A Whiff of Trouble: Navigating Allergic Contact Dermatitis to Fragrance

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PRACTICE **POINTS**

- Fragrance allergy is common due to daily exposure from many sources, ranging from personal care products and cosmetics to cleaning products, foods/spices, and workplace materials.
- More than 100 different fragrances can cause contact allergy, but patch testing in routine practice usually is limited to a few key screening allergens with important limitations.
- Fragrance avoidance is challenging, and comprehensive patient education is critical, including the provision of a list of safe products that are truly fragrance free.

Fragrances are found in abundance in everyday life—from obvious sources such as perfumes, colognes, and air fresheners, to not-so-common sources, such as workplace exposures. Problematically, even products labeled as "fragrance free" may contain covert fragrances. Patients and physicians alike should be aware that fragrances are a common cause of allergic contact dermatitis (ACD) and that patient education is critical to treatment success. In this review, we discuss the chemistry and epidemiology of fragrance ACD, patch test considerations, skillful patient education on avoidance, and potential pitfalls for patients with fragrance allergy—all to empower treating clinicians with the knowledge to effectively address patient needs.

Fragrances are complex organic compounds that are sufficiently volatile to produce an odor—most often a pleasant one—or at times intended to neutralize unpleasant odors. They can be further divided into natural fragrances (eg, essential oils) and synthetic ones. Fragrances are found in abundance in our daily lives: in perfumes; colognes; lotions; shampoos; and an array of other personal, household, and even industrial products (Table). These exposures include products directly applied to the skin, rinsed off, or aerosolized. A single product often contains a multitude of different fragrances to create the scents we know and love. To many, fragrances can be an important part of everyday life or even a part of one's identity. But that once-intoxicating aroma can transform into an itchy skin nightmare; fragrances are among the most common contact allergens.

Given the widespread prevalence of fragrances in so many products, understanding fragrance allergy and skillful avoidance is imperative. In this review, we explore important aspects of fragrance allergic contact dermatitis (ACD), including chemistry, epidemiology, patch test considerations, and management strategies for patients, with the goal of providing valuable clinical insights for treating physicians on how patients can embrace a fragrance-free lifestyle.

How Fragrances Act as Allergens

A plethora of chemicals emit odors, of which more than 2000 are used to create the fragranced products we see on our shelves today.[1] For many of these fragrances, contact allergy develops because the fragrance acts as a hapten (ie, a small molecule that combines with a carrier protein to elicit an immune response).[2] Some fragrance molecules require "activation" to be able to bind to proteins; these are known as *prehaptens*.[3] For example, the natural fragrance

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Common Products Containing Fragrance[1]

Cosmetics: cologne, perfume, makeup
Essential oils: lavender, tea tree oil, and many others (including aromatherapy and diffusers)
Foods/spices: cinnamon, clove
Household: hand/dish soap, laundry detergent, air fresheners, cleaning products
Industrial: plastics, rubber, glue, paint thinner, paint, solvents, waxes
Personal care: shampoos and other hair care products, moisturizer, sunscreen, deodorant/antiperspirant, shaving cream, mouthwash, toothpaste, wipes

linalool is generally considered nonallergenic in its initial form. However, once it is exposed to air, it may undergo oxidation to become linalool hydroperoxides, a well-established contact allergen. Some fragrances can become allergenic in the skin itself, often secondary to enzymatic reactions—these are known as *prohaptens*.[3] However, most fragrances are directly reactive to skin proteins on the basis of chemical reactions such as Michael addition and Schiff base formation.[4] In either case, the end result is that fragrance allergens, including essential oils, may cause skin sensitization and subsequent ACD.[5,6]

Epidemiology

Contact allergy to fragrances is not uncommon; in a multicenter cross-sectional study conducted in 5 European countries, the prevalence in the general population was estimated to be as high as 2.6% and 1.9% among 3119 patients patch tested to fragrance mix I (FMI) and fragrance mix II (FMII), respectively.[7] Studies in patients referred for patch testing have shown a higher 5% to 25% prevalence of fragrance allergy, largely depending on what population was evaluated.[1] Factors such as sociocultural differences in frequency and types of fragrances used could contribute to this variation.

