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Fragrance Contact Allergy – A Review Focusing on Patch Testing

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Fragrance materials are widely used in various types of products in daily life and many of them can be contact sensitizers. Contact allergy to fragrances has been reported to be common worldwide. Unlike other groups of contact allergens such as metals and preservatives, fragrance materials in consumer products can be present as single fragrance chemicals or in the form of mixtures known as natural complex substances. Due to the complexity of the fragrance materials and the high number of fragrance substances known to cause contact sensitization, selecting suitable materials for patch testing is challenging. Emerging fragrance markers have been additionally introduced in different baseline series for screening to enhance the rate of fragrance contact allergy detection. Moreover, there have been continual updates on basic knowledge, clinical perspectives, sources of exposure, and regulations on the use of fragrance materials. Avoiding pitfalls while performing patch testing with fragrance test materials is also crucial and should not be overlooked. Therefore, this review aims to update knowledge to provide a high-quality holistic approach to fragrance contact allergy diagnosis and management.

Key words: patch test; fragrance mix; colophonium; limonene; linalool; essential oils; terpene; oxidation; TRUE test; IQ chamber; Finn Chamber; clinical relevance; cosmetic regulations.

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SIGNIFICANCE

Fragrances are among the most reported contact allergens. As several fragrance materials have been researched and used for patch testing to diagnose fragrance contact allergy, it is challenging for clinicians to understand the whole gamut. There has been a debate regarding which patch test preparations are beneficial for routine testing in baseline series. The complexities of fragrance chemicals and their use in products also cause difficulties in dealing with patch test results in patients. To provide the best patient care, having a profound understanding of fragrance contact allergy will allow clinicians to avoid pitfalls and test patients most advantageously.

Fragrances can be obtained through chemical extraction from nature, or synthesized through laboratory processes (1). They are usually low-molecular-weight chemicals and many of them have the capacity to cause skin sensitization. As they are extensively used and connected to use in close contact with the skin, they are amongst the most commonly reported contact allergens (2). More than 150 fragrance materials have been confirmed by *in vivo* and/or *in vitro* studies to be able to sensitize the skin (3).

CONTACT ALLERGY TO FRAGRANCES

Terms and definitions

The word "fragrance" *per se* is difficult to define exactly. Focusing on fragrance contact allergy, the terms used should be considered based on the definitions stated by world-recognized organizations, including the US Food and Drug Administration (4), European Commission (5), and Research Institute for Fragrance Materials, Inc. (6). Terms related to fragrance contact allergy are listed in **Table I**. The terms "fragrance substance" and "fragrance material" should be used when describing a single fragrance chemical or a fragrance mixture that is generally used in products. When a fragrance material is known to cause skin sensitization, it is called a fragrance allergen, which may contain a single or several chemicals as in a mixture.

Fragrance materials as contact allergens

Fragrance materials are usually a complex mixture. Fragrance contact allergy may mean allergy to a single fragrance chemical in analogue to nickel allergy but, as fragrance materials usually are natural complex substances (7), fragrance contact allergy may mean allergies to several defined fragrance chemicals. Most of the single fragrance chemicals of natural complex substances can be defined. However, there are often unidentified fractions.

Fragrance materials can be haptens, prehaptens, and/or prohaptens. The substances causing contact allergy are usually haptens, which are sensitizing chemicals that can penetrate through the skin and bind directly to the protein, resulting in a protein–hapten complex. However, many fragrance chemicals are prehaptens and/or prohaptens (8). Prehaptens and prohaptens are themselves non-sensitizing or low-sensitizing unless they are transformed to haptens outside and inside the skin, respectively (5, 8). A prehapten can be transformed into a hapten by oxidation or photoactivation (9). A prohapten

Table I. Common terms and definitions used to describe fragrance contact allergy

Terms	Definitions
Fragrance (4) Perfume (5)	"Any natural or synthetic substance or substances used solely to impart an odour to a product" OR "a complex mixture which may contain up to several hundreds of different fragrance ingredients" Generally used for any liquid mixtures or products used to emit a pleasant scent, such as eau de toilette and eau de parfum
Fragrance substance (5) Fragrance material (6)	"An organic compound with characteristic, usually pleasant odour", which by observation can be divided into 2 forms: 1. Single fragrance chemical 2. Complex fragrance chemical (fragrance mixture)
Single fragrance chemical	Any 'chemical' substance or material that acts as a fragrance Examples: hexyl cinnamic aldehyde, benzyl alcohol, and linalool
Fragrance mixture (6) Fragrance compound Fragrance oil	A "formulation" consisting of specific combinations of individual materials or mixtures, i.e., a fragrance mixture contains 2 or more chemical substances Examples: Fragrance mix I, Myroxylon pereirae resin, Jasmine absolute, Oakmoss (*Evernia prunastri*) absolute, and lavender oil
Natural complex substances (7)	A heterogeneous family of substances from nature that are notably used as ingredients in several products classified as food supplements, medical devices, cosmetics, and traditional medicines Myroxylon pereirae resin is one of the natural complex substances, whereas "Fragrance mix I" is not.
Fragrance ingredient (4)	Any single fragrance chemical entity or fragrance mixture used as a component in the manufacture of a product
Fragrance allergen	A fragrance material that has been found to be a contact sensitizer
Fragrance (patch) test preparation	A finished preparation containing a fragrance material(s) dissolved in a vehicle at a decided concentration used for patch testing
Flavour substance (5)	An organic compound, the same as described for a fragrance substance, used in foods, beverages, and dental products
Cosmetic product (4)	A finished cosmetic the manufacture of which has been completed

is transformed in the skin by bioactivation, mainly via enzyme catalysis (9). Examples of fragrance prehaptens that require air oxidation to cause contact allergy are linalool and limonene (5), whereas eugenol and isoeugenol are known as prohaptens (5, 9). Some fragrance materials can be both prehaptens and prohaptens such as geraniol and cinnamyl alcohol (9-11), whereas geranial can act as all 3: a hapten, a prehapten, and a prohapten (5).

Skin exposure to prehaptens remains the most problematic since it is difficult to know whether a prehapten has altered to a hapten(s) before skin contact. For example, linalool and limonene are prehaptens, as fragrance materials added to the products, whereas the oxidized forms are the haptens causing contact allergy. It is, therefore, impossible to establish positive clinical relevance exclusively by assessing the ingredient labels even if the prehaptens are among the allergens that must be declared. In order to establish the amount of each oxidation product of the prehaptens, chemical analysis has to be performed.

