteroids, anti-inflammatory drugs, wound healing, antiseptic-disinfectant, and antihemorrhoidal preparations, can cause iatrogenic allergic contact dermatitis.^{3,4}

Fragrance sensitization may lead to continuous or periodic dermatitis, sick leave, and impaired quality of life, especially in recently diagnosed young women.^{109,110}

Pigmented Cosmetic Dermatitis

In Japan, in the 1960s and 1970s, many female patients developed pigmentation of the face after having facial dermatitis.¹¹¹ The skin manifestations of this so-called pigmented cosmetic dermatitis consisted of diffuse or patchy brown hyperpigmentation on the cheeks and/or forehead, and sometimes, the entire face was involved. In severe cases, the pigmentation was black, purple, or blue-black, and in mild cases, it was pale brown. Occasionally, erythematous macules or papules, suggesting a mild contact dermatitis, were observed, and itching was also noted at varying times. Pigmented cosmetic dermatitis was shown to be caused by contact allergy to components of cosmetic products, notably essential oils, other fragrance materials, antimicrobials, preservatives, and coloring materials.^{53,111,112} The number of patients with pigmented cosmetic dermatitis decreased strongly after 1978, when major cosmetic companies began to eliminate strong contact sensitizers from their products.⁵³ Since 1980, pigmented cosmetic dermatitis has become a rare disease

TABLE 8. Fragrances that Have Caused Pigmented Cosmetic Dermatitis^{53,111–113}

Benzaldehyde
Benzyl alcohol
Benzyl propionate*
Benzyl salicylate ^{114,115}
Cedrol methyl ether
Cinnamyl alcohol
Citral diethyl acetal*
5-Cyclohexadecenone*
Eugenol
<i>E. prunastri</i> (oakmoss) extract
Geraniol ¹¹⁶
Hydroxycitronellal
Ionone
α -Isomethyl ionone
Isosafrole
Methoxycitronellal*
Methyl- α -ionone
Methyl isoeugenol
Musk moskene
Rose ketone-4
Tetramethyl acetyloctahydronaphthalene
5,5,6-Trimethylbicyclohept-2-ylcyclohexanol
Vetiveryl acetate*

*Has only caused pigmented cosmetic dermatitis in Japan in the past; details not available.

in Japan.¹¹³ Fragrances that have been implicated as causes of pigmented cosmetic dermatitis are shown in Table 8.

PRODUCTS RESPONSIBLE FOR ALLERGIC CONTACT DERMATITIS FROM FRAGRANCES

Approximately 80% of the positive patch test reactions to FM I and FM II are clinically relevant.^{8,3} Perfumes and deodorants are the most frequent sources of sensitization to and allergic contact dermatitis caused by fragrance ingredients in women, whereas after-shave products and deodorants are most often responsible in men. Thereafter, eczema may appear or be worsened by contact with other fragranced products, such as cosmetics, toiletries, household products, industrial substances, and flavorings.^{3,8,59}

Products that have caused allergic contact dermatitis from fragrances in (convincing or likely) case reports or case series with the responsible fragrances are shown in Table 9. Details with corresponding literature for all cases have been published recently.¹

OCCUPATIONAL CONTACT DERMATITIS FROM FRAGRANCE ALLERGY

General

It may be expected that fragrances will cause dermatological problems for workers in the cosmetics industry (cosmetic chemists, workers handling the raw materials and the final products, salespeople), beauticians, hairdressers, and aromatherapists (the latter group especially from essential oils).³ Analyses of IVDK data indeed showed an increased risk of fragrance allergy among masseurs/physiotherapists and also for beauticians, nurses, geriatric nurses, and metal surface workers exposed to metalworking fluids.^{117,118} It was found that metalworkers added fragrances to the metalworking fluid to mask their odor.¹¹⁹ Remarkably, hairdressing was not an occupation associated with an increased risk. Housewives and cleaning personnel may also be endangered by frequent contact with soap, cleansers, dishwashing liquids, and other fragranced products.³

