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Fragrances as allergens

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Abstract Contact allergies due to fragrances are common. If one adds up the reaction incidences of the indicators of fragrance allergy (fragrance mix [FM] I + II, balsam of Peru and turpentine), these reach 17% in a hospital collective (Information Network of Departments of Dermatology [IVDK] data 2016) and are thus higher than those for nickel allergy (approximately 16%). In the case of positive reactions to FM I, >50% do not react to one of the components. This type of reaction should be interpreted as allergic with caution, unless other data (e.g., positive history, application test) support this interpretation. FM-I-positive individuals often react to oak moss (27.2%) and isoeugenol (18.2%). These are followed by hydroxycitronellal (10.9%), cinnamal (10.6%), cinnamyl alcohol (8.4%), eugenol (7.3%), geraniol (5.5%), and amyl cinnamal (1.5%). The frequency of sensitization (SF) to the individual fragrances depends on their allergenic potency (measured using the local lymph node assay, LLNA) and the frequency of use (extent of exposure). The relationship between SF and exposure is described by the sensitization exposure quotient (SEQ). The SEQ is a measure of the risk of sensitization. In general, it correlates with the SF on the one hand and with the allergenic potency (hazard) on the other. Exceptions to this rule indicate a newly recognized problem: (1) Although methyl 2-octynoate plays no role in SH statistics, it came third after tree moss

and oak moss with its SEQ (=risk); (2) despite its low potency, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall®) had a relatively high risk. In this particular case, potency (the inherent hazard) was not the determinant of risk, but rather the overly high doses used. Allergy monitoring by clinical epidemiology needs to be more heavily supplemented by data on exposure.

Keywords Fragrances · Contact allergy · Patch test · Allergy monitoring · Sensitization risk

Abbreviations

ACD	Allergic contact dermatitis
BP	Balsam of Peru
FM	Fragrance mix
HICC	Hydroxyisohexyl 3-cyclohexene carboxaldehyde
IFRA	International Fragrance Association
INCI	International Nomenclature of Cosmetic Ingredients
IVDK	Information Network of Departments of Dermatology (<i>Informationsverbund dermatologischer Kliniken</i>)
LLNA	Local lymph node test
MOAHLFA	Male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, age (index)
PT	Patch test
ROAT	Repeated open application test
SF	Sensitization frequency
SEQ	Sensitization exposure quotient

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Introduction

Fragrances are the commonest cause of allergic contact dermatitis (ACD) due to cosmetic products and the commonest cause of positive patch test reactions after nickel sensitization [1]. This is explained first by the sensitizing capacity of fragrances and, second, by their widespread use: virtually everyone is exposed to products containing fragrances, often on a daily basis. They are used in all conceivable types of cosmetics and hygiene products, cleaning agents, room fragrances, topical pharmaceuticals, sun protection creams, toys, textiles, and industrial products—often to cover unpleasant odors (odor mask), e.g., paints and cooling lubricants. As essential oils, they also play an important role in aromatherapy [1, 2].

Definitions

Fragrance: The International Fragrance Association (IFRA) defines fragrance substances as substances that are used in the production of fragrance compositions for their odorous, odor-enhancing, or odor-masking properties [3]. These can be of natural or synthetic origin. Many of them belong chemically to the group of terpenes or the group of monocyclic aromatic hydrocarbons (“benzenoids”), with the majority of molecules used today being produced in a nature-identical, synthetic manner. However, some fragrances are obtained via extraction from certain plants, e.g., to produce essential oils [1].

Contact allergen: Contact allergens are defined as—generally low-molecular weight—substances that cause ACD in humans. Following clinically silent sensitization involving Langerhans cells and T lymphocytes, ACD develops 2–4 days after re-exposure to the allergen [4]. A positive patch test reveals not only the patient’s sensitization to the substance, but also that the substance is a contact allergen [5]. Substances are also identified using suitable animal tests and in vitro methods [6]. Over 100 fragrances have been classified as contact allergens on the basis of published clinical evidence and positive animal experiments (local lymph node test, LLNA; [7]).