PATCH TESTING WITH FRAGRANCES

General considerations

Patch testing is the standard procedure used to diagnose contact allergy (12, 13). The baseline series are recommended by experts from different working groups and countries to be used for patch testing in consecutive patients for contact allergy screening. Fragrance markers have been continually introduced to baseline series for screening patch testing since the 1960s (14). The prevalence of fragrance contact allergy in the general population was 4.5% in Europe during 2008–2011 when patch tested with several fragrance markers, including fragrance mix (FM) I, *Myroxolon pereirae* resin (Balsam of Peru, BOP), colophonium, FM II, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), and sesquiterpene lactone mix (15). In routine patch testing, the prevalence of fragrance contact allergy reported is usually based on the tested substances included as fragrance markers, which might be different between clinics and research studies. Amongst the common fragrance markers within most baseline series, the highest prevalence of fragrance contact allergy has been reported to FM I, up to about 20% in dermatitis patients (3).

Having a positive patch test reaction to a fragrance test preparation means having a fragrance contact allergy. Having a contact allergy should not be confused with diagnosing allergic contact dermatitis. Allergic contact dermatitis to fragrances is a clinical diagnosis when there is clinical relevance of a positive patch test reaction(s), which means there must be evidence of skin exposure in a sufficient amount to the relevant fragrance materials causing dermatitis.

Clinical manifestations of fragrance contact allergy are varied. The main presentation is eczematous dermatitis or eczema (**Fig. 1**). Dermatitis or mucosal inflammation can appear in limited areas where a scented product is directly applied or spread in generalized fashion if the skin has been extensively exposed. In general, being of greater age has been found to be associated with fragrance contact allergy, presumably from constant exposure to scented products throughout the lifetime. Specifically from research studies, a high-age patient group was related to contact allergy to *Evernia prunastri* (Oakmoss) absolute and HICC (16). On the other hand, contact allergy to hydroperoxides of linalool and limonene was reported to be common in a younger group and children (17, 18). Regarding gender, females appeared to be more likely to have fragrance contact allergy than males, particularly, cinnamal, cinnamyl alcohol, isoeugenol, and geraniol contact allergies, whereas males were found to have a higher prevalence of contact allergy to Oakmoss absolute and coumarin (16, 19).

Common fragrance markers in the baseline series

Fragrance test preparations included in different baseline series may range from a few to more than 10 test prepa-

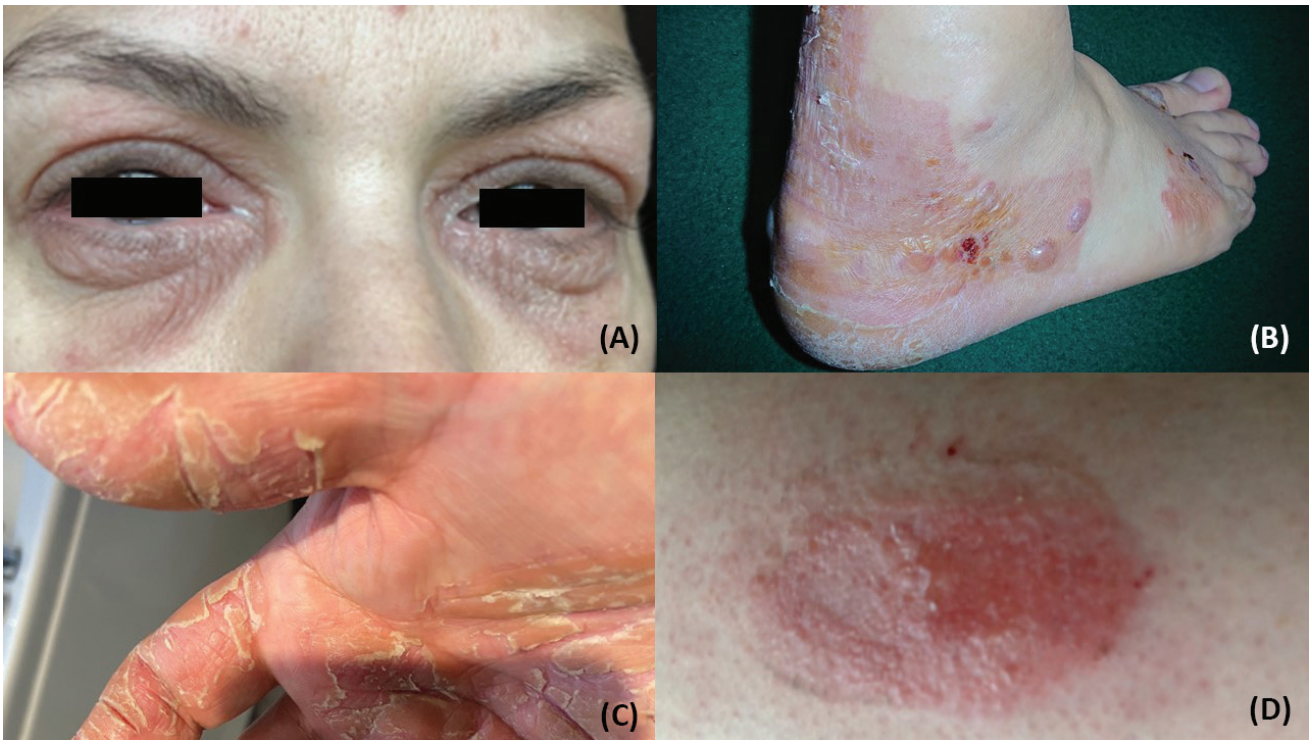

Fig. 1. Clinical manifestations in patients with contact allergy and allergic contact dermatitis to fragrances and/or fragrance markers. (A) a yoga instructor with periorbital dermatitis from essential oils; (B) a soldier with foot and ankle dermatitis from adhesive tapes used to prevent chafing when marching; (C) a medical staff member with hand eczema; (D) a patient with diabetes mellitus with dermatitis underneath a glucose sensor.

rations, including FM I, FM II, BOP, hydroperoxides of linalool and limonene, some essential oils, some individual ingredients of FM I and FM II, and other non-mix fragrances. In addition, colophonium, Compositae mix II/ sesquiterpene lactone mix, and phenol-formaldehyde resin-2 (PFR-2) are considered to be established/possible fragrance markers widely included in the baseline series (20–22). **Table II** summarizes commercially available patch test preparations used in baseline series for diagnosing fragrance contact allergy, their concentrations, vehicles, and important remarks.

Myroxylon pereirae resin, Fragrance Mix I, II, and their ingredients. BOP, FM I, and FM II are the most common mixture test preparations used for screening patch testing in most of the baseline series (3). As previously clarified, BOP, being a natural complex compound, actually contains several of the allergens included in FM I and II but at different concentrations (14). BOP was the earliest fragrance marker introduced in the baseline series (14). It is mixed in petrolatum at a concentration of 25% for patch testing (14). However, the number and concentrations of the individual fragrance chemicals in BOP have not been clearly described. Around a few hundred compounds have been identified, and many of them are potent sensitizers (14).