Despite this, surprisingly, little information on occupational allergic contact dermatitis from fragrances can be found in literature. This may be because in most people at risk, a definite relationship between dermatitis and fragrances is hard to prove. In many occupations (hairdressers, beauticians, housewives, health personnel,¹²⁰ cleaning personnel), irritant factors may also be relevant in the etiology of dermatitis, and sometimes other allergens are considered of paramount importance. In addition, nonoccupational exposure to fragrances also occurs in virtually everybody.³

It seems that fragrances may play a role in some cases of occupational contact dermatitis, but in no single profession are they a major cause of occupational allergic contact dermatitis, and rarely are they the sole etiological factor.³ However, fragrances may play an important role in aggravating hand eczema of other origin (atopic hand eczema, irritant dermatitis, allergic contact dermatitis) by contact with hand cleansers, barrier creams, moisturizing preparations, and so on. In addition, flavors and spices

may be involved in occupational contact dermatitis in bakers, cooks, caterers, and others working in the food industry.¹²¹ Only limonene,¹²² citral,¹²³ and cinnamal have caused a considerable number of occupational sensitizations.³

Case Series

In an early study, all workers in a factory became sensitized to cinnamal.¹²⁴ In Germany, 26 female workers in a perfume factory were investigated, of whom 6 had dermatitis of the hands, the forearms, and the face. All 26 were tested with 4 perfumes from the factory and 30 of their ingredients, both individual fragrance compounds and essential oils. The 6 patients with eczema had many positive reactions. Twelve others were also sensitized to fragrances but never developed allergic contact dermatitis from working in the factory. The high prevalence of fragrance allergy (18/26, 69%) in this population was the result of poor work hygiene and permanent direct and airborne skin contact. The degree of automation was very low; even the bottle-filling machines had to be operated by hand.³¹

For 2 years, 5 beauticians working in the same high-end luxury health spa in the United Kingdom developed bilateral hand dermatitis from citral present in massage products and essential oils.¹²³

In Finland, in 2008–2013, occupational limonene allergy was observed in 14 workers who used limonene-containing machine-cleaning detergents and hand cleansers, surface cleaners, or dishwashing liquids. In 3 cases, the occupational limonene allergy resulted from work-related use of limonene-containing leave-on cosmetic products.¹²²

Case Reports

Case reports and a few small case series of occupational allergic contact dermatitis from specific fragrances (cases caused by fragrances where the causative fragrance chemical was not identified^{125–127} were excluded) are shown in Table 10.

OTHER ADVERSE EFFECTS OF FRAGRANCES

Other adverse effects reported from fragrances include immediate-type reactions (mostly nonimmune immediate contact reactions, contact urticaria), photosensitivity, respiratory disorders, and miscellaneous adverse effects including irritant contact dermatitis, depigmentation, and systemic adverse effects. None of these currently cause significant clinical problems.

Immediate-Type Reactions

Several fragrances have been reported to cause immediate-type reactions, mostly nonimmune immediate contact reactions (synonym: contact urticaria). Well-known examples are MP, cinnamal, and cinnamic acid (important ingredient of MP). These substances can, in the proper concentration and vehicle, induce immediate contact reactions in most healthy individuals, mostly with erythema only, sometimes with wheals. Other fragrances that