During patch testing, the primary fragrance screening allergens are FMI, FMII, and balsam of Peru (BOP) (*Myroxylon pereirae* resin).[7] In recent years, hydroperoxides of linalool and limonene also have emerged as potentially important fragrance allergens.[8] The frequencies of patch-test positivity of these allergens can be quite high in referral-based populations. In a study performed by the North American Contact Dermatitis Group (NACDG) from 2019 to 2020, frequencies of fragrance allergen positivity were 12.8% for FMI, 5.2% for FMII, 7.4% for BOP, 11.1% for hydroperoxides of linalool, and 3.5% for hydroperoxides of limonene.[8] Additionally, it was noted that FMI and hydroperoxides of linalool were among the top 10 most frequently positive allergens.[9] It should be kept in mind that NACDG studies are drawn from a referral population and not representative of the general population.

Allergic contact dermatitis to fragrances can manifest anywhere on the body, but certain patterns are characteristic. A study by the NACDG analyzed fragrance and botanical patch test results in 24,246 patients and found that fragrance/botanical-sensitive patients more commonly had dermatitis involving the face (odds ratio [OR], 1.12; 95% CI, 1.03-1.21), legs (OR, 1.22; 95% CI, 1.06-1.41), and anal/genital areas (OR, 1.26; 95% CI, 1.04-1.52) and were less likely to have hand dermatitis (OR, 0.88; 95% CI, 0.82-0.95) compared with non–fragrance/botanical-sensitive patients.[10] However, other studies have found that hand dermatitis is common among fragrance-allergic individuals.[11-13]

Fragrance allergy tends to be more common in women than men, which likely is attributable to differences in product use and exposure.[10] The prevalence of fragrance allergy increases with age in both men and women, peaking at approximately 50 years of age, likely due to repeat exposure or age-related changes to the skin barrier or immune system.[14]

Occupational fragrance exposures are important to consider, and fragrance ACD is associated with hairdressers, beauticians, office workers exposed to aromatherapy diffusers, and food handlers.[15] Less-obvious professions that involve exposure to fragrances used to cover up unwanted odors—such as working with industrial and cleaning chemicals or even metalworking—also have been reported to be associated with ACD.[16]

Patch Test Considerations

Patch testing is essential to confirm fragrance allergy and guide treatment, but because there are so many potential fragrance allergens, there is no perfect patch test strategy. In a standard patch test series, the most important screening allergens are considered to be FMI, FMII, and BOP; tested together, they are thought to detect a large proportion of cases of fragrance allergy. Strikingly, in a large European study (N=1951), patch testing with the fragrance markers in the baseline panel failed to detect more than 40% of cases of allergy compared to testing with 26 individual fragrance allergens.[17] Other studies have reported that a smaller proportion of fragrance allergies are missed by

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using baseline screening allergens alone.[18,19] Limonene and linalool hydroperoxides also are potentially important fragrance allergens to consider adding to the patch test panel, as unoxidized limonene and linalool commonly are used in many products and could theoretically undergo auto-oxidation under use conditions.[8] However, because of the high number of irritant, questionable, and potentially false-positive reactions, the Information Network of Departments of Dermatology has recommended against adding these hydroperoxides to a standard screening tray for patch testing.[20] It must be remembered that a positive patch test to a fragrance does not necessarily represent ACD unless the patient has a clinically relevant exposure to the allergen.[21]

In patients who test negative to the baseline fragrance-screening allergens and in whom a high degree of suspicion remains, further testing with supplemental fragrance allergens (commercially available from patch test suppliers) is warranted.[17] The thin-layer rapid use epicutaneous (T.R.U.E.) test (SmartPractice) includes FMI and BOP but not FMII or linalool or limonene hydroperoxides. More comprehensive patch test panels are available that include additional fragrances, such as the North American 80 Comprehensive Series and the American Contact Dermatitis Society Core Allergen Series.[22-24] It is important to remain vigilant and consider expanded patch testing if patients initially test negative but suspicion remains.

Furthermore, patch testing with the patient's own products is an important consideration. Uter et al[25] evaluated patch testing using patients' perfumes, deodorants, and shaving lotions, and approximately 41% (53/129) of patients who tested positive to their own product tested negative for fragrance-screening allergens. Although it can be difficult to ascertain which exact component of a commercial product is the culprit, a positive patch test may still provide clinically relevant information for patients and treating physicians. In cases of questionable or weak-positive results, repeat testing or repeated open application tests can help re-evaluate suspected products.