FM I and FM II altogether consist of 14 of the fragrance materials that have to be indicated in the cosmetics ingredient list when the concentrations exceed the limits (5, 23). The other fragrance materials (also called non-mix fragrances) can be tested separately. **Table III** demonstrates 26 fragrance materials included in European Union (EU) cosmetics regulation and concentrations used for patch testing in FM I and FM II and their ingredients as individual test preparations.

FM I preparation is mixed from known allergenic fragrance materials (24, 25). FM I contains 7 single-fragrance chemicals, Oakmoss absolute, and sorbitan sesquioleate as an emulsifier in the test preparation (Table III) (24–26). When FM I was first produced in the 1970s, the concentration was 16%, containing 2% of each ingredient (24). The concentration of FM I was later reduced from originally 16% to 8% (1% of each ingredient) because 16% was deemed to cause an irritant reaction, and 8% is still widely used (25, 27).

FM II comprises 6 prevalent fragrance allergens (Table III) (28). Unlike FM I, the individual ingredients of FM II are mixed in different concentrations (0.5% to 5.0% of each). FM II, at a concentration of 14% in petrolatum, was introduced and recommended for screening in the European baseline series in 2008, together with HICC, which is also one of the ingredients of FM II but tested separately at double the concentration of that in the mix (2.5% in FM II and 5% in the individual preparation) (28). Adding FM II as a screening patch test preparation has been found to improve fragrance contact allergy with a contact allergy rate of FM II up to 5% (28). Later in 2014, it was suggested that the separate patch test preparation with HICC be removed from the Swedish

Table II. Available patch test preparations in international and national baseline series used for diagnosing fragrance contact allergy

Test preparation (CAS #)	Concentration and vehicle	Remarks
Most commonly included in baseline series		
Myroxylon pereirae resin (Balsam of Peru) (8007-00-9)	25.0% pet.	– The first fragrance marker (1960s) – A mixture of hundreds of chemical substances with unknown exact concentrations – Sorbitan sesquioleate added as an emulsifier – Co-reactions with fragrance mixes, due to mutual haptens in the test preparation – Possible systemic exposure through spices and flavour additives in food
Fragrance mix I†	8.0% pet.	– Commonly identified fragrance haptens combined as a fragrance marker in the late 1970s – A mixture of 7 single fragrance compounds and Oakmoss absolute (1% of each) – Sorbitan sesquioleate added as an emulsifier – Usually demonstrates the highest rate of contact allergy among fragrance patch test preparations – Contains a few mutual fragrance allergens with *Myroxylon pereirae* resin
Fragrance mix II†	14.0% pet.	– Identified commonly found fragrance haptens combined as a fragrance marker in the 2000s to improve the diagnosis of fragrance contact allergy – A mixture of 6 single fragrance compounds – Not present in T.R.U.E. test panels
Colophonium (8050-09-7)	20.0% pet.	– A marker for fragrance contact allergy – Known as rosin, a type of resin from conifers – Mainly used as an adhesive substance – Contains terpenes, which are related to fragrance compounds – Oxidation products of resin and abietic acid are the main sensitizers (common sensitizers in Oakmoss and Treemoss extracts)
Sometimes included in baseline series		
Hydroperoxides of linalool‡ (linalool 78-70-6) *AND* Hydroperoxides of limonene‡ (limonene 5989-27-5, 5989-54-8, 138-86-3)	0.5% & 1.0% pet. 0.2% & 0.3% pet.	– Linalool and limonene are prehaptens – The major oxidation products are hydroperoxides: the culprit causes of contact allergy – The 2 most common fragrance materials used in consumer products in non-oxidized forms – As the substances are tested today, they may often yield doubtful reactions – Hydroperoxides of limonene test preparations may contain the contact sensitizer carvone (spearmint-like smell) in the test preparation** – Allergic contact dermatitis is difficult to diagnose as the amounts of hydroperoxides found in products have been found to be very low to cause an allergic reaction
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) (31906-04-4)	5.0% pet.	– A synthetic fragrance material – One of the ingredients in fragrance mix II – Was introduced to the European baseline series due to a high rate of contact allergy in 2008 – Has been recommended to be removed from the Swedish baseline series in 2014 due to the decreasing prevalence of contact allergy and its existence in FM II (2.5%) – Has been banned in cosmetics produced and marketed in the EU countries
Compositae mix II/sesquiterpene lactone mix (SLM)†	0.1% pet.	– Possible markers for fragrance contact allergy – Major sensitizing compounds in Compositae plant extracts – SLM contains each 0.033% of alantolactone (CAS 546-43-0), costunolide (CAS 553-21-9), and dehydrocostus lactone (CAS 477-43-0) – Simultaneous positive reactions with other fragrance markers
Occasionally included in baseline series		
Ylang-ylang oil (8006-81-3)	2.0% pet.	– Also called Cananga oil – Essential oil compriseing several fragrance compounds including linalool, geraniol, and benzyl benzoate – Has yielded the highest prevalence among essential oils tested – Present in the American Core, North American, Chinese, and German baseline series
Tea tree oil (oxidized) (68647-73-4)	5.0% pet.	– Essential oil with a mixture of terpene substances, mainly terpinen-4-ol(51) – May in part act as prehapten, i.e., oxidation products are more sensitizing – Present in the New Zealand, American core, Australian, and Chinese baseline series
Jasmine absolute (84776-64-7)	2.0% pet.	– Essential oil containing several fragrance compounds including benzyl acetate, benzyl benzoate, phytol, and linalool – Present in the American Core and German baseline series
Peppermint oil (8006-90-4)	2.0% pet.	– Essential oil with several fragrance compounds, such as menthol, menthone, limonene, carvone, linalool, linalyl acetate – Present in the American Core baseline series
Benzyl alcohol (100-51-6)	10.0% softisan	– Rare sensitizer (110) – Also used as a preservative in consumer products – Present in the American Core and Australian baseline series
Cinnamal (104-55-2) *AND* Isoeugenol (97-54-1) *AND* Geraniol (106-24-1)	1.0% pet. 2.0% pet. 2.0% pet.	– Ingredients of fragrance mix I – Sometimes suggested to be tested simultaneously with other fragrance mix I ingredients – Cinnamal: present in the North American and Chinese baseline series – Isoeugenol and geraniol: present in the Australian baseline series
Citral (5392-40-5)	2.0% pet.	– An ingredient in fragrance mix II – Sometimes suggested to be tested simultaneously with fragrance mix II ingredients – Present in the Australian baseline series
Evernia furfuracea extract (Treemoss absolute) (68648-41-9)	1.0% pet.	– Oxidized resin acids – Not included in fragrance mixes (a non-mix fragrance material) – Contains atranol and chloroatranol, as found in Oakmoss absolute – Reported to have the highest prevalence of contact allergy among non-mix fragrances – Present in the British baseline series
Benzyl salicylate (118-58-1)	10.0% pet.	– An ingredient in essential oils, mainly ylang-ylang oil. – Was more commonly reported to cause contact allergy in Japan than in Europe and the United States(111) – Present in the Chinese baseline series
Lichen acid mix†	0.3% pet.	– Contains each 0.1% of atranorin (CAS 479-20-9), evernic acid (CAS 537-09-7), and usnic acid (CAS 125-46-2) found in lichens – Humans could be sensitized to the substances in nature – Present in the Swedish baseline series
Phenol formaldehyde resin-2 (9003-35-4)	1.0% pet.	– A synthetic polymer based on phenol and formaldehyde used in industrial products – A possible marker for fragrance contact allergy – The same and similar components in PFR-2, colophonium, and fragrances are thought to be the cause of simultaneous positive reactions – Present in the Swedish baseline and the International Contact Dermatitis Research Group series