TABLE 9. Products That Have Caused Allergic Contact Dermatitis From Fragrances*¹

Product	Causative Fragrances [†]
Cosmetics	
Aftershave	Cinnamyl alcohol; eugenol; <i>E. prunastri</i> (oakmoss) extract; hydroxycitronellal; isoeugenol; linalool; methyl 2-octynoate
Bath product	Hydroxycitronellal
Deodorant/antiperspirant	Acetylcedrene; benzyl salicylate; butylphenyl methylpropional; coumarin; <i>E. prunastri</i> (oakmoss) extract; farnesol; geraniol; hexyl cinnamal; hydroxycitronellal; HICC; isoeugenol
Eye cosmetic	Isoeugenol
Eye cream [‡]	Allyl cyclohexylpropionate; caprylic alcohol; heliotropine; heptanal; musk; nonanal; nonyl alcohol
Fine fragrance (perfume)	Benzyl salicylate; benzylidene acetone; butylphenyl methylpropional; citral; coumarin; α -damascone; eugenol; <i>E. prunastri</i> (oakmoss) extract; farnesol; <i>cis</i> -3-hexenyl salicylate; hexyl cinnamal; hydroxycitronellal; HICC; α -isomethyl ionone; limonene; linalool; methyl ionones; musk xylene
Foundation lotion/tonic	Hydroxycitronellal; isoeugenol; musk moskene
Hair conditioner	Benzyl salicylate
Hair cream	Eugenol
Hair dye	Benzyl alcohol
Hair lotion	Hydroxycitronellal; linalool; musk ketone
Hair pack	Limonene
Lip cosmetic	Benzyl alcohol; cinnamal; cinnamyl alcohol; citral; geraniol; maltol; methyl 2-octynoate
Make-up, face	Citronellol; geraniol; hydroxycitronellal
Massage cream	Eugenol
Massage oil	Geraniol
Moisturizer	Benzyl alcohol; <i>E. prunastri</i> (oakmoss) extract; limonene; linalool; musk moskene
Mouthwash	Eugenol; menthol
Nail polish remover	Benzyl salicylate
Permanent waving solution	<i>E. prunastri</i> (oakmoss) extract
Rouge	Musk moskene
Shampoo	Benzyl salicylate; limonene; linalool
Shampoo, dry	Cinnamyl alcohol; linalool
Shaving foam	Geraniol
Shower gel	Benzyl salicylate; limonene
Skin care product	Citronellol; dihydrocitronellol; hexyl cinnamal; hydroxycitronellal; α -isomethyl ionone; linalool; methyl 2-octynoate
Soap	Geraniol
Sunscreen	Amyl cinnamal; benzyl alcohol; cinnamyl alcohol; eugenol; <i>E. prunastri</i> (oakmoss) extract; geraniol; linalool
Toilet paper/wet wipe/tissue	Cinnamyl alcohol; linalool
Toothpaste	Amyl cinnamal; anethole; carvone; cinnamal; eugenol; menthol
Cosmetics, unspecified	Amyl cinnamal; amylcinnamyl alcohol; anise alcohol; benzyl alcohol; benzyl benzoate; benzyl cinnamate; benzyl salicylate; butyl acetate; butylphenyl methylpropional; cinnamal; cinnamyl alcohol; citral; citronellal; citronellol; coumarin; <i>E. furfuracea</i> (treemoss) extract; <i>E. prunastri</i> (oakmoss) extract; farnesol; geraniol; hexyl cinnamal; hydroxycitronellal; HICC; isoeugenol; α -isomethyl ionone; limonene; linalool; musk ambrette; trimethylbenzenepropanol
Essential oils	Cinnamal; citral; citronellal; eucalyptol; geraniol; geranyl acetate; limonene; linalool; myrcene; α -phellandrene; α -pinene; β -pinene; α -terpinene; terpinolene
Foods, spices, and beverages	Cinnamal; eugenol; limonene
Pharmaceutical products	Amyl cinnamal; amylcinnamyl alcohol; anethole; benzyl alcohol; benzyl benzoate; benzyl salicylate; camphor; cinnamal; cinnamyl alcohol; coumarin; eucalyptol; eugenol; geraniol; heliotropine; hydroxycitronellal; limonene; menthol; methyl salicylate; musk ketone; terpineol; thymol; vanillin
Household products	
Cleanser	Limonene
Fabric softener	Benzyl salicylate
Floor mop	Limonene
Washing detergent	Anethole; eugenol; hydroxycitronellal; limonene; linalool

(Continued on next page)

TABLE 9. (Continued)