Occurrences

In their primary areas of application, i.e., cosmetics and household products, the mainly synthetically produced fragrances are found as mixtures. Up to 300 different components can go towards creating the fragrant effect of a perfume. They can also be used in isolation as the only aromatic substance in other products such as toothpaste, chewing gum, or bakery products. A perfume usually contains 10–15% fragrance components, eau de colognes 3–5%, deodorants 1%, creams 0.4%, and soaps 0.5–2%. Analyses revealed that the proportion of allergenic fragrances in a variety of cosmetics (perfumes, shampoos, creams,

and shower gels) was higher in the more expensive categories, whereas quantitatively, everyday household products tended to contain allergens of lower potency. Not only did children’s cosmetics, including those designed as toys, also contain highly potent allergenic fragrances, some of these were found in high concentrations (the use of fragrances in toys has since been restricted in Europe [8]). Perfumes claiming to be of “natural origin” were also found to contain allergenic components as well as purely synthetic chemicals (alpha-hexyl cinnamaldehyde, diethyl phthalate, and propylene glycol). Products falsely stated to be “fragrance-free”, may contain essential oils (containing limonene or eugenol) to “mask” odors [2, 9].

In the period between 2006 and 2009, the German Chemical and Veterinary Laboratory in Karlsruhe, Germany (*Chemisches und Veterinäruntersuchungsamt*, CVUA) documented the ingredients of 4991 products—including 26 fragrances subject to declaration according to the German Cosmetic Regulation (*Kosmetikverordnung*)—and assigned these to various product categories [10]. Creams, emulsions, lotions, and similar products contained up to around 80% fragrances, 2.5 different ones on average (median), while perfumes contained on average nine and a maximum of 26 fragrances. On average, two different fragrances were used across all product categories. Limonene and linalool were those most commonly found, sometimes in combination with each other and in virtually all product categories. Fig. 1 shows the distribution of “coupled” use in the various product categories.

The extent of occupational fragrance exposure is unknown. However, the frequency of contact allergies in different occupations is an indicator of relevant exposure, since an allergy is unable to develop without exposure. Analyses of IVDK data showed an increased risk of fragrance allergy among masseurs/physiotherapists, beauticians, nurses, geriatric nurses, and metal surface workers [11, 12]. Risk was particularly increased among metal surface workers exposed to metalworking fluids (MWF). It also emerged that workers added fragrances to the MWF in order to mask their odor [13]. Remarkably, hairdressing was not an occupation associated with an increased risk. One can deduce relatively high use of fragrances in the areas mentioned, albeit non-quantifiable.

Clinical aspects

Sensitization due to fragrances followed by the onset of ACD after re-exposure is by far the most important adverse effect of some fragrances.

ACD involving itchy, reddened, and sometimes weeping skin lesions develops in the areas exposed to the perfume, e.g., behind the ears, on the side of the neck, or in the armpits, for instance following deodorant use (Fig. 2). The axillae are the site at highest risk for perfume allergy (for FM I odds ratio [OR] > 2; for

Fig. 1 Distribution of the number of fragrances subject to labelling in individual product categories (shown as a *violin plot*). The vast majority of make-ups contained no fragrances whatsoever, whereas perfumes and deodorants (*Deo*) often contained several fragrances [10]. © 2013 John Wiley and Sons, Contact Dermatitis