CAS: Chemical Abstracts Service number; Pet: petrolatum; EU: European Union. *Some are called "standard series". **Test preparations from Chemotechnique Diagnostics AB, Vellinge; Sweden. †Intentionally mixed for patch testing in a laboratory. ‡CAS not applicable for hydroperoxides.

Table III. List of the 26 allergenic fragrances in accordance with European Union regulations available for patch testing

Fragrance mix I			Fragrance mix II			Non-mix fragrances (30)	
	Concentration (%)			Concentration (%)			
Substance	Mix	Individual	Substance	Mix	Individual	Substance	Concentration (%)
Amyl cinnamal	1.0	2.0	Citral	1.0	2.0	Amyl cinnamyl alcohol	5.0
Cinnamal	1.0	1.0	Citronellol	0.5	1.0	Anise alcohol	10.0
Cinnamyl alcohol	1.0	2.0	Coumarin	2.5	5.0	Benzyl alcohol	10.0
Eugenol	1.0	2.0	Farnesol	2.5	5.0	Benzyl benzoate	10.0
Evernia prunastri (Oakmoss) absolute	1.0	2.0	Hexyl cinnamic aldehyde	5.0	10.0	Benzyl cinnamate	10.0
Geraniol	1.0	2.0	HICC*	2.5	5.0	Benzyl salicylate	10.0
Hydroxycitronellal	1.0	2.0				Butylphenyl methylpropional*	10.0
Isoeugenol	1.0	2.0				*Evernia furfuracea* (Treemoss) absolute	1.0
Sorbitan sesquioleate**	5.0	20.0				α-Isomethyl ionone	10.0
						D-limonene	10.0
						Linalool	10.0
						Methyl 2-octynoate	0.2

All test preparations are in petrolatum. HICC: Hydroxyisohexyl 3-cyclohexene carboxaldehyde. *Banned in European Union countries. **Not a fragrance material, used as an emulsifier in fragrance mix I.

baseline series as the positive reaction rate was low after being banned in EU countries, and the additional yield for detecting cases of fragrance contact allergy has been found to be minimal when compared with FM II in which it is still present (29).

Additionally, individual ingredients of FM I and FM II are sometimes tested in consecutive patients as screening allergens for fragrance contact allergy, which can help to detect an additional 10% of overall fragrance contact allergy patients (16). Patients with distinct single fragrance contact allergy or with a low reactivity might be missed if only the mixes are tested (16). In detail, patients who reacted positively to only one ingredient of FM I and/or FM II, or reacted weakly to the individual ingredients, might not demonstrate any positive reactions when tested with only the mixes in the baseline series (16).

Non-mix fragrances. Non-mix fragrances refer to the other 12 fragrance materials that are not included in FM I and FM II but have to be declared as product ingredients when the concentration exceeds the limits according to the EU cosmetics regulations (Table III). Standardized test doses (mg/cm^2) and concentrations (% w/w) have been recommended (30). Among these fragrances, *Evernia furfuracea* (Treemoss) absolute at 1% in petrolatum has been found to be the most common culprit (2–3% contact allergy prevalence) in dermatitis patients in Europe and Asia (31, 32). Other non-mix fragrance contact allergy prevalences have been reported to be low (less than 1%) (31, 32).

Hydroperoxides of linalool and limonene. Linalool ($C_{10}H_{18}O$, CAS no. 78-70-6) is a discrete fragrance chemical found in plants and is known as a fragrance that gives the smell of lavender (33). Linalool itself is a prehapten that is non- or low-allergenic (34, 35), but can be oxidized when exposed to air and transformed into several potential skin sensitizers (33). The main oxidation products of linalool are hydroperoxides, linalool-7-hydroperoxide (Lin-7-OOH) and linalool-6-hydroperoxide (Lin-6-OOH) (36). Hydroperoxides of linalool at 0.5% and 1.0%, containing mainly Lin-7OOH and Lin-6-OOH, are commercially available for patch testing and are included in some baseline series.

Limonene ($C_{10}H_{16}$, *R*-limonene CAS no.5989-27-5, *S*-limonene CAS no. 5989-54-8, dipentene CAS no. 138-86-3) is also a terpene fragrance referred to as a lemon-like smell or citrus taste (37, 38). Air oxidation of limonene can also occur in a similar way, as described for linalool (39). Two major hydroperoxides of limonene, limonene-1-hydroperoxide (Lim-1-OOH) and limonene-2-hydroperoxide (Lim-2-OOH), are known to be potent sensitizers (40, 41). Hydroperoxides of limonene at 0.2% and 0.3%, containing not just Lim-1-OOH and Lim-2-OOH but also carvone and other related chemicals, are commercially available for patch testing.

Hydroperoxides of linalool and limonene are commonly called oxidized terpene fragrances. Recently, 1.0% hydroperoxides of linalool and 0.3% hydroperoxides of limonene have been widely tested in consecutive patients in many countries. The prevalence of contact allergy to these oxidized terpenes has been high when compared with the rates of contact allergy to fragrance mixes and BOP. The highest prevalence of contact allergy has been reported up to 20% and 9.4% for hydroperoxides of linalool (1% in petrolatum) and limonene (0.3% in petrolatum), respectively (42). Patients with contact allergy to these oxidized terpenes have significant concomitant contact allergies to other fragrances and cosmetic-related allergens (43).