Product	Causative Fragrances [†]
Washing-up liquid	Geraniol; limonene
Miscellaneous products	
Breath freshener	Cinnamal; cinnamyl alcohol
Cigarette	Menthol
Cod liver oil	Coumarin
Dentistry materials [§]	Eugenol
Exfoliating socks	Linalool
Insect repellent (wipe)	Hydroxycitronellal; linalool
Incense	Musk ambrette; santalol
Lichens	<i>E. prunastri</i> (oakmoss) extract
Odor-masking powder	Cinnamal
Ostomy deodorant	Citronellal; <i>E. prunastri</i> (oakmoss) extract; limonene
Paint stripper	Limonene
Skin softener plant extract	Cinnamal; cinnamyl alcohol
Throat spray	Menthol
Occupational products	
Baking powder	Anethole
Bark of aspen	Salicylaldehyde
Cleanser	3-Carene; limonene; terpinolene
Coolant	<i>E. prunastri</i> (oakmoss) extract
Cosmetics	Citral
Cutting oil	Benzyl alcohol
Degreasing product	Limonene
Dental materials	Eugenol
Essential oils	β-Caryophyllene; citral; geraniol; limonene
Foods, spices, and beverages	Benzyl alcohol; cinnamal; limonene
Fragranced powder (noncosmetic)	Cinnamal
Glue	Benzyl alcohol
Massage cream/oil	Citral; eugenol
Paint thinner	Limonene
Perfume/fragrance	Benzaldehyde; camphor; cinnamal; citronellol; dipentene; geraniol; linalool; methyl 2-octynoate; phenylacetaldehyde; vanillin
Permanent waving solution	<i>E. prunastri</i> (oakmoss) extract
Pinewood sawdust	Limonene
Pressure additive	Limonene
Skin protection cream	Citronellol; geraniol
Solvent	Limonene
Wax polish	Limonene

*Case reports of photoallergic contact dermatitis are not mentioned in this table.

[†]Includes occupational contacts.

[‡]All fragrances mentioned in the right column reacted when the components of the perfume in an eye cream were tested in a female patient previously shown to be allergic to the cream; however, they were negative on retesting.^{44,45}

[§]Impression materials, filling materials, dental cements, endodontic sealers, periodontal dressing materials, and dry socket dressings.

^{||}Includes contacts with the pure fragrance chemical.

have been reported as causes of contact urticaria are shown in Table 11.^{164–168} Only a few have caused 1 or more clinical cases of immediate contact reactions, but rarely from their presence in a perfume (geraniol, terpinyl acetate). All others have been shown to induce such reactions in patch testing with them, where the materials were removed after 20 to 30 minutes. Usually, however, there was erythema only. Currently, fragrance materials seem not to cause clinical problems from immediate-type reactions. However, it cannot be excluded that such reactions may be responsible for

mild intolerance symptoms that are experienced by some users shortly after application of fragrances or fragranced products.

Photosensitivity

At the end of the 1970s up to the mid-1980s, the fragrance material musk ambrette caused many cases of photoallergic contact dermatitis, especially in men, mostly from its presence in aftershave lotions.¹⁷⁹ Also in the late 1970s, an epidemic of photocontact dermatitis

TABLE 10. Case Reports of Occupational Allergic Contact Dermatitis From Specific Fragrances