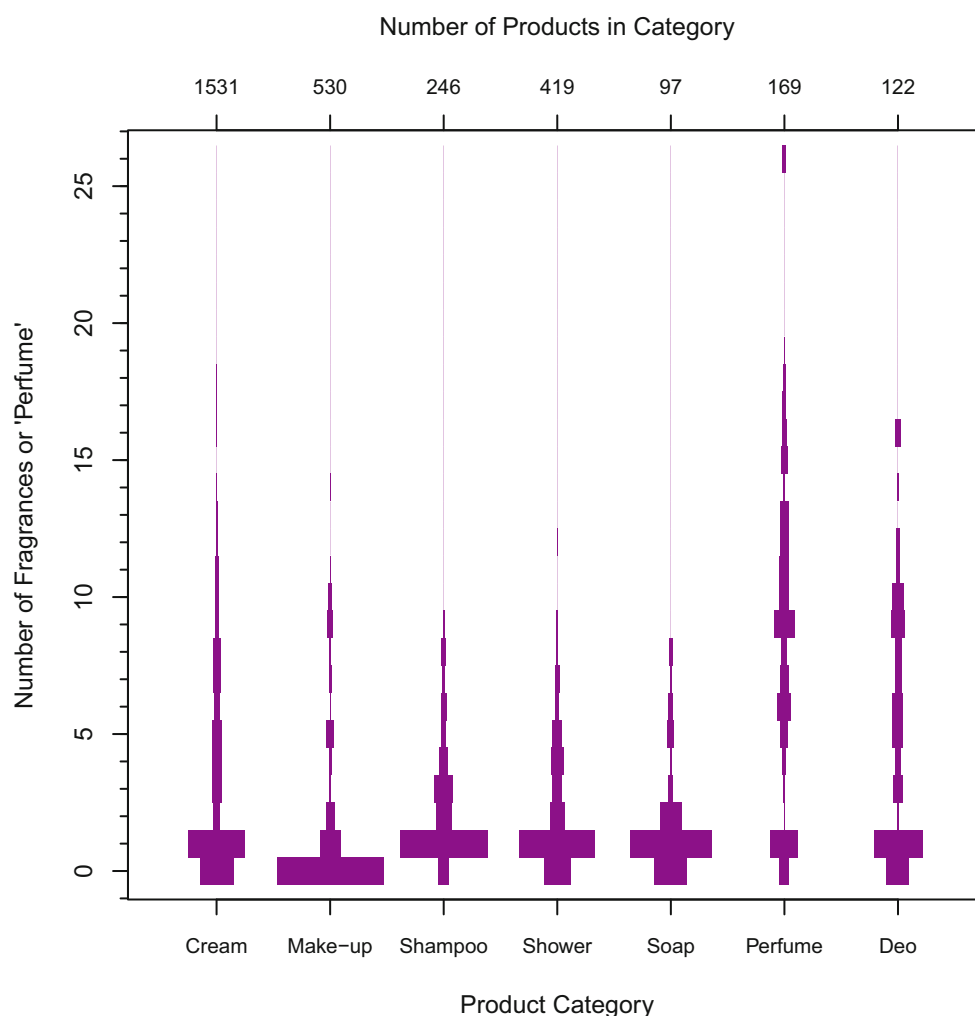


Fig. 2 Allergic contact dermatitis in the axillary region in a patient with a positive PT reaction to fragrance mix I. (© A. Schnuch)

FM II OR > 4) due to the thin skin that facilitates permeation and its semi-occluded state (“skin on skin”; [12]). Facial dermatitis is a classic manifestation of fragrance allergy caused by cosmetics. In men, after-shave lotions can cause dermatitis in the beard and lateral neck regions. Large studies have confirmed that perfumes and deodorants in women and after-

shave lotion and deodorants in men are the most common causes of fragrance allergy [2]. In the case of high-grade sensitization or high exposure dose, generalized dermatitis may occur, i.e., affecting the whole body (also referred to as hematogenous contact dermatitis, since, once the allergen has permeated the skin, it can be transported virtually “internally” to non-exposed skin). Oral intake of flavored foods can also cause generalized ACD, particularly in the case of sensitization to balsam of Peru [14, 15].

Although the cause of sensitization to fragrances is exposure, there are promoting cofactors such as existing inflammatory dermatosis (e.g., lower leg eczema in varicose veins), which creates a molecular environment that promotes pathogenesis (in the sense of “danger signals”; [16]). The question of a particular genetic disposition can generally be answered today to the effect that existing genetic repertoire is “overruled” in the case of potent allergens, while an existing tendency to allergy is of importance in the case of weak allergens. In recent years, investigations on polymorphisms in “candidate genes” have identified a number of polymorphic genes that are associated with an increased risk for ACD—although it is not yet