As linalool and limonene are prehaptens, it is difficult to identify whether skin exposure exists to the hydroperoxides, haptens, in consumer products because the amounts of the hydroperoxides have been reported to be too low to sensitize and elicit skin reactions (44). Only a few cases have been reported to have dermatitis possibly caused by oxidized linalool (45, 46). Repeated open application test studies have been conducted with hydroperoxides of linalool and limonene and these studies have demonstrated that hydroperoxides in creams and ethanol preparation can elicit dermatitis (47, 48). However, the doses used in these previous studies were considerably higher than those that have been identified in products

used in real life. A recent repeated open application test study was performed in 2023 with hydroperoxides of linalool cream at realistic concentrations ranging from 44 to 440 ppm, which could not elicit dermatitis on normal skin within 4 weeks in 31 individuals with contact allergy to hydroperoxides of linalool (49).

Essential oils. Essential oils mainly contain terpenes (50–52). BOP and Oakmoss absolute in FM I can also be considered essential oils generally used for screening patch testing. The use of essential oils in cosmetics is not only for their pleasant scent but also for medical purposes. Ylang-ylang (*Cananga odorata*) oil, tea tree oil, peppermint oil, and jasmine absolute are included in some international baseline series (53) (Table II) due to their extensive use in herbal regimens, aromatherapy, and cosmetics (50, 51).

Among essential oils tested in 2009–2014 in the United States and Europe, ylang-ylang oil was reported to have the highest rate of contact allergy among the essential oils, up to about 2.5% (54). Other commonly reported essential oils causing contact allergy were clove oil, Treemoss absolute, sandalwood oil, and turpentine oil. As many compounds are found in different essential oils and concurrent exposure to multiple essential oils is common, concomitant positive reactions to more than one essential oil when patch testing can be expected (55). Moreover, concurrent positive patch test reactions between essential oils, fragrance mixes, and single-fragrance compounds have been demonstrated (54, 55). An additional 1.4% of the tested patients were diagnosed as having contact allergy to essential oils without having contact allergy to FM I, FM II, and BOP (54).

Other possible fragrance markers. Colophonium and sesquiterpene lactone mix, along with Compositae mix II are possibly defined as fragrance markers. Several research studies include patients with contact allergy to one or more of these allergens as having fragrance contact allergy since they are by some means chemically related to fragrances. Even if there is an association between these possible fragrance markers and ordinary fragrance materials, it is unusual for dermatologists to recommend that patients with contact allergy to these allergens should avoid using fragrances or scented products unless the patient also reacts positively to other fragrance test preparations.

The chemical composition of colophonium is varied and complex. Oxidation products of resin acids, abietic acid (15-hydroperoxy abietic acid) and dehydroabietic acid (7-oxo-dehydroabietic acid), are major contact sensitizers in colophonium (56). Treemoss extract, a fragrance material, which has been used for patch testing, also contains the same major sensitizers, the (oxidized) resin acids, as well as chloroatranol and atranol (56, 57). On the other hand, Oakmoss absolute, which exists in FM I, does not contain the (oxidized) resin acids but chloroatranol and atranol as main sensitizers. Hence, co-reactivity between colophonium and Tree moss absolute is expected due to the (oxidized) resin acids whereas the co-reactivity between Treemoss and Oakmoss absolutes can be explained by the presence of chloroatranol and atranol.

Theoretically, there should not be co-reactivity between Oakmoss absolute and colophonium since the main sensitizers are not related. However, concomitant positive reactions between colophonium, Treemoss, and Oakmoss absolute have been reported (58–60). The explanation could be that Oakmoss extracts used in fragrant products might be contaminated by the (oxidized) resin acids. In a different population such as in Thailand, there was no significant correlation between colophonium contact allergy and fragrance contact allergy based on patch testing with screening allergens in the baseline series (61).

Compositae plant extracts have been used for patch testing as markers for plant contact allergy, mainly the family Asteraceae (Compositae). The main contact sensitizers in the plant extract are sesquiterpene lactones. Therefore, patch testing preparation with sesquiterpene lactones as a mix (alantolactone, costunolide, and dehydrocostus lactone) was introduced for patch testing, which could help to detect more cases of contact allergy than Compositae mix I & II alone (62). Compositae plant extracts are not usually considered a fragrance marker. However, Compositae contact allergy has been reported to be significantly related to fragrance contact allergy, including fragrance mixes, hydroperoxides of linalool and limonene, and essential oils (55, 63).

PFR-2 is a synthetic polymer based on phenol and formaldehyde, widely used in many industrial products. The prevalence of contact allergy to PFR-2 was reported in 1.2% of the patients visiting clinics worldwide (20). Thus, it was also suggested to be included in other baseline series. Simultaneous positive patch test reactions to PFR-2, colophonium, hydroabietyl alcohol, BOP, and FM I were reported (21). The same and similar chemical compounds in these preparations are suspected to be the cause of the simultaneous reactions.

Patch test systems and procedures

There are generally 2 patch test systems available. Patch testing can be performed with either manually loaded or preloaded allergen patches. For a manually loaded patch test system, a patch test preparation can be prepared by applying the material from a syringe to a patch test chamber before patch application on the test area, whereas Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) test® (also called Ready-to-Use Patch Test Panels, SmartPractice, Phoenix, AZ, USA) contains preloaded allergens in individual patch test chambers thats can be applied directly on the skin. Testing with fragrance patch test preparations from different manufacturers, using different patch test systems and having non-standardized patch testing procedures, can affect

the results of patch test reactions and the prevalence of contact allergy to fragrances.

Manually loaded patch test system. All fragrance test preparations are dissolved in petrolatum. The concentrations of the same substances and the use of sorbitan sesquioleate as an emulsifier in the syringes might differ between manufacturers. Test preparations containing sorbitan sesquioleate may cause false-positive reactions to tested fragrance materials (64, 65). When performing patch testing with petrolatum-based patch test preparations, fragrance test materials should not be prepared in advance as false-negative results may occur due to allergen evaporation (66).

Choosing patch test chambers for patch testing is important (67). There might be a variation in the prevalence of positive and doubtful patch test reactions when using patch test fragrance materials with Finn Chamber and Finn Chamber Aqua (Chemotechnique Diagnostics Vellinge, Sweden) (68). According to a study performed patch testing with 2-chamber systems simultaneously in patients, patch testing with Finn Chamber seemed to show a higher yield of detected cases of contact allergy to BOP, whereas testing with Finn Chamber Aqua might be more beneficial to elicit positive and doubtful reactions for FM I and hydroperoxides of linalool (68).