Cross-reactivity should be considered when patch testing for fragrances. Atwater et al[10] found that cross-reactivity between FMI, FMII, and BOP was common; for instance, approximately 40% of patients testing positive to FMII or BOP also had positive reactions to FMI (522/1182 and 768/1942, respectively). Understanding this concept is important because in some cases (as detailed below) patients will need to avoid all fragrances, not just the ones to which they have previously been exposed, given the limitations on fragrance labeling in the United States. However, this may change with the Modernization of Cosmetic Regulation Act of 2022.[26]

Avoiding Fragrances: Improving Patient Education and Outcomes

Once a relevant contact allergy to fragrance is established after patch testing, successful avoidance is critical but challenging, as there are numerous potential pitfalls. Missing just 1 hidden source of fragrance exposure will often be the difference between success or failure. Dermatologists play a crucial role in guiding patients through the intricate process of identifying and avoiding potential allergens.

Optimal Safety: Embracing a Fragrance-Free Lifestyle

For fragrance-allergic patients, it generally is safest to completely avoid fragrance.

First, if a patient only shows positive patch-test reactions to fragrance screening mixes (and not to the particular fragrances in these mixes), there is no way to be certain which fragrances the patient needs to avoid.

Second, even if specific fragrance allergens are identified, numerous chemically related fragrances to which the patient may be allergic are not commercially available for patch testing. One review provided evidence of 162 fragrance allergens that have been documented to cause contact allergy.[1] Dermatologists generally patch test to screening mixtures and/or the 26 fragrance chemicals required on labels in European products (European Directive fragrance).[27] Therefore, there are more than 100 known fragrance allergens that are not routinely tested to which patients could be allergic.

Third, certain fragrances, such as limonene and linalool, are found in many products with fragrance, and it is difficult to find products without these substances. Limonene and linalool themselves are not potent allergens; however, upon air exposure, they may auto-oxidize to hydroperoxides of limonene and linalool, which are increasingly common positive patch tests.[19]

Additionally, patients should be advised that many products labeled "fragrance free," "unscented," or "free and clear" are not truly fragrance free, and patients should not choose products based on these claims. There are no legal definitions for these claims in the United States, and industries are allowed to choose the definition they prefer. Numerous products labeled "unscented" use this term to indicate that the product had an odor, the company used a masking fragrance to hide the odor, and then the product can be considered unscented. In many holistic stores, most products labeled "fragrance free" are only free of artificial fragrances but contain essential oils. Of the 162 documented fragrance allergens, 80 are essential oils.[6] Essential oils are perceived to be safe by the vast majority of the population because they are viewed as "natural" and "unprocessed" sources of fragrance.[28] However, numerous allergenic terpenes have been discovered in essential oils, including functionalized variations of alcohols (eg, geraniol, bisabolol) and aldehydes (eg, citronellal).[6] Essential oils also consist of nonterpenic compounds produced through the phenylpropanoids pathway, including eugenol and cinnamaldehyde. One review showed that most essential oils contain one or more European Directive fragrance.[29]

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Therefore, many products labeled "unscented," "fragrance free," or "natural" are not free of fragrance and may be unsafe for fragrance-allergic patients.

Although not required, manufacturers sometimes voluntarily list one or more of the 162 currently identified fragrance allergens on product labels. Also, there are more than 50 potentially allergenic essential oils that can be listed on labels by their common names or by genus or species. In addition, there are synonyms for fragrance, such as *aroma*, *parfum*, *perfume*, and *scent*. Therefore, there are several hundred different ingredient names on labels that indicate the presence of fragrance, and patients are very unlikely to successfully identify fragrance-free products by trying to read product labels on their own.

Lastly, in the United States product labels only require products to state that they contain "fragrance" and do not mandate the listing of specific fragrances. If a patient is allergic to a specific fragrance, there is no way to determine if that fragrance is present in these products. This will change with the enactment of Modernization of Cosmetics Regulation Act of 2022, which empowers the US Food and Drug Administration to require manufacturers to disclose many, but not all, fragrance allergens on the labels of cosmetic and topical products.[26]

For all these reasons, patients should be advised to use a medical database to choose safe alternative products instead of trying to read labels themselves to avoid fragrance. The American Contact Dermatitis Society's Contact Allergen Management Program (CAMP) database (https://www.contactderm.org/resources/acds-camp) is designed to identify safe alternative products for patients with contact allergies. When CAMP is programmed to avoid "fragrance," it will list only "safe" products free of all fragrances found in a comprehensive fragrance cross-reactor group.[30] This customizable database is available as an application that can be downloaded onto a patient's mobile device. Fragrance-allergic patients should be encouraged to use the CAMP application or other similar applications (eg, SkinSAFE)(https://www.skinsafeproducts.com/) to find all the products they use.