Occupation	Culprit Product(s)	Culprit Fragrance(s)	Reference
Aromatherapist(s) (1 or 2)	Essential oils	β -Caryophyllene; geraniol (n = 2); linalool; linalyl acetate; α -pinene (n = 2)	128
Baker	Cinnamon	Cinnamal	129
Baker	Cinnamon	Cinnamal	130
Bakers (n = 2)	Baking cake	Anethole in aniseed oil	131
Bakers (n = 2)	Cinnamon	Cinnamal	132
Beauticians (n = 5)	Cosmetics and essential oils	Citral	123
Bottle fillers (n = 6)	Perfumes	Benzaldehyde (n = 3); camphor (n = 2); cinnamal (n = 2); citronellol (n = 1); dipentene (n = 3); geraniol (n = 6); linalool (n = 3)	31
Car mechanic	Degreasing agent	D-Limonene	133
Car mechanic	Pinewood sawdust	Limonene	134
Confectioner	Cardamom powder	Limonene	135
Dental assistant	Liquid dental material	Eugenol	136
Dental nurse	Restorative material	Eugenol	137
Dentist	Washing-up liquid	Geraniol	138
Elk researcher	Bark of aspen	Salicylaldehyde	139
Engineer	Coolant	Oakmoss extract	140
Food handler	Beverages	Benzyl alcohol	141
Geriatric nurse	Aftershave	Oakmoss extract	142
Hairdresser	Permanent waving solution	Oakmoss extract	143
Handler of vinyl covers	Odor-masking powder	Cinnamal	144
Histopathology medical worker	Solvent	Limonene	145
Honing machinists (n = 3)	Honing oil	Dipentene (DL-limonene)	146
Installer of windows	Degreaser	Limonene	147
Joiner in perfume factory	Phenylacetaldehyde	Phenylacetaldehyde	148
Laboratory assistant	Methyl 2-octynoate and methyl octine carbonate	Methyl 2-octynoate and methyl octine carbonate	149
Machine cleaner	Cleanser	3-Carene and terpinolene	150
Masseuse	Massage oil	Geraniol	151
Mechanic	Hand cleanser	Limonene	152
Metal grinder	Cutting oil	Benzyl alcohol	153
Metal worker	Protection cream	Geraniol	154
Not specified (n = 6)	Cleaning products	D-Limonene	133
Not specified (n = 4)	Fruits, flavors, vegetables	D-Limonene	133
Painter/car mechanic	Wax polish	Dipentene (DL-limonene)	155
Painter/decorator	Hand cleansers	D-Limonene	156
Paint mixer in car factory	Paint thinner	Dipentene (DL-limonene)	157
Parquet layers (n = 2)	2-Part glue catalyst	Benzyl alcohol	158
Physiotherapist	Massage cream	Eugenol	159
Porter	Lemon oil	Limonene	160
Production worker	Vanillin	Vanillin	161
Restaurant worker	Cinnamon	Cinnamal	132
Waiter	Cassia extract	Cinnamal	162
Worker in fragrance plant	Perfume concentrates	Cinnamal	152
Workers in spice factory (n = 3)	Cinnamon powder	Cinnamal	163

occurred in people using a popular sunscreen with an increased level of 6-methyl coumarin.¹⁸⁰ The reactions occurred primarily in women and developed within several hours after they applied the suntan lotion and went into the sun. The reactions were particularly severe, requiring hospitalization in many cases. Most of the patients' eruptions took weeks to resolve and left (temporary) hyperpigmentation.¹⁸⁰

These fragrances were banned by the International Fragrance Association and are not used anymore. Other fragrances that have caused photocontact allergy are shown in Table 12. Musk ketone, musk moskene, musk tibetene, and musk xylene have only photo cross-reacted to musk ambrette. The other fragrances showed some positive photopatch tests performed in groups of patients suspected

TABLE 11. Fragrances That Have Caused Immediate-Type Reactions^{164–168}

Amyl cinnamal
Amylcinnamyl alcohol
Anise alcohol
Benzaldehyde ¹⁶⁹
Benzyl alcohol*, ¹⁷⁰
Benzyl benzoate
Camphor
Carvone ¹⁷¹
Cinnamal ^{169,172}
Cinnamic acid
Cinnamyl alcohol
Coumarin
Ethyl vanillin ¹⁷³
Eugenol ¹⁷⁴
<i>E. prunastri</i> (oakmoss) extract
FM I and II
Geraniol ¹⁷⁵
α -Isomethyl ionone ¹⁷⁶
Limonene
Menthol ¹⁷⁷
Methyl salicylate
<i>M. pereirae</i> resin
Terpinyl acetate ¹⁷⁸
Vanillin

*Some cases of contact urticaria, but mostly immediate-type reactions from benzyl alcohol present as preservative in drugs for injection.

of having photosensitivity disorders including photosensitivity dermatitis with actinic reticuloid syndrome,¹⁸¹ but their relevance was never mentioned. Photosensitivity to fragrances currently seems not to be a problem, considering the absence of published case reports.