Preloaded patch test systems. The T.R.U.E. test comprises FM (FM I), BOP, and colophonium as fragrance markers, while FM II has not been included in the panels. Therefore, testing with the T.R.U.E. test without FM II can neglect some fragrance contact allergy cases. Earlier, FM I in the T.R.U.E test had been tested at a concentration of 0.43 mg/cm^2 in hydroxypropyl cellulose, a similar amount to that in 8-mm diameter Finn Chamber (0.4 mg/cm^2 in petrolatum). At that time, freshly prepared FM I in the Finn Chamber from the test preparation syringe could detect more contact allergy cases than the T.R.U.E. test in the general European population (69, 70). A significantly lower prevalence of positive reactions to FM I in the T.R.U.E. test was also reported in dermatitis patients (71). The concordance of patch test reactions performed by using an IQ chamber and T.R.U.E. test was also reported with FM I (72). The concentration of FM I available in the T.R.U.E. test was later increased to 0.5 mg/cm^2 due to the change of vehicle to polyvinylpyrrolidone (73). To the best of the authors' knowledge, there has been no additional study comparing the prevalence of positive patch test reactions between the new T.R.U.E. test FM I and FM I petrolatum-based test preparation since then. Additionally, the prevalence of BOP contact allergy was reported to be lower when tested with the T.R.U.E. test compared with testing with the IQ chamber (72). The preload system is useful for contact allergy screening in clinics where patch testing is not routinely performed or due to a lack of resources. As patch testing with additional suspected allergens is unavailable for this system, extended patch testing with a manually loaded patch testing can be performed.

EXPOSURE TO FRAGRANCES

Regulations and risk assessment

According to the EU cosmetics regulations, the International Nomenclature of Cosmetic Ingredients (INCI) names of 26 fragrances have had to be declared on the list of ingredients if the amount of the individual exceeds the limits (5, 23, 74). Recently, 2 of them, HICC and butylphenyl methylpropional (lilial), have been banned for use in EU countries (EC 2009/1223, Annex III, 67–92). If the fragrances are used below the limits and/or other materials that are perfume and aromatic compositions are contained in products, they should be declared as "parfum" or "aroma" in the list of ingredients.

In June 2023, the European Commission added 56 new entries of fragrance substances to the Annex, including several oils and extracts that have to be labelled on the products (**Table IV**) (23). Overall, 80 fragrance materials must be disclosed on cosmetic product labels. New cosmetic products that will enter the EU market after 31 July 2026 and those which are already on the EU market after 31 July 2028 will be affected (23). The purpose of this amendment is for patients with known contact allergies to avoid the allergens. In countries outside the EU, this amended regulation might be adapted following the EU regulations and may not come directly into force during the same period as in the EU.

While having regulations focusing on product labelling can help mainly for secondary prevention, primary prevention should commence with reducing the risk of skin sensitization by allowing consumer products with safe amounts of fragrances on the market. To reach this goal, proposals for quantitative risk assessments of fragrance materials have been published to set concentration limits for fragrance materials in consumer products to reduce the risk of induction of sensitization (75–77). Theoretically, patch testing in Europe will deliver a very low rate of contact allergy to these fragrance materials (78). However, this measurement will take several years until the outcomes can be established.

Fragrances in cosmetic products

In a self-reported study of the general population in Europe, female participants and those aged less than 40 years were most exposed to cosmetic products with fragrances (79). The most significant sources of contact sensitization to fragrances were reported to be leave-on products (79). According to an extensive analysis of 2,044 cosmetic products, limonene and linalool were found to be the major fragrance substances in around 30% of the products (80). Concerning cosmetic product categories, shampoo contained a maximum number of

Table IV. New sensitizing fragrance substances must be declared on the labels when a concentration exceeds the limits according to the new amendment (European Union cosmetics regulation 2023/1545)

Name of common ingredients glossary	CAS number	Name of common ingredients glossary	CAS number
List of 11 entries that are replaced			
*Pinus mugo**	90082-72-7	*Myroxylon pereirae* oil/ extract*	8007-00-9
*Pinus pumila**	97676-05-6	Rose ketones*	43052-87-5
			23726-94-5
			24720-09-0
			23696-85-7
			57378-68-4
			71048-82-3
			23726-92-3
			23726-91-2
Cedrus atlantica oil/extract*	92201-55-3	3-Propylidenephthalide	17369-59-4
	8023-85-6		
Turpentine	9005-90-7	*Lippia citriodora* absolute	8024-12-2
	8006-64-2		85116-63-8
	8052-14-0		
alpha-Terpinene	99-86-5	Methyl salicylate	119-36-8
Terpinolene	586-62-9		
List of 45 entries that are added			
Acetyl cedrene	32388-55-9	*Citrus aurantium* flower oil	72968-50-4
		Citrus aurantium dulcis flower oil	8028-48-6
			8016-38-4
Amyl salicylate	2050-08-0	*Citrus aurantium amara* peel oil	68916-04-1
		Citrus aurantium dulcis peel oil	72968-50-4
		Citrus sinensis peel oil	97766-30-8
			8028-48-6
			8008-57-9
Anethole	104-46-1	*Citrus aurantium bergamia* peel oil	8007-75-8
	4180-23-8		89957-91-5
			68648-33-9
			85049-52-1
Benzaldehyde	100-52-7	*Citrus limon* peel oil	84929-31-7
			8008-56-8
Camphor	76-22-2	*Cymbopogon citratus/schoenanthus flexuo*sus oils	8007-02-1
	21368-68-3		89998-16-3
	464-49-3		91844-92-7
	464-48-2		
beta-Caryophyllene	87-44-5	*Eucalyptus globulus* leaf/twig oil	97926-40-4
			8000-48-4
Carvone	99-49-0	*Eugenia caryophyllus* oil*	8000-34-8
	6485-40-1		8015-97-2
	2244-16-8		84961-50-2
Dimethyl phenethyl acetate	151-05-3	Jasmine oil/extract*	84776-64-7
			90045-94-6
			8022-96-6
			8024-43-9
Hexadecanolactone	109-29-5	*Juniperus virginiana* oil	8000-27-9
		Juniperus virginiana wood oil	85085-41-2
Hexamethylindanopyran	1222-05-5	*Laurus nobilis* leaf oil	8002-41-3
			8007-48-5
			84603-73-6
Linalyl acetate	115-95-7	Lavandula oil/extract*	91722-69-9
			8022-15-9
			93455-96-0
			93455-97-1
			92623-76-2
			84776-65-8
			8000-28-0
			90063-37-9
Menthol	89-78-1	*Mentha piperita* oil	8006-90-4
	1490-04-6		84082-70-2
	2216-51-5		
	15356-60-2		
Trimethylcyclopentenyl methylisopentenol	67801-20-1	*Mentha viridis* leaf oil	8008-79-5
			84696-51-5
Salicylaldehyde	90-02-8	Narcissus extract*	90064-26-9
			68917-12-4
			90064-27-0
			90064-25-8
Santalol	11031-45-1	*Pelargonium graveolens* flower oil	90082-51-2
	115-71-9		8000-46-2
	77-42-9		

