

Fragrance Allergic Contact Dermatitis

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Fragrances are a common cause of allergic contact dermatitis in Europe and in North America. They can affect individuals at any age and elicit a spectrum of reactions from contact urticaria to systemic contact dermatitis. Growing recognition of the widespread use of fragrances in modern society has fueled attempts to prevent sensitization through improved allergen identification, labeling, and consumer education. This review provides an overview and update on fragrance allergy. Part 1 discusses the epidemiology and evaluation of suspected fragrance allergy. Part 2 reviews screening methods, emerging fragrance allergens, and management of patients with fragrance contact allergy. This review concludes by examining recent legislation on fragrances and suggesting potential additions to screening series to help prevent and detect fragrance allergy.

Fragrance products are ubiquitous in today's world. Fragrance materials are used as flavoring agents in oral hygiene products, foods, and drinks. In industrial products, they are found in paints, rubber, plastics, insecticides, and herbicides; in the household, in paper products, fabric and clothes, sunscreens, as well as topical medicaments. Within its more commonly known realm of use in cosmetics and toiletries, fragrances are present in lip balms, lipsticks, deodorants, lotions, creams, wet wipes, and a variety of baby products.¹ Nearly everyone is exposed to fragrances and mostly on a daily basis.

Not surprisingly then, fragrances are the most common cause of allergic contact dermatitis (ACD) from cosmetic products² and are the second most common cause of positive patch test results after nickel.³ Worldwide, the incidence of a positive patch test result is 4% to 11% for fragrance mix I (FMI)⁴ and 1.6% to 10.8% for *Myroxylon pereirae* (*M. pereirae*).⁵ Allergic contact dermatitis can have an extensive impact on individuals' lives because it often involves the face and hands and can affect fitness for work, quality of life, and frequency of sick leave.^{6,7}

The purpose of this review is to provide an update on fragrance contact allergy. Part 1 reviews the epidemiology, clinical patterns, and evaluation of suspected fragrance allergy. Part 2 reviews screening methods, emerging allergens, management of fragrance-allergic patients, recent legislation on fragrances, and public health options.

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Definition of Fragrances

International Fragrance Association (IFRA) defines a *fragrance ingredient* as "any basic substance used in the manufacture of fragrance materials for its odorous, odor-enhancing, or blending properties."⁸ Fragrances can be natural or synthetic: natural fragrances are typically isolated from plants and include materials such as balsams, essential oils, concretes, or absolutes. Synthetic fragrances are produced from chemical compounds with a simple odor. They are commonly used now because of their cost-effectiveness, purity, compatibility, and ease of quality control.⁹

Epidemiology

Fragrance allergy affects at least 1% of the adult population.^{9,10} The typical fragrance-allergic patient is female, in her mid-40s, with facial or hand eczema.^{11,12} Fragrance allergy peaks earlier for women compared with men (ie, sixth decade of life for women and seventh decade of life for men), likely caused by a higher use of fragranced products (eg, cosmetics) among women.¹³ Sensitization peaks at an older age because of age-related poor skin barrier function from asteatotic eczema,¹³ increased use of topical medicaments and over-the-counter emollients with fragrance, and/or cumulative exposure to these materials with age.¹⁴

Individuals working in health care (eg, medicine, dentistry, nursing, veterinary) have a high prevalence of allergy to FMI. In these occupations, irritant hand contact dermatitis from repeated washing often disrupts the skin barrier, allowing better allergen penetration. Subsequent application of soaps, antiseptic cleansers, and emollient creams containing fragrances introduces a source for allergen exposure.¹³ A North American Contact Dermatitis Group (NACDG) study examining the prevalence of occupation-related ACD among health care workers compared with non-health care workers found that sensitivity to *M. pereirae* (25% pet) was significantly more common among the former, especially among dentists.¹⁵

Food handlers have a higher risk for allergy to cinnamal, cinnamic alcohol, and *M. pereirae* from their frequent handling of

spices and essential oils. Dentists, through their exposure to eugenol in mouthwashes, dressings, impression materials, and periodontal packings, also have a higher risk for allergy to eugenol.¹⁶

Evaluation of Suspected Fragrance Contact Allergy

History

The workup of suspected ACD to fragrance begins with eliciting a history of use of cosmetics, toiletries, hygiene products, new products, and medicaments. Also important in the history are occupation, environment, hobbies, and exposure to light.⁹ First-time symptoms of fragrance allergy are often associated with deodorants.¹⁷ If occupation seems to be causative, material safety data sheets may help identify fragrance additives. It is also helpful to inquire about parents' or siblings' products because of potential exposure to their products, "connubial" dermatitis.¹⁸ Case reports of connubial ACD have been reported for perfumes,¹⁹ hair regrowth lotion,²⁰ fragrance in deodorant spray,²¹ and oak moss in aftershave lotion.²²

Modes of Contact

Contact allergy may result from direct application of an allergen to the skin or mucous membranes (eg, lotions, deodorants, toothpaste), contact with a contaminated fomite (eg, pillow), contact with products used by partners or coworkers, airborne exposure, or systemic exposure (eg, food flavorings, drinks).⁹

Physical Examination

Although any part of the body can be affected by fragrance allergy, common areas include the axilla, face, hands, neck (eg, "atomizer sign"²³), and well-circumscribed areas on the wrist and behind the ear where perfume may be dabbed on.^{9,24} Lesions are usually papular or vesicular, but the most common presentation is patchy dermatitis with eczematous papules. The distribution varies from widespread in a nummular pattern to erythroderma.²⁵ In chronic forms, lichenified pruritic plaques may be seen. Itch is a commonly expected symptom (Zug, KA. [KZug@hitchcock.org, e-mail, May 21, 2014].²⁵

Face

The face is often affected from direct application of cosmetics or indirect transfer from contaminated hands. The pattern of ACD may be patchy or bilateral or it may affect only part of the face. When a "rinse-off" pattern affecting the lateral sides of the face, forehead, eyelids, and, occasionally, the chest is noted, products applied to the scalp (eg, shampoo, conditioner, perm solution) should be suspected.²⁶ Other susceptible areas include the eyelids, owing to the thinness of the skin,²⁶ and the lips, especially the unkeratinized (mucocutaneous) epithelium.²⁷ Flavorings are often to blame when the lips are involved.²⁷