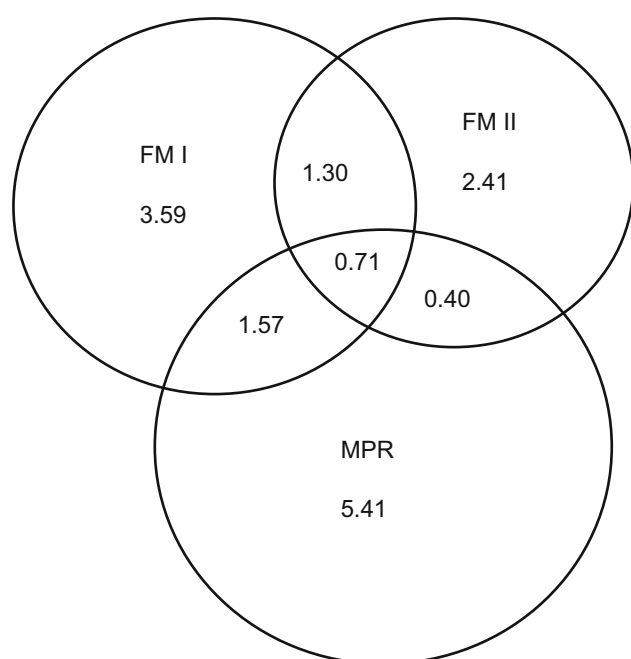


Fig. 3 Pattern of positive reactions to patch test screening preparations ($n = 35,361$): 84.9% of patients did not react to any of the allergen mixtures. It is evident that fragrance mix (FM) I does not by any means detect all fragrance allergies, since only 27% of those that tested positive to FM I also tested positive to FM II and 32% to balsam of Peru [20]. *FM I* fragrance mix I, *FM II* fragrance mix II, *MPR* *Myroxylon balsamum* var. *pereirae* (balsam of Peru)

Table 1 Ingredients of fragrance mix I

INCI name	CAS number
Amyl cinnamal	122-40-7 1
Cinnamal	104-55-2 1
Cinnamyl alcohol	104-54-1 1
Eugenol	97-53-0 1
<i>Evernia prunastri</i> (oak moss extract)	90028-68-5 1
Geraniol	106-24-1 1
Hydroxycitronellal	107-75-5 1
Isoeugenol	97-54-1 1
/INCI International Nomenclature of Cosmetic Ingredients, CAS Chemical Abstracts Service	

Table 2 Ingredients of fragrance mix II

INCI name	CAS number
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
Farnesol	4602-84-0
Hexyl cinnamal	101-86-0
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyrall®)	31906-04-4
/INCI International Nomenclature of Cosmetic Ingredients, CAS Chemical Abstracts Service	

Table 3 Other fragrances subject to declaration (available as patch test preparation)

INCI name	CAS number
Alpha-Isomethyl ionone	127-51-5
Amylcinnamyl alcohol	101-85-9
Anisyl alcohol	105-13-5
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Butylphenyl methylpropional (Lilial®)	80-54-6
<i>Evernia furfuracea</i> extract (tree moss extract)	90028-67-4
D-limonene	5889-27-5
Linalool	78-70-6
Methyl 2-octynoate	111-12-6
/INCI International Nomenclature of Cosmetic Ingredients, CAS Chemical Abstracts Service	

possible to adequately characterize the risk for developing ACD [17].

Diagnostic testing for fragrance allergy

Sensitization to a contact allergen is generally demonstrated using the patch test. This involves placing small amounts of known sensitizing substances (usually 1% in 20 mg petrolatum) in aluminum chambers and applying these to the back for 48 h. A test “reading” is taken after 3 days. Skin redness, potentially with vesicles as in dermatitis, indicates sensitization to the applied substance. In the early days of patch testing, balsam of Peru (PB, *Myroxylon balsamum* var. *pereirae*) was used to diagnose fragrance allergy. Although this proved at the time to be the most important fragrance contact allergen, it was not sufficient to diagnose all fragrance allergies. Therefore, the FM I was included in standard diagnostic testing in the mid 1970s and FM II in the early 2000s [18, 19]. However, all three indicators of a fragrance allergy are still required as diagnostic instruments, since they are only partially redundant [20], as shown in Fig. 3.