(*Continued*)

Table IV (Continued). New sensitizing fragrance substances must be declared on the labels when a concentration exceeds the limits according to the new amendment (European Union cosmetics regulation 2023/1545)

Name of common ingredients glossary	CAS number	Name of common ingredients glossary	CAS number
Sclareol	515-03-7	*Pogostemon cablin* oil	8014-09-3 84238-39-1
Terpineol	8000-41-7 98-55-5 138-87-4 586-81-2	Rose flower oil/extract*	8007-01-0 90106-38-0 93334-48-6 84696-47-9 84604-12-6 84604-13-7 92347-25-6
Tetramethyl acetyloctahydronaphthalenes	54464-57-2 54464-59-4 68155-66-8 68155-67-9	*Santalum album* oil	8006-87-9 84787-70-2
Trimethylbenzenepropanol	103694-68-4	Eugenyl acetate	93-28-7
Vanillin	121-33-5	Geranyl acetate	105-87-3
Cananga odorata oil/extract	83863-30-3 8006-81-3 68606-83-7 93686-30-7	Isoeugenyl acetate	93-29-8
Cinnamomum cassia leaf oil	8007-80-5 84961-46-6	Pinene	80-56-8 7785-70-8 127-91-3 18172-67-3
Cinnamomum zeylanicum bark oil	8015-91-6 84649-98-9		

CAS: Chemical Abstracts Service number. *Can be declared with several names.

A quick guide – patch testing with fragrances

1. What should be included in the baseline series?

- Fragrance mix I, fragrance mix II, *Myroxolon pereirae* resin, and colophonium are the main fragrance markers, and should always be in the baseline series.
- Testing with the individual ingredients of fragrance mixes and non-mix fragrances (26 EU fragrance materials) could increase the chance by about 10–20% of detecting fragrance contact allergy cases apart from the screening fragrance test preparations.
- Hydroperoxides of linalool and limonene may be routinely tested in patients. However, evaluating clinical relevance is challenging due to a lack of evidence of clinical exposure to the hydroperoxides.
- Essential oils may supplement a 1–2% additional rate of contact allergy to fragrance apart from testing with the mixes.
- Compositae mix, sesquiterpene lactone mix, and phenol formaldehyde resin-2 are possibly considered fragrance markers. Simultaneous positive reactions between these test preparations and fragrance markers are significantly common.

2. What to be aware of regarding the patch test systems, chambers, and procedure.

- When the T.R.U.E. Test is used, additional patch testing with fragrance mix II should be supplemented.
- Different patch test chamber systems may affect the patch test results.
- False-positive and false-negative reactions may occur.
  i. Concentrations in fragrance mixes and their ingredients' test preparations are not equal.
  ii. Sorbitan sesquioleate, an emulsifier in fragrance mix I and *Myroxolon pereirae* resin test preparations, may itself cause an allergic reaction.
  iii. Fragrance test materials from the syringes should not be prepared in advance in the test chambers.

fragrance allergens, followed by oral care products and deodorants (80). Amongst the oral products, more than 90% contained limonene (80).

Essential oils are commonly used in aromatic products, including cosmetics with herbal and flower scents. Unlike other single-fragrance chemicals, INCI names for essential oils used for cosmetic product labelling might be misapprehended as "plant" extracts, not fragrances, by consumers. Post-patch test allergen avoidance counselling should raise patients' awareness that the essential oils listed on their cosmetics may contain fragrance contact allergens under other names. Moreover, essential oils have been reported to be more commonly used in cosmetics claiming to be "natural" than in other general products (81). Therefore, "natural" or "herbal" products can be sources of fragrance exposure.

Children are also at risk of being sensitized by fragrances. Focusing on the baby care product category compared with other product categories, baby care products might contain fewer allergens, including fragrances (80). Nevertheless, about half of the child and baby care products in the United States and Denmark were reported to contain fragrances (82, 83). As in the UK, fragrances were also one of the most abundant allergens in baby cosmetics (84). Benzyl alcohol, limonene, and linalool were the top 3 common fragrances labelled on the products for babies and children (80, 83).

*Fragrances in other products we are exposed to in daily life (***Fig. 2***)*

Topical pharmaceutical products may contain fragrances, which can be an important iatrogenic cause of

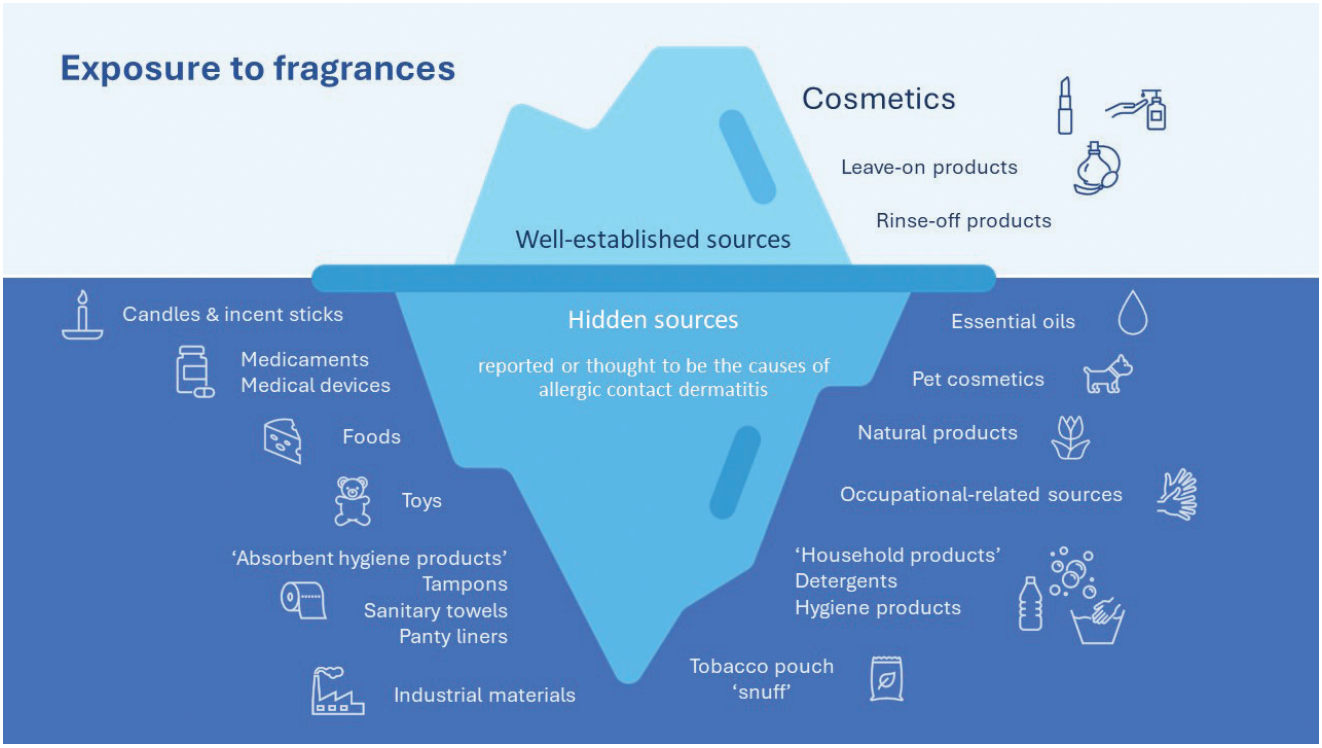

Fig. 2. Sources of exposure to fragrances.

contact allergy. Moreover, they are usually applied on barrier-defected skin such as wounds or rashes. The most common fragrances used in these products were reported to be menthol, essential oils (lavender oil and peppermint oil), camphor, and eucalyptol (85).