In men, fragranced aftershave products may cause eczema in the beard area and the adjacent neck. Men who wet shave compared with those who dry shave have an increased risk for fragrance allergy, likely from microtrauma and allergenic substances in shaving foam.²⁸

Axilla

Deodorants commonly cause fragrance ACD in both sexes because of the axilla's natural predisposition to moisture, friction, and occlusion, which reduces barrier function.²⁶ Shaving further disrupts the skin barrier and increases penetration of allergens. Deodorants often also contain irritants, which facilitate the sensitization response to an allergen.²⁹ According to a Danish study among individuals with eczema, deodorant allergy is often associated with positive patch test reactions to fragrance mix II (FMII) and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). This is not surprising, given that 50% of deodorants in the European market contain HICC.³⁰ Deodorants in spray formulation also cause more allergic reactions compared with the stick formulations even at equal concentrations.²⁹

Hands

Hand involvement may be the direct result of allergic contact sensitization or as a complication of irritant or atopic hand eczema. The number of positive patch test results correlates with the duration of hand eczema, which suggests that sensitization may complicate long-term hand eczema.²⁸ Nardelli et al³¹ reported that, in fragrance-allergic women, the hands are the most commonly involved area likely from the use of fragrance-containing household products, cosmetics including moisturizing lotions and creams, and topical medications. Although the hands are not the most commonly involved site in men, hand dermatitis in males is more often caused by occupation-related allergens.³¹

Anogenital

Although genital ACD is uncommon, among 37 patch-tested individuals with genital dermatitis, FMI and *M. pereirae* were the most common allergens.³² Fragrance is commonly added to topical products used in the genital area, which underscores the importance of using fragrance-free products in this area.³² Physical findings range from edema, erythema, and vesicles in the acute stage to hyperpigmented, lichenified plaques in the chronic stage.³³

Generalized

Fragrance allergy is also relevant in patients with a scattered, generalized dermatitis distribution.³⁴ In a cross-sectional analysis of NACDG data from 2001 to 2004, *M. pereirae* and FMI were among the 5 most frequently positive allergens in patients with scattered, generalized dermatitis. Men and individuals with a history of atopic eczema were, in particular, more likely to have scattered, generalized dermatitis.³⁴

Airborne

Classic airborne ACD involves the exposed areas of the face including the "V" of the neck, forearms, arms, behind the earlobe (the Wilkinson triangle), bilateral eyelids, nasolabial folds, and under the chin.³⁵ Exposed area dermatitis may be difficult to distinguish from photo-related dermatitis, but involvement of photo-protected sites such as the eyelids and the Wilkinson triangle is suggestive of the former.³⁶ Sources of fragrance-related

airborne ACD include plants, citrus fruits, and essential oils.³⁵ Hobbies, such as soapmaking, can also elicit airborne ACD from the fumes.³⁶ String-instrument musicians and athletes may develop colophony (rosin)-induced airborne dermatitis from rosin applied to strings and handgrip powder, respectively.^{37,38}

Factors Influencing Allergy

Dose of allergen per unit area of skin is one of the most important factors that influence the induction and elicitation of fragrance contact allergy. There is a higher risk for becoming sensitized when exposed to products of high concentration in a small area of skin compared with products of low concentration over a large area of skin.¹² Consequently, perfumes, which are often applied over a small surface area, carry a higher risk for inducing sensitization. Other factors influencing sensitization include the region of application, individual level of sensitivity, exposure time, occlusion, the combination of allergens/irritants, potential for synergistic response, and abraded skin.¹² Areas that are occluded or abraded through shaving (ie, axilla, face) increase the risk for contact allergy. Individuals sensitized by a high concentration of allergens also acquire greater sensitivity compared with those sensitized through a low concentration. The former group of individuals is more likely to respond with ACD upon re-exposure. With low concentrations, longer exposure times (ie, weeks) may be required to elicit a reaction compared with high concentrations.¹²

Consumer products containing a combination of allergens and irritants (eg, shampoos, detergents, deodorants) may elicit a greater response compared with exposure to single ingredients. Similarly, fragrance allergens combined in a single product (eg, hydroxycitronellal and oak moss) can cause a synergistic response.³⁹

Spectrum of Reactions

Fragrance allergens can elicit a spectrum of reactions including contact urticaria (*M. pereirae*, cinnamic aldehyde, cinnamal, FMI),^{1,9,40} delayed hypersensitivity, irritant contact dermatitis, photo-allergic dermatitis (sandalwood oil, oak moss),²⁸ respiratory tract irritation, asthma exacerbation, and systemic contact dermatitis.⁹ Pigmented contact dermatitis and berloque dermatitis, once prevalent, have decreased over the years from growing recognition of their causative allergens, coal tar dyes and bergamot oil, respectively.^{9,41}

Irritant contact dermatitis has been reported by Rothenborg et al⁴² among cleaning personnel using a citral-containing detergent. The patients experienced a burning sensation when their hands were submerged in hot detergent solution. On patch testing at both hot and cold temperatures, citral was a strong primary irritant at high temperatures only.

Eye and airway symptoms can result from exposure to volatile fragrances.³⁷ These reactions may be elicited simply by others wearing perfume, other persons' clothes washed in fragrant fabric softener, entering places with air fresheners, or entering recently cleaned places. Symptoms usually begin within seconds to minutes after exposure to fragrance products.⁴³

Lastly, among sensitized patients, systemic contact dermatitis can be induced through ingestion or inhalation of allergens. Schnuch et al⁴⁴ observed that, upon inhalation of isoeugenol and HICC, flares of eczema lesions could be elicited in areas protected by clothing among presensitized patients.