Respiratory Disorders

Fragrances are volatile, and therefore, in addition to skin exposure, a perfume also exposes the eyes and nasorespiratory tract. Already 35 years ago, it was suspected and later confirmed that fragrances can induce or worsen respiratory problems including asthmatic attacks.^{185–187} People may experience symptoms not only from wearing perfume themselves but also around cosmetic counters, candle shops, and from perfumes worn by other people. Currently, it is estimated that 2% to 4% of the adult population is affected by respiratory or eye symptoms from such exposures.¹⁸⁸ Frequently reported symptoms include dry, itching, or watery eyes; nasal irritation; congestion; and sneezing; as well as mouth and throat irritation, shortness of breath, and cough. Generally, ocular and nasal symptoms are reported more frequently than respiratory symptoms at other locations.¹⁸⁹

In one investigation, a significant association has been found between respiratory complaints related to fragrances and contact allergy to fragrance ingredients, in addition to hand eczema.¹⁹⁰ In another study, however, inhalation of high concentrations of fragrance contact allergens in allergic individuals induced some subjective symptoms in a few subjects, but without objective changes.¹⁰⁷

The mechanisms by which fragrance chemicals induce respiratory symptoms in some individuals are unclear. There are no indications that immunological processes are generally involved, but sensory mechanisms may influence the symptoms.^{189,191}

As to specific fragrance materials, airway irritation has been observed from limonene, and asthma and/or rhinitis has been ascribed to eugenol, limonene, menthol, methyl salicylate, and vanillin (Table 13).

Miscellaneous Adverse Effects

Other adverse effects attributed to fragrances are shown in Table 13. The causal relationship was not always established beyond doubt.

SUMMARY

This article gives an overview of fragrance allergy. The following subjects are discussed: composition of perfumes, contact with fragrances, diagnosing fragrance allergy, frequency of allergy, clinical picture of allergic contact dermatitis, culprit products, occupational contact dermatitis, and other adverse effects of fragrances.

The use of fragrances, either as single chemicals or mixtures such as essential oils and botanical extracts, is ubiquitous and not limited to perfumes and other cosmetics. Other scented items include household products, topical drugs, paper products, industrial products, and foods and drinks (flavors). In cosmetics and household products, linalool and limonene seem to be most frequently present, followed by citronellol, geraniol, hexyl cinnamal, butylphenyl methylpropional, and benzyl salicylate.

Fragrance allergy is an important cause of allergic contact dermatitis. The pooled prevalence of reactions to FM recently calculated to be 3.5%, and to MP (balsam of Peru, a marker of fragrance allergy), 1.8%. In a study in the general population, 1.9% of the subjects had

TABLE 12. Fragrances That Have Caused Photosensitivity Reactions¹⁸¹

Acetyl hexamethyl indan
3-Carene
Cinnamal*
Cinnamyl alcohol
Coumarin
Eugenol*
<i>E. prunastri</i> (oakmoss) extract*
FM I
Hydroxycitronellal*
Methyl anthranilate
6-Methyl coumarin ^{180,182*}
Musk ambrette ^{179,183,184*}
Musk ketone
Musk moskene
Musk tibetene
Musk xylene
<i>M. pereirae</i> resin*

*Also immediate-type photoreactions reported (mostly interpreted as phototoxicity).