A number of preparations are used in the patch test standard series (a set of allergens that are tested in all patients with suspected ACD) to diagnose fragrance allergy. These include fragrance mix I (FM I), fragrance mix II (FM II), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyrall®), and balsam of Peru. The individual components of the mixes as well as other fragrances are also available for testing (Tables 1, 2 and 3). More recently, oxidized fragrance allergens, in particular those from linalool and limonene, have been tested. Although these fragrances, which are seen as “prehaptens,” were unequivocally identified in animal experiments as potent haptens (allergens) following oxidation and positive patch test reactions were seen in numerous studies [21], the relevance

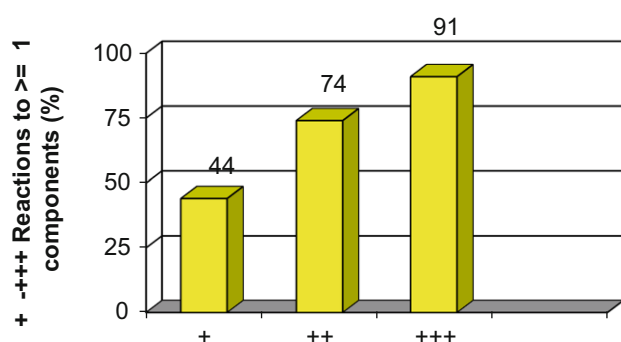


Fig. 4 Reactions to at least one of the components in fragrance mix I in patients that tested positive to fragrance mix I ($n = 2798$, [22])

(see below) of these frequent reactions has yet to be demonstrated.

The aim of testing with allergen mixes such as the fragrance mix is to detect sensitization to at least one of the ingredients. In the case of allergic reactions to the mix, individual components should be retested in order to inform the patient of the contact allergens that are relevant to him or her, thereby ensuring that further exposure can be avoided as far as possible. Ideally, patients who test positive to the mix should also test positive to at least one of the mix components. However, this is not the case. A total of 43% of FM-positive patients showed no reaction whatsoever to individual components [22]. Several causes could potentially explain this, e.g., excessively low test concentrations (1%) of the individual components or a nonspecific irritative reaction caused by the FM I tested at 8% (meaning that there was no contact sensitization whatsoever to an FM I component). Alternatively, reactivity to the components is increased when they are applied in combination with the other

mix components. Here one refers to the synergy of allergens in combination [23, 24]. This synergy may be based on a permeation-promoting [25] and non-specific immune-activating [24] effect caused by other mix components. Synergistic effects of this kind are absent in individual testing and patients test negative. These considerations and findings demonstrate that, in practice, fragrance mixes are probably better diagnostic indicators of fragrance allergy compared with the individual substances—particularly since a mixture better simulates exposure conditions anyway [2].

Thus, Fig. 4 shows that the percentage of patients that tested positive to at least one component of the FM I rises with the strength of the allergic reaction to the mix [22]. Approximately 56% of patients with a “+” positive reaction showed no reaction to one ingredient, whereas this percentage was 26% for “++” reactions and only 9% for “+++” reactions. In terms of diagnosis, this means that weak reactions to FM I do not necessarily indicate contact allergy to the fragrances (see below).

The frequency of reactions to individual components of the FM I is subject to considerable variation. As shown in Fig. 5, oak moss and isoeugenol are the most frequent triggers of positive reactions, whereas geraniol and amyl cinnamal are the least frequent [22].

A breakdown of tests was also performed for patients that tested positive to FM II ($n = 1058$; [22, 26]). Of those exhibiting a weak (“+”) reaction to the mix, 47% showed no reaction to at least one of the components. However, this percentage was lower in the case of stronger reactions to the mix (11% for “++” and 7% for “+++” reactions). The contribution of individual components also differs for FM II (Fig. 6). HICC was the most important fragrance allergen over the evaluation period (2005–2013). However, there were significant changes over this period. While the percentage

Fig. 5 Percentages of positive reactions to individual components in fragrance mix I in patients that tested positive to fragrance mix I ($n = 2798$, [22])