Patch Testing

Delayed-type hypersensitivity to a fragrance material is established by diagnostic epicutaneous patch testing. A patient with suspected contact allergy should be tested with a standard screening series and to his/her own products. "Leave-on" personal care products including lipstick, makeup, deodorant, creams, and lotions are tested "as is." "Rinse-off products," such as hand soap, hair conditioner, shampoo, shave preparations, toothpaste, and liquid soaps should be diluted to 2% aqueous solution or not tested.⁴⁵ In general, leave-on products are safe for closed patch testing, but rinse-off products are likely to be irritating when tested undiluted. Open testing can be tried with irritating substances, but it is less reliable than closed patch testing.⁴⁶ In an open test, the product is applied uncovered to the upper arm or upper back twice a day for at least 2 days without washing the area.⁴⁷ Perfumes may be tested at 10% to 30% concentrations in petrolatum or alcohol. Individual components, if available, may be diluted to 1% or 5% concentrations.^{9,48} If an essential oil allergy is suspected, patients may be patch tested with the essential oils diluted to 1% with alcohol or 2% in petrolatum.⁴⁹ as well as their own products.⁵⁰ If contact urticaria is suspected, readings should be performed 15 to 60 minutes after application.¹⁸

A positive reaction to FMI, *M. pereirae*, or colophony suggests fragrance allergy. An unknown or positive reaction to FMI without any reaction to other fragrance indicators or the patient's products may represent an irritant reaction, rather than a true allergy. Although it is rarely done because of practical reasons, it may be useful to further investigate by patch testing the patient's own leave-on products again, the 8 individual ingredients in FMI, and sorbitan sesquileate 20% in petrolatum.⁹ Sorbitan sesquileate is a common emulsifier found in skin-care products, topical steroids, moisturizers, antifungal creams, and toothpaste.⁵¹ It is also found in FMI (Trolab, Chemotechnique) to allow adequate dispersion of its 8 constituents⁵² and enhance the diagnostic power of patch test materials.⁵³ However, it also increases the number of irritant patch test reactions.⁵⁴ Fragrance mix II, a mix of 6 fragrance materials (Chemotechnique), does not contain sorbitan sesquileate, and contains paraffin instead to improve dispersion.^{55,56}

Repeated Open Application Test

Certain patch test allergens such as FMI can have a high prevalence of weak positive reactions but low relevance because of irritancy.^{56,57} To help determine the clinical relevance and evaluate whether a patient with a positive patch test result to a fragrance allergen may safely use a scented product, a repeated open application test (ROAT) can be conducted. In a ROAT, a putative product (eg, lotion) containing "fragrance" on the label is applied twice daily on the

antecubital skin for 7 to 14 days.^{58,59} A positive ROAT reaction is defined as erythema, infiltration (edema), and scaling at the site of application.⁶¹

Part 2

Screening Methods for the Detection of Fragrance Allergy

For the vast majority of patients who are patch tested for suspected contact dermatitis, allergy to a fragrance material is discovered through the use of a screening allergen series. Patch test screening series most commonly used in the United States include the TRUE (thin-layer rapid use epicutaneous test), the NACDG screening series, and the American Contact Dermatitis Society (ACDS) core series.

TRUE Test

Fragrance allergens in the TRUE test include (1) FMI (430 mcg/cm²) and (2) *M. pereirae* (800 mcg/cm²). Table 1 provides a listing of the constituents in FMI, summary information, and pertinent findings identified in recent studies. Colophony (1200 mcg/cm²) is also an allergen on the TRUE test that can be considered a fragrance-related allergen. The TRUE test is often used as a first-line screening series, given its simplicity and cost-effectiveness.^{51,72}

Fragrance Mix I

FMI (also known as “Larsen Mix”) was originally designed in the 1970s by Dr Walter Larsen when he was investigating allergic reactions to fragrances in Mycolog cream (Bristol-Myers Squibb, Princeton, NJ).^{56,73,74} His findings on which fragrances were responsible for allergy later informed his choice of allergens included in FMI,⁷⁴ some of which are still part of the current mix. In the original FMI, the concentration of each allergen was 2%, but this was lowered to 1% in 1984 because of large numbers of irritant reactions.⁵⁶ FMI (Chemotechnique Diagnostics Mx0776⁷⁵) has since become a global standard for testing or confirming allergy. FMI and *M. pereirae* are among the top 5 most frequently positive allergens in the TRUE test.⁷⁶

Among 13,332 patients patch tested in Europe from 1990 to 2011, a total of 9.6% reacted positively to FMI and 6% to FMII.⁷⁷ Among 4232 individuals patch tested by the NACDG from 2011 to 2012, a total of 12.1% tested positive for FMI and 5.2% to FMII (Zug, KA. [KZug@hitchcock.org, e-mail, May 21, 2014]). The FMI-positive patch test was deemed possibly relevant in 60.5% of positive patients and probably relevant in 29.7% of positive patients. Fragrance mix I was the second most commonly positive allergen in this NACDG 2-year cycle and FMII was the tenth most frequently positive allergen in the screening series (Zug, KA. [KZug@hitchcock.org, e-mail, May 21, 2014]).

Myroxylon Pereirae

M. pereirae is derived from a Central American tree⁷⁸ and is used as a marker for fragrance allergy. Derivatives of this complex resin are present in a wide spectrum of products from drugs to foods. The most important allergen of *M. pereirae* is formed by the

polymerization of a “protoresin,” an ester of benzoic acid or cinnamic acid and coniferyl alcohol.³¹ In 1982, IFRA banned the use of crude *M. pereirae* in perfumes. However, extracts and distillates can still be used in perfumes.⁷⁸ The frequency of positive patch test results to *M. pereirae* resin (25% pet) in 4234 patients tested by the NACDG from 2011 to 2012 was 7.9%. This was down from 11.9% in 2005 to 2006 and 11.0% in 2007 to 2008. *M. pereirae* was the fifth most frequently positive allergen in the NACDG 2011 to 2012 cycle and was deemed possibly relevant in 52% and probably relevant in 36.5% (Zug, KA. [KZug@hitchcock.org, e-mail, May 21, 2014]).

Multiple studies and case reports have shown that exposure to constituents of *M. pereirae* in food can elicit a systemic contact dermatitis.⁷⁹ Foods containing *M. pereirae*-related constituents include marmalade, juice with pulp, cinnamon, ginger, ketchup, pickles, wine/beer/gin, flavored tea, pizza and tomato-containing products, as well as spiced soft drinks (eg, Dr Pepper).⁸⁰

NACDG Standard Series

The NACDG screening series over the last 20 years has included FMI and *M. pereirae*. Additional fragrance allergens contained in the current 2013–2014 NACDG screening include (1) FMII (14% pet) and (2) various essential oils including tea tree oil, lavender oil, peppermint oil, ylang ylang oil, jasmine absolute, and propolis.