TABLE 13. Other Adverse Effects Attributed to Fragrances

Adverse Effect	Implicated Fragrances
Airway irritation	Limonene ¹⁹²
Alopecia (reversible)	<i>M. pereirae</i> resin ¹⁹³
Asthma and/or rhinitis	Eugenol; limonene; menthol ¹⁹⁴ ; methyl salicylate ¹⁹⁵ ; vanillin ¹⁹⁶
Bullous pemphigoid	Benzyl benzoate ¹⁹⁷ ; cinnamal ¹⁹⁸
Conjunctival cicatrization	Cinnamal ¹⁹⁹
Depigmentation	Benzyl alcohol ²⁰⁰ ; cinnamal ²⁰¹
Depigmented airborne contact dermatitis	Musk ambrette ²⁰²
Irritant contact dermatitis	Benzyl benzoate ²⁰³ ; citral ²⁰⁴ ; eugenol; isoeugenol; limonene ²⁰⁵ ; menthol; methyl salicylate
Irritant contact mucositis	Eucalyptol
Nonthrombocytopenic purpura	Menthol
Oral lichen planus	Cinnamal ²⁰⁶ ; eugenol
Orofacial granulomatosis	Carvone ²⁰⁷ ; cinnamal; cinnamyl alcohol; piperitone ²⁰⁷
Pigmented contact dermatitis	Musk ambrette ^{208,209} ; see also Table 8
Poikiloderma of Civatte	Unspecified ²¹⁰
Psoriasis (Köbner reaction)	Linalool ¹⁰⁸
Systemic adverse effects	Benzyl alcohol; benzyl benzoate; benzyl salicylate; camphor ^{211,212} ; eucalyptol ²¹¹ ; menthol ²¹¹ ; methyl salicylate ²¹³ ; thymol ²¹⁴
Urticaria	Cinnamal ²¹⁵ ; eugenol; methyl salicylate ²¹⁶

a positive patch test to FM II. The author of this article estimates that up to 4.5% of the adult population in certain countries may be allergic to fragrance materials (which does not mean that all these individuals experience or have experienced fragrance-allergic contact dermatitis). In consecutive patients patch tested for suspected contact dermatitis, the frequency of positive reactions to fragrance materials in some centers may even reach 20% to 25%. Women are more often allergic to fragrances than men, and the prevalence rises with increasing age.

More than 160 fragrance chemicals have been reported to cause contact allergy or allergic contact dermatitis. For a large number of these, (very) few data are available with regard to frequency of sensitization and relevance of positive patch test reactions. The most frequent sensitizers are linalool and limonene hydroperoxides, HICC, treemoss and oakmoss absolute, isoeugenol, cinnamyl alcohol, and cinnamal.

When fragrance allergy is suspected on the basis of the patient's history or clinical picture, it is advisable to test not only the baseline series, containing 3 markers for fragrance allergy (FM I, FM II, MP), but also an additional series of fragrances as well, because these markers fail to detect a considerable number of sensitizations. More than 50 fragrance chemicals are commercially available for patch testing. It is advised that a fragrance series should minimally contain the 8 ingredients of FM I (amyl cinnamal, cinnamal, cinnamyl alcohol, eugenol, *E. prunastri* extract [oakmoss absolute], geraniol, hydroxycitronellal, isoeugenol), the 6 of FM II (citral, citronellol, coumarin, farnesol, hexyl cinnamal, HICC), linalool and limonene hydroperoxides, butylphenyl methylpropional, and *E. furfuracea* extract (treemoss absolute). Which other chemicals (or essential oils) would qualify has not adequately been investigated.

Many individuals with contact allergy to fragrance ingredients are aware that they cannot tolerate scented products on their skin. However, in a recent study, 75% of patients who proved to be

fragrance allergic by patch testing were not aware of this before. Perfumes and deodorants are the most frequent sources of sensitization to and allergic contact dermatitis caused by fragrance ingredients in women, whereas aftershave products and deodorants are most often responsible in men. Thereafter, eczema may appear or be worsened by contact with other fragranced products, such as cosmetics, toiletries, household products, topical pharmaceuticals, industrial substances, and flavorings. Occupational contact dermatitis from fragrances is seen occasionally.

Other adverse effects of fragrance chemicals have included immediate-type reactions (notably MP, cinnamal, cinnamic acid), photosensitivity (musk ambrette, 6-methyl coumarin), respiratory disorders, and various other adverse effects. In the latter category, the causal relationship between effect and fragrance was not always established beyond doubt. Adverse effects from fragrances other than allergic contact dermatitis currently seem to be rare, based on lack of published evidence.

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