Potential Pitfalls in Fragrance Avoidance

Most physicians, even dermatologists, will not know which products on the market are fragrance free from a contact allergy standpoint. Patients should instruct their physicians to use the allergen-avoidance application of choice whenever recommending new topical products, whether prescription or nonprescription. In 2009, Nardelli and colleagues[31] found that 10% of topical pharmaceutical products contained a total of 66 different fragrance substances.

Individuals who are allergic to fragrance also can react to fragrances used by close contacts (ie, consort dermatitis).[32] Therefore, fragrance-allergic individuals who do not improve after changing their personal products should consider urging their spouses or significant others to choose their personal care products using an allergen-avoidance application. Also, physical contact with pets can cause reactions, and the use of a fragrance-free pet shampoo is recommended. Additionally, allergic individuals who are providing care for small children should select fragrance-free products for them.

Some of the most heavily fragranced products on the market are found at hair salons. One exposure to an allergen often can keep patients broken out for up to 4 weeks and occasionally longer, a typical frequency for salon visits—even if the individual is taking great care to avoid fragrance at home. Patients should be instructed to bring their own shampoo, conditioner, and styling products to the salon. These patients also should bring safe moisturizer and nail polish remover for manicures. Additionally, aromatherapy used in most massages can cause flare-ups, and it is recommended that allergic patients purchase fragrance-free massage oil to bring to their sessions.

Fragranced soaps and cleansers can leave a residue on the palmar surface of the hands and fingers. This residue may not meet the threshold for causing a reaction on the thick skin of these surfaces, but it is sufficient to passively transfer fragrance to other more sensitive areas, such as the eyelids. Passive transfer of fragrance can be a major source of allergen exposure and should not be overlooked. Allergic patients should be instructed to bring safe hand cleansers to friends' houses, restaurants, or work.

Airborne fragrances in a patient's environment can reach sufficient concentration to cause airborne contact dermatitis. In one case report, an Uber driver developed facial airborne ACD from a fragrance diffuser in his vehicle and his condition improved upon removing the diffuser.[33] Therefore, patients should be instructed to avoid fragranced diffusers, scented candles, room deodorizers, incense, and wax melts.

Fragrance in household products also can be an issue. Fragrance-allergic patients should be instructed to choose fragrance-free cleaning products and to avoid fragranced wipes on surfaces that may be touched. In addition, they should be instructed to use fragrance-free laundry products. It is not required for household products in the United States to list their ingredients, and the majority do not have complete ingredient lists. Therefore, it is imperative that the patient use an allergen-avoidance application that identifies products that have full ingredient disclosure and are free of fragrance.

For individuals who enjoy perfume and/or cologne, it may be possible for them to resume use of these products in some cases after their condition has fully cleared with complete fragrance avoidance. They should avoid spraying products into the air or applying them directly onto the skin and should instead dip a cotton swab into the perfume/cologne and dab a small amount onto their clothing. This technique can sometimes satisfy the patient and improve compliance.

If a patient who is allergic to fragrance does not clear after 6 weeks of complete fragrance avoidance, it is worth considering systemic contact dermatitis due to ingestion

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of fragrance-related substances in foods.[34] A large number of fragrance materials also are food flavorings. For patients allergic to a specific fragrance(s), systemic avoidance needs to be specific to the allergen, and the Flavor and Extract Manufacturers Association's flavor ingredient library is most helpful (https://www.femaflavor.org/flavor-library). If the patient is allergic to the complex mixture BOP, a balsam-free diet can be attempted.[35,36]

Final Thoughts

Dermatologists must equip themselves with the knowledge to educate fragrance-allergic patients on proper avoidance. The multifaceted nature of fragrance avoidance requires a personalized approach, combining label scrutiny, utilization of a safe-product application, and tailored recommendations for specific situations. By guiding patients through these complexities, dermatologists can empower patients to manage their fragrance allergy and enhance their quality of life.

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