Fragrance Mix II

Table 2 provides a listing of the constituents in FMII, summary information, and pertinent findings identified in recent studies.

As much as 33% of fragrance allergy may be missed by patch testing with only FMI.⁹² As a result, FMII was devised by Frosch et al in 2005 in a European multicenter study (Germany, Denmark, Sweden, United Kingdom, and Belgium) to supplement the original fragrance mix.^{55,78,93,94}

Essential Oils

Essential oils may each contain more than 100 constituents, including terpenes, sesquiterpene hydrocarbons, alcohols, aldehydes, and phenols.^{95,96} Reactions to essential oils include ACD, irritant contact dermatitis, phototoxic reactions, and contact urticaria.⁹⁶

Table 3 contains information about essential oil allergens in the 2013–2014 NACDG screening series.

ACDS Core Series

In an attempt to provide a recommendation to the dermatologist interested in testing with a more comprehensive screening patch test allergen series, the ACDS devised a core series of 80 patch test allergens sorted by decreasing prevalence of expected reaction frequency on the basis of prior published North American patch test results.¹¹¹

Compared with other national screening series, the ACDS core series contains similar but a greater number of allergens.⁵¹ Table 4 compares different fragrance allergens present in the ACDS core series, NACDG series, European series, British baseline series, German Contact Dermatitis Research Group series, and Swedish baseline series. Notable differences include the inclusion of sorbitan sesquiolate and tea tree oil in the ACDS series but not in

TABLE 1. Constituents of FMI (8% pet)

Allergen	Recent Studies
Geraniol (1% pet) • Fresh, flowery odor • Composed of a mixture of citral and 2 aldehydes (geranial, neral) • Autoxidizes in air to form sensitizing oxidation products: geraniol hydroperoxide, geranial, neral	Hagvall et al ⁶² : Among 2227 consecutive patch test patients in Sweden, oxidized geraniol detected more cases of allergy to geraniol than pure geraniol did (0.55% vs 0.13%). Hagvall et al ⁶³ : Murine local lymph node assay demonstrates that autoxidized mixtures of geraniol have greater sensitization potency than pure geraniol has.
Cinnamaldehyde (1% pet) • Spicy aroma • Found in deodorant, cinnamon bark, <i>M. pereirae</i> • IFRA concentration restriction of 0.02% in creams and lotions	Bruze et al ⁶⁴ : In Denmark, among 17 patients with dermatitis who have hypersensitivity to cinnamic aldehyde, deodorant containing cinnamic aldehyde at 0.01% to 0.32% wt/vol applied twice a day on healthy axillary skin can induce an allergic reaction.
Cinnamyl alcohol (1% pet) • Hyacinth-like odor • Found in deodorant, cinnamon bark, <i>M. pereirae</i> • May cross-sensitize with cinnamaldehyde through common hapten • IFRA concentration restriction 0.1% for deodorants, lip products	Foti et al ⁶⁵ : In Italy, all 15 patients with ACD or photo-ACD to topical ketoprofen were also allergic to cinnamyl alcohol. The authors propose cinnamyl alcohol as a potential marker for ketoprofen allergy.
Isoeugenol (1% pet) • Chrysanthemum-like odor • Found in domestic products, fine fragrances, nutmeg, ylang ylang oil	White et al ⁶⁶ : Incidence of isoeugenol allergy in the United Kingdom increased from 2.95% (2001) to 3.46% (2005), despite more stringent IFRA concentration restrictions from 0.2% to 0.02% in 1998. Increase in incidence may be from substitution of isoeugenol with similar compounds, such as isoeugenyl acetate and isoeugenyl phenylacetate.
Eugenol (1% pet) • Dental-type smell of cloves • Found in toothpaste, oral products, inhalers • High rate of simultaneous sensitivity with isoeugenol likely from concomitant sensitization	
Hydroxycitronellal (1% pet) • Lily-like scent • Used in decorative cosmetics, fine fragrances, shampoos, household cleaners, detergents • 1987: IFRA concentration restriction 1%	Svedman et al ⁶⁷ : Among 7 patients in Sweden with known hypersensitivity to hydroxycitronellal, hydroxycitronellal could still elicit axillary dermatitis when applied at low (0.032%) or high (0.32%) concentrations twice a day on healthy skin. Concentrations represent typical concentrations found in deodorants.
α -Amylcinnamaldehyde (1% pet) • Jasmine-like odor; floral, honey-like flavor in food • Found in soaps, detergents, perfumes	
Oak Moss (<i>Evernia Prunastri</i>) (1% pet) • Woody, earthy odor • Found in scented products marketed to men • Major allergens are oxidized resin acids (abietic acid, dehydroabietic acid), atranolol, chloroatranolol	Johansen et al ⁶⁸ : Among 13 patients previously shown to be patch test positive for oak moss absolute and chloroatranol, more than 90% of subjects developed a reaction to chloroatranol 0.0005% in open exposure testing. The ROAT tests were terminated on median day 4 because all test subjects developed positive reaction. As of 2003, chloroatranol is the most powerful allergen present.
SSO (5%) • Used as an emulsifier in FMI (Trolab, Chemotechnique) • Found in creams, medications, topical corticosteroids • Prevalence of allergy (tested at 20% pet) among patients with dermatitis ranged from 0.5 to 0.9%^{69,70}	Asarch et al ⁷¹ : Of 112 patch-tested patients with dermatitis, 8.9% reacted to SSO (20% pet). Seventy-five percent of SSO-positive individuals were using topical corticosteroids emulsified with sorbitan derivatives or sorbitol.