Household detergents were also investigated for mandatory labelled fragrances (86). Textile detergents ranked the highest average number of fragrance allergens per product (86). Limonene and linalool were labelled on about 20% of overall detergents (86). Apart from detergents, absorbent hygiene products including tampons, sanitary towels, and panty liners have not been regulated as for cosmetics. In a chemical analysis study of 10 absorbent hygiene product samples to find 24 single fragrance allergens, the concentrations of some fragrance materials were found to be higher than 10 ppm, suggesting that they would have to be declared if they had been under the EU cosmetics regulations (87). Another possible exposure source might be from pet cosmetics, for which INCI names do not need to be declared. Nearly 80% of dog cosmetics labels comprised fragrances (88).

There might be various other hidden sources of exposure in daily life that are overlooked. In Sweden and neighbouring countries, it is extremely common to use smokeless tobacco pouches, "snuff", instead of smoking. They are regulated by the European Food Safety Authority (EFSA), not by the EU cosmetics regulations. There have been case reports of patients having oral lichenoid lesions caused by the fragrance material carvone (an oxidation product of limonene) (89) identified in snuff pouches that are placed between the gum and buccal mucosa (90). These patients also reacted positively to patch testing with hydroperoxides of limonene (90). Some fragrance materials are not only used for their pleasant smells. Terpenes may sometimes be used as raw materials in some other industries for other purposes. For example, limonene is used as a solvent and a degreaser in various industries (37). Linalool has been investigated to be used as a raw material by several manufacturers, including to produce high-performance sustainable aviation fuel (91).

Occupational-related exposure

The majority of occupational-related fragrance contact allergy patients have been reported to present with hand dermatitis due to direct exposure. Massage therapists, reflexologists, and physiotherapists were reported to have occupational contact dermatitis due to several fragrances and essential oils (92). Compared with other occupational dermatitis patients, massage therapists had significantly higher risks of having contact allergies to FMs, BOP, ylang-ylang, and jasmine oils (93). Concerning patch testing with individual ingredients of FMs, citral, isoeugenol, and geraniol ranked as the highest prevalent causes of contact allergy in this group of patients (93). Hairdressers and beauticians were also at risk (94). Salespersons in cosmetic stores were reported as having multiple fragrance contact allergies due to bath bomb use demonstrations in the shop (95). Fragrances could also be the cause of hand eczema in healthcare workers,

sources of exposure to which could be both when at work (disinfectants and hand sanitisers) and during personal product use (96, 97). In the United States, fragrances were found to be the second most common allergen labelled on healthcare hand sanitisers (98).

Young soldiers with allergic contact dermatitis to colophonium in adhesive tapes used on their feet and ankles during marching were found to have an overrepresentation of fragrance contact allergy, mainly to PFR-2, and hydroperoxides of linalool and limonene (99). The cause of skin sensitization to fragrances might not be only from fragrances themselves but from chemically related substances such as oxidized abietic acid in colophonium in the tapes. Athletes (ice-hockey players) were also reported to have a comparable prevalence of fragrance contact allergy to dermatitis patients, which was significantly higher than in the general population (100).

OVERREPRESENTATION OF FRAGRANCE CONTACT ALLERGY IN PARTICULAR GROUPS OF PATIENTS

Chronic actinic dermatosis patients

Patch and photopatch testing is usually performed in patients with clinically suspected chronic actinic dermatosis. The clinical presentations of these patients are similar to airborne contact dermatitis, in which chronic eczema is located on the face and other sun-exposed areas. Simultaneous contact allergies to Compositae mix II, sesquiterpene lactone mixes, and fragrances have commonly been reported (101, 102).

Patients with diabetes and allergic contact dermatitis to medical devices

Overrepresentation of contact allergy to fragrances, colophonium, and sesquiterpene lactone mix was reported among patients with diabetes who were allergic to their medical devices, including glucose sensors and insulin pumps (103, 104). However, there was no definite clue of skin exposure to establish the clinical relevance of contact allergy to fragrances in these patients.

Patients with photoallergic contact dermatitis to ketoprofen

Patients with photocontact allergy to ketoprofen had higher significant rates of contact allergies to multiple fragrances (mainly FM I), including hydroperoxides of linalool and limonene, than general dermatitis patients and the general population (105–108). The pattern of simultaneous reactions to the ingredients of FM I was also different between those with photocontact allergy to ketoprofen and dermatitis patients (106).

Fibromyalgia patients

Patients with a diagnosis of fibromyalgia had significantly higher odds of having fragrance contact allergy, mainly to FM I and BOP. The cause of this association has not yet been identified (109). FM I and BOP ingredients have been suggestively related to flavours in food. Fragrance allergy might be a cause of systemic inflammatory response in fibromyalgia patients. Whether the fragrance allergy is due to different exposures or whether this patient group is prone to develop contact allergy to compounds used in the oral cavity or through the oral mucosa is not known.

CONCLUSIONS

Humans are exposed to an abundance of scented material in daily life and fragrances are amongst the most common culprits reported to cause contact allergy. Fragrance test preparations in most of the baseline series are considered to be sufficient to be tested as screening fragrance markers. However, many studies have demonstrated that testing with additional fragrance materials could be beneficial. This includes testing with individual ingredients of the fragrance mixes, other non-mix fragrance materials, and essential oils. False-positive and false-negative reactions may arise due to several factors from different patch test chamber systems, concentrations, vehicles of the test preparations, and non-standardized procedures. Allergic contact dermatitis to fragrances should be diagnosed based on the presence of contact allergy and sufficient actual exposure to fragrances. Sources of exposure are not limited to mainly cosmetics. A high-quality holistic approach to fragrance contact allergy diagnosis and management is crucial for dermatologists to provide the best patient care.

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