Allergeaze 2013–2014 series.⁶¹

SSO, sorbitan sesquioleate.

other series. In the United States, sorbitan sesquioleate is widely used in topical products. Because it is a component of FMI, testing sorbitan sesquioleate individually can be informative in a patient with a positive patch test result to FMI.⁵¹ Likewise, tea tree oil is

TABLE 2. Constituents of FMII (14% pet)⁶¹

Allergen	Recent Studies
HICC, Lyrall (2.5% pet) • Lily-like odor • Found in antiperspirants, alcoholic lotions, deodorant sticks, fabric softeners, surface cleaners, shampoo • Higher frequency of HICC sensitivity in Europe (2.1%) compared with North America (0.4%), likely caused by higher concentration of HICC in European deodorants³¹ Citral (1% pet) • Lemon-like odor; bittersweet taste • Found in domestic, occupational products; lemongrass, lemon/lime leaf oils • Debate over whether citral is a contact allergen or skin irritant^{82–84} Farnesol (2.5% pet) • Floral odor • Found in essential oils (neroli, tuberose, rose, lemongrass, musk), cosmetics, deodorants (used as a natural microbiocide) Coumarin (2.5% pet) • Sweet herbaceous odor • Found in cosmetic products (as fragrance or masking agent), food, tobacco Citronellol (0.5% pet) • Rosy, citrus, green odor; imitate citrus, peach flavors • Found in cosmetic, household products α-Hexyl cinnamal (5% pet) • Sweet, floral, citrus odor and taste • Found in cosmetics	Uter et al⁸¹: Risk factors associated with HICC sensitization: polysensitization (≥ 3 more positive reactions to unrelated allergens in baseline series), dermatitis of axilla, cosmetic exposure Heydorn et al⁸⁵: Citral is a common allergen in patients with hand eczema. In multicenter European study, 658 patients with hand eczema tested with 14 fragrances found in household products yielded a frequency of positive patch test results ranging from 0.3% (0.5% pet) to 4.3% (2% pet). Schnuch et al⁸⁶: Among 2021 consecutively tested patients in Germany, individuals who had positive patch test reactions to farnesol were more likely to be young females, office workers, with hands/face more commonly affected. Gilpin et al⁸⁷: No clear causative link that farnesol is a contact allergen. Two LLNAs suggest that farnesol is a strong sensitizer. Guinea pig maximization tests and predictive human data suggest farnesol is a nonsensitizer or has low potential for sensitization. Clinical reports show low-level or questionable reactions to farnesol. Vocanson et al^{88,89}: Previous reports of coumarin allergy may be caused by contaminants; pure coumarin is a weak sensitizer. In LLNAs, pure coumarin elicited no reaction, but commercially available coumarin-containing contaminants (eg, 6-chlorocoumarin, 3,4-dihydrocoumarin, and dibenzodioxocin) were found to be weak and moderate sensitizers. Yazar et al⁹⁰: One of the most commonly identified fragrances (32%) in a survey of 204 cosmetic products marketed in Sweden. Krautheim et al⁹¹: Among 35,633 patients with suspected ACD patch tested with FMII in Germany from 2005 to 2008, only 3.8% with a positive patch test reaction to FMII also had a positive reaction to α-hexyl cinnamal. Compared with other ingredients of FMII, the authors deemed α-hexyl cinnamal, coumarin, and citronellol to be of lesser importance.

*Allergeaze 2013–2014 series.*⁶¹
LLNA, local lymph node assay.

included in the ACDS core and NACDG 2013–2014 series because it is found in many over-the-counter products in North America⁵¹ and elicited positive patch test reactions in 1.4% of tested individuals in the 2005–2006 NACDG study.^{113,114} Conversely, Lyrall (hydroxyisohexyl 3-cyclohexene carboxaldehyde), a constituent of FMII, is included in the European series but not in the ACDS series because Lyrall dermatitis and sensitization frequency is much lower in North America (0.4%) compared with Europe (2.1%).^{31,110} The discrepancy in sensitization frequency is likely caused by higher Lyrall concentrations in European deodorants.³¹

Propolis is present in the ACDS core allergen patch test series and NACDG series but not in the TRUE test.

Propolis

Propolis, otherwise known as bee's glue, is a poplar-derived resinous substance collected by honeybees to maintain the structure of hives. It is composed of a mixture of wax, balsams, essential oils, cinnamic alcohol, and flavonoids.^{115,116} Propolis is commonly found in "natural cosmetics" including cough syrups, lozenges, shampoo, lip balms, lotions, toothpastes, and cosmetics.²⁴ It is thought to have

TABLE 3. Essential Oils Included in the NACDG Screening Series

Essential Oil	Reactions	Recent Studies
TTO (5% pet) - Marketed as a “natural” anti-inflammatory and topical antimicrobial agent - Found in shampoos, massage oils, aromatherapy candles, compresses, inhalers, mouthwashes, laundry detergents, fabric softeners, moisturizers⁹⁷	ACD, ⁹⁸ airborne facial lesions (inhalation for treatment of bronchitis), ⁹⁹ systemic contact dermatitis, ⁹⁹ erythema multiforme-like reaction, ⁹⁹ linear IgA disease ¹⁰⁰	Rudback et al ¹⁰¹ : Degradation products from photo-oxidation (e.g. α -terpinene) are powerful sensitizers. Old TTO- containing products may be more sensitizing than new ones
Peppermint oil (2% pet) - Composed of menthol and menthone - Provides fresh odor, topical cooling effects - Found in lip balms, mouthwashes, breath fresheners, toothpastes, teas, chewing gums⁵⁷	Allergic contact cheilitis (lip balm), ¹⁰² vulvar dermatitis (ingestion of peppermint tea), ¹⁰³ burning mouth syndrome, ¹⁰⁴ recurrent oral ulceration, ¹⁰⁴ oral lichenoid reaction ¹⁰⁴	
Lavender oil (2% pet) - Composed of linalool, linalyl acetate, camphor - Sweet, floral odor - Used as an antibacterial, fragrance, sedative, muscle relaxant, antidepressant - Found in soaps, cleansers, moisturizers, massage oils, aromatherapy oils¹⁰⁵	Irritant dermatitis, ACD, photo-dermatitis	Hagvall et al ¹⁰⁶ : Oxidized lavender oil, linalool, and linalyl acetate are sources of allergenic hydroperoxides and can elicit ACD Sköld et al ¹⁰⁷ : Autoxidation increases the sensitizing potency of linalyl acetate
Ylang ylang oil (2% pet) - Fresh, floral scent - Dihydrodi-isoeugenol and derivatives of geraniol and linalool are suspected allergens¹⁰⁸ - Used in aromatherapy	ACD	
Jasmine absolute (2% pet) - Used to treat apathy, hysteria, uterine disorder, cough, and muscular spasms of limbs¹⁰⁹ - Women are more likely than men to be allergic.¹¹⁰ - Used in aromatherapy	ACD	Uter et al ⁵⁰ : Among 15,682 patients patch tested with an essential oil from 2000 to 2008 in Europe, the frequency of positive patch test reactions to jasmine absolute was 1.6%.

IgA, immunoglobulin A; TTO, tea tree oil.

antibacterial, antiviral, antifungal, anti-inflammatory, antioxidant, and chemopreventive activities.¹¹⁵ Its main sensitizers are 3-methyl-2-butenyl caffeate and phenylethyl caffeate, and it also shares some minor sensitizers with *M. pereirae*.¹¹⁷

Propolis is a known cause of occupational ACD in apiarists¹¹⁸ as well as in violin players and stringed instrument makers through their exposure to propolis in varnish.¹¹⁶ Propolis is part of the standard testing series in Germany and Austria, where the sensitization frequency has previously been 3.5%.^{24,119} Interestingly, an online search of propolis yielded several products touted as “fragrance free” containing propolis.

“Emerging” Fragrance Allergens

Hydroperoxides of Linalool

Linalool is a synthetic and naturally occurring terpene found in natural oils, prestige perfumes, and deodorants in the European market.¹²⁰ Although pure linalool itself rarely causes positive patch test reactions, its primary oxidation products, linalool hydroperoxides, are important contact allergens.¹²¹ The oxidized forms are also more irritating to the skin compared with the nonoxidized counterparts.¹²²

In a Swedish study by Christensson et al,¹²¹ oxidized linalool in 6% or 11% petrolatum elicited positive patch test reactions in 5% to 7% of consecutive patients with dermatitis, which is as high as the prevalence for FMI or *M. pereirae* previously reported in Sweden.¹²³ The authors suggest testing oxidized linalool at 6.0% pet (2.4 mg/cm²).¹²¹

Oxidized Limonene

Limonene is commonly used in perfumes, household products, and, in high concentrations, for cleansing and degreasing agents. Similar to linalool, the nonoxidized state is relatively nonallergenic,^{120,124} but the oxidized forms of *R*-limonene (limonene oxide, carvone, and limonene 2-hydroperoxide) are irritating, especially the hydroperoxides.^{122,125,126} *d*-Limonene 2% pet was tested as part of the NACDG series from 2009 to 2012; however, it was removed from the series in 2013 to 2014 because of low frequency of positives (0.1% in 2009–2010).¹²⁷

In a multicenter European study by Matura et al,¹²⁵ 2.3% of consecutive patients with dermatitis were allergic to oxidized *R*-limonene, a frequency that is comparable with the top 10 substances of the standard series in Europe.¹²⁵ Furthermore, almost 50% of patients allergic to oxidized limonene had fragrance-related

TABLE 4. Comparison of Fragrances in Various Standard Series in 2013 to 2014

Allergen Core Series	Germany ¹¹² , (Cuddihy L info@smartpracticecanada.com, e-mail, January 29, 2014)					
	ACDS ¹¹¹	NACDG ⁷⁵	European ^{61,75}	United Kingdom ^{61,75}		Sweden ⁷⁵
<i>M. pereirae</i>	25% pet	25% pet	25% pet	25% pet	25% pet	25% pet
FMI	8% pet	8% pet	8% pet	8% pet	8% pet	8% pet
Colophony	20% pet	20% pet	20% pet	20% pet	20% pet	20% pet
FMII	14% pet	14% pet	14% pet	14% pet	14%	14% pet
Cinnamic aldehyde	1% pet	1% pet				
Propylene glycol	30% aq	30% aq				
Sorbitan sesquioleate*	20% pet					
Benzyl alcohol	10%	1% pet				
Propolis	10% pet	10% pet			10% pet	
Ylang ylang oil	2% pet	2% pet			10% (I & II)	
Jasmine absolute	2% pet	2% pet			5% pet	
Tea tree oil oxidized	5% pet	5% pet				
Non-ACDS Core Allergens						
Carvone		5% pet				
Lavender oil		2% pet				
Peppermint		2% pet				
Hydroxymethylpentyl- cyclohexenecarboxaldehyde (Lyril)			5% pet	5% pet	5% pet	
Sandalwood oil					10% pet	

*Not a fragrance ingredient but is added to FMI.

contact allergy or a history of adverse reaction to fragrances.¹²⁵ The authors recommend testing with 3% oxidized d-limonene.^{125,126} The 2014 Belgian standard series includes hydroperoxides of linalool (1.0% pet) and hydroperoxides of limonene (0.3% pet).⁷⁵

Case reports have demonstrated a wide variety of reactions to oxidized linalool and limonene. One 75-year-old woman with a 7-year history of hand dermatitis had 3+ patch reactions to linalool hydroperoxide, nonoxidized linalool, FMI, and FMII as well as 2+ reactions to limonene hydroperoxide, lavender absolute, ylang ylang oil, and citral. The dermatitis was exacerbated after gardening, peeling citrus fruit, and using lavender to make furniture polish. All her detergents were found to contain linalool or limonene. A 71-year-old woman developed a widespread eczematous eruption that worsened after exposure to pine trees and using a bottle of old perfume. She had 2+ reactions to linalool hydroperoxide and limonene hydroperoxide, 3+ reactions to FMII, as well as negative reactions to colophony. Many of her cosmetics and detergents contained linalool and limonene. With avoidance, her dermatitis improved. A 61-year-old woman experienced episodes of facial redness, swelling, and weeping for 4 years. She exhibited 2+ reactions to linalool hydroperoxide and 1+ reactions to *M. pereirae*, propolis, and *Evernia furfuracea* (tree moss). The episodes of facial eczema were associated with use of an herbal cosmetic cream containing essential oils that expired years prior.¹²⁸

Management of Patients With a Fragrance ACD

Advice for patients with fragrance allergy even among clinician experts runs the spectrum from full avoidance of anything fragrance-related to select avoidance. A very strict conservative approach is to

advise the patient with a positive patch test result to a fragrance allergen to avoid all topical leave-on and rinse-off products that have fragrance on the label and to only use products labeled as “fragrance-free.” Fragrance-free personal care toiletry and cosmetic alternatives for such a patient to choose from are very limited. This approach makes good sense in patients with a chronic dermatitis that is otherwise poorly controlled and recalcitrant. After 3 months of strict avoidance, if certain products with a fragrance material are desired by the patient, a limited “use test” can be performed before a more widespread use of the particular product (Zug, KA. [KZug@hitchcock.org, e-mail, May 21, 2014]. Patients with a relatively weak allergy may be able to tolerate certain scented products used infrequently and on the clothing.¹²

Total avoidance of fragrances is difficult because they are present in occupational cleansers, industrial, and consumer products. Furthermore, fragrance-free and “unscented” labels may be misleading because they can contain botanicals or “hidden” fragrance-related ingredients used to mask odor, preserve (eg, benzyl alcohol, propolis), or prevent infection (eg, hydroxycitronellal, propolis).¹²⁹ Alternatively, a fragrance may be present at a concentration that is below the threshold for labeling. Isoeugenol in deodorants can elicit allergic reactions at concentrations below its 0.001% threshold for labeling.¹³⁰

The Contact Allergen Management Program provided by the American Contact Dermatitis Society can help patients with ACD find products free of their patch test positive allergens. The Contact Allergen Management Program allows the provider to enter a patient’s known contact allergens and generate a list of products that are void of those substances, including cross-reactors.¹³¹

Patients with a positive patch test result for *M. pereirae* may benefit from a balsam-restricted diet. A study by Salam and Fowler⁸⁰ found that 50% of individuals who are patch-test positive for *M. pereirae* or FMI experience significant improvement in their dermatitis after following a reduced *M. pereirae* diet. Veien et al¹³² devised guidelines to help define which populations would benefit most from a restricted diet. These patients have a chronic dermatitis persisting for at least 1 year despite avoidance of known allergens, a dermatitis that symmetrically involves the hands and/or feet, anogenital area, and/or skin folds as well as a positive patch test result for *M. pereirae* and/or fragrance mix. Patients should be placed on a balsam-restricted diet for 8 weeks, and if the dermatitis improves, long-term compliance may be recommended. Individual food groups may be reintroduced every several weeks; if they exacerbate the dermatitis, these foods should be avoided in the future.¹³³

Lastly, if fragrance-sensitive patients choose to apply products with potential fragrance sensitizers,¹³⁴ they should be warned about applying these products in areas of skin that are potentially traumatized (eg, beard region, hands, shaved areas) or occluded (eg, axilla). Areas of high absorption (eg, eyelids, genitals, axilla) and areas of chronic dermatitis (eg, stasis dermatitis) should also be avoided. Furthermore, given that certain fragrance compounds such as geraniol, linalool, and limonene are known to autoxidize into allergenic products, a shelf life of 1 year is recommended to limit exposure to oxidative products. The lid should be replaced between uses of fragrance products to limit exposure to air and oxidation.¹²⁰

For connubial dermatitis, management involves the partner's cessation of use of the offending product.²¹ Diagnosing connubial dermatitis is challenging, but a clinician's suspicion may be raised when a positive patch test result fails to correlate with the products used by the patient. The clinician should then consider products used by the partners that match the distribution of dermatitis.²¹

Preventing exposure in infants and young children seems a very good idea because sensitization to an allergen generally, once acquired, is lifelong. Components of FMI have previously been detected in a vapo-spray deodorant for babies.²⁹ However, fragrance is common on ingredient labels for many other baby products, including wet wipes, creams for diaper rash, baby lotions, bubble baths, baby powders, and baby shampoos. The European Union (EU) currently has restrictions on labeling of allergenic fragrances in toys through the Cosmetics Directive as of July 20, 2013.^{78,135}

Fragrance Legislation

Because fragrance contact allergy has become an increasingly common and troublesome problem, attempts to prevent sensitization through allergen identification and labeling have increased.²⁸ In 2003, the EU passed the seventh amendment of the Cosmetics Directive, which mandates that cosmetic products containing any fragrance material include the word "parfum" in the ingredients list. In addition, it designated 26 fragrance chemicals that must be labeled 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 5).¹³⁶ The rule was extended to detergents in October 2005. These 26

substances were identified as important causes of contact allergy reaction in fragrance-sensitive individuals by the Scientific Committee on Consumer Products and Non-Food Products draft opinion in 1999.¹³⁶ However, the choice of allergens remains controversial,^{56,136} because expert groups have not reached a unanimous conclusion regarding the allergenic potential of the 26 fragrances.¹³⁶ In fact, Schnuch et al¹³⁷ in 2007 demonstrated that, whereas some of the fragrances are important allergens and clearly demonstrate allergenicity (Group I in Table 5), others are rare or nonsensitizers (Group III in Table 5). However, Van Oosten et al¹⁰ determined that certain clinical relevance exists for the majority of positive patch test results to the 26 EU-labeled fragrances.

The EU Cosmetics Regulation replaced the EU Cosmetics Directive on July 11, 2013, and additionally mandates the labeling of nanomaterial ingredients.¹³⁸

Impact of Fragrance Regulations

The level of benefit fragrance-allergic individuals in the EU derive from the "26 allergens rule" is unclear. More than 50% of cosmetic and cleansing products in Germany contain 1 of the 26 allergens,¹³⁶ and consumers continue to buy these brands despite the new ingredient declarations.¹³⁶ According to a 2007 questionnaire among individuals with ACD by Noiesen et al,¹³⁹ most individuals found International Nomenclature of Cosmetic Ingredients names difficult to remember and half indicated that they did not trust the indications on the labels. The EU's experience with more specific product labeling may help US policy makers determine whether similar legislation in the United States would benefit the public. Currently, in the United States, fragranced products covered under the Federal Food, Drug, and Cosmetic Act only need to list the word *fragrance* but not the specific fragrance materials in a product label.^{140,141}

It is uncertain whether a label containing 1 or several of the individual fragrance chemical names (eg, farnesol, linalool) is more helpful to the consumer who is told that they have an allergy to "fragrance" as a concept, for example, on the basis of a positive patch test result for FMI, rather than a label simply stating the word *fragrance*. Because most patch testing series are limited and not comprehensive, a label identifying any fragrance material content would seem to be, on the whole, more helpful to more consumers than individual names, which, although perhaps numerous and specific, may also be misleading and misinterpreted.

Public Health Options

Looking toward the future, there are several promising strategies to decrease sensitization and exposure to fragrance allergens. Structure-activity relationships can help predict the sensitization potency of new compounds introduced into the market. These predictions are based on chemical structures that have previously been shown to exhibit reactivity (eg, aliphatic aldehyde, α,β -unsaturated carbonyl groups).⁷⁸

To limit exposure, public health agencies may use multiple tactics. They can prohibit or restrict the maximum concentration of allergens in a product.²⁸ Chloroatranol and atranol, both found

TABLE 5. 26 Fragrance Allergens in the EU Cosmetics Directive

Name	Test Concentration ¹⁰	Allergen Group (Schnuch et al) ^{139*}	Products Containing the Allergen ¹³⁸
Amyl cinnamal	2%	III	Soap, cleansing products
Amylcinnamyl alcohol	1%	II	Perfumes, soaps, cosmetics
Benzyl alcohol	1%	III	Preservative, solvent
Benzyl salicylate	2%	III	Cosmetics, essential oils
Cinnamyl alcohol	2%	II	Cosmetics, laundry detergents, soap
Cinnamal	1%	I	Cosmetics
Citral	2%	II	Cosmetics, flavor in food
Coumarin	5%	II	Cosmetics, perfumes, pesticides
Eugenol	2%	II	Toothpaste, mouth wash, perfume, soap, antiseptics
Geraniol	2%	II	Perfumes, skin care
Hydroxycitronellol	2%	I	Cosmetics, perfumes, soaps, insecticides, antiseptics
Hydroxymethylpentyl-cyclohexenecarboxaldehyde (HICC, Lyrall)	2%	I	Cosmetics
Isoeugenol	2%	I	Essential oils, perfumes, cosmetics, soaps, detergents
Anisyl alcohol	5%	III	Perfume, flavor
Benzyl benzoate	5%	III	Antiparasitic insecticide, perfumes, plasticizer
Benzyl cinnamate	5%	II	Perfumes, cosmetics
Citronellol	2%	II	Essential oils, deodorants, midge spray
Farnesol	5%	I	Deodorants
Hexyl cinnamaldehyde	5%	III	Essential oils
Lilial (butylphenyl methylpropional)	1%	II	Cosmetics, washing products
d-Limonene	2%	III	Cosmetics, flavoring, botanical insecticide, cleaning products
Linalool	10%	III	Perfume
Methyl heptene carbonate	0.5%	III	Washing products
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (alpha-isomethyl ionone)	5%	III	Cosmetics, perfumes
Oak moss†	2%	I	Shaving products, deodorants
Tree moss†	2%	I	Shaving products, deodorants

*Group I: important allergens; positive reaction index except farnesol (number of positive reactions minus questionable and irritant reactions divided by the sum of all 3) and low positivity ratio except cinnamic aldehyde (percentage of + reactions out of total number of allergic reactions). Group II: lower sensitization frequency compared with group I. Group III: rare or nonsensitizers.

†Natural.

in oak moss, are extremely allergenic and, consequently, may be candidates for elimination from cosmetic products.⁷⁸ Fragrance companies can also substitute less allergenic compounds or avoid the use of fragrances that are not essential to function.³⁸ To reduce exposure to oxidized linalool and limonene, the recommended shelf life may be shortened and made clearer to the consumer through package labeling, or extended with antioxidants. IFRA recommends using antioxidants such as ascorbic acid, α -tocopherol, and butylated hydroxytoluene to limit the peroxide concentration to below 20 mmol/L.^{120,126} Such antioxidants serve to slow the oxidation process of products and are consumed as the product ages.

Finally, providing information to consumers through improved labeling (eg, clearer labeling, more visible placement on package) would allow consumers to avoid products containing their known allergens.²⁸ In a 2009 Danish survey by Lysdal et al,⁶ of 117 patients

with fragrance allergy, the majority found labeling to be helpful but found that clearer labeling, bigger letter size, and visible placement on the package would increase its benefit.⁷⁹

Potential Adjustments to Current Screening Panels

Several studies have pointed out that the current FMI contains fragrance materials to which there is now a low frequency of positive patch test results.^{9,61,137,142} As first suggested by De Groot and Frosch,⁹ geraniol and α -amylcinnamal are 2 such ingredients. Wohrl et al confirmed their speculation when only 0.9% of 747 patients with suspected fragrance allergy tested positive for geraniol and 0.3% to α -amylcinnamal.¹⁴² Consequently, replacing geraniol and α -amylcinnamal in FMI in the future may better reflect allergens that are now in more current use.

For replacing allergens, studies conducted by Hagvall et al⁶³ suggest that screening with oxidized geraniol along with geraniol and neral (metabolites of geraniol) could detect more cases of contact allergy to geraniol. Oxidized geraniol is more sensitizing compared with pure geraniol and detected more cases of allergy compared with its pure form (0.92%–4.6% vs 0.15%–1.1%).^{3,62} Furthermore, a large proportion of patients reacting positively to oxidized geraniol concomitantly reacted to other fragrance markers in the baseline series, which supports its clinical relevance. The authors recommend a patch test concentration of oxidized geraniol 6% in petrolatum.³ However, testing with oxidized geraniol alone is imperfect because it did not detect all cases of allergy to geraniol (missed 4/8 cases).

Alternatively, oxidized linalool or limonene could be added to screening trays. In 1 study, 57% of patients who were patch test positive for oxidized limonene did not react to FMI or *M. pereirae*. Consequently, it would likely be helpful to include oxidized limonene in a screening tray to avoid missing this fragrance allergen.¹²⁶

Will the current contents of FMI still reflect the most common allergens in products in the coming years? This review has suggested several candidates that show potential for improving the detection of contact allergy to fragrance materials. In addition, we have reviewed several primary and secondary prevention strategies that have the potential to reduce exposure to allergenic fragrances while still enabling the public to enjoy the benefits of fragrance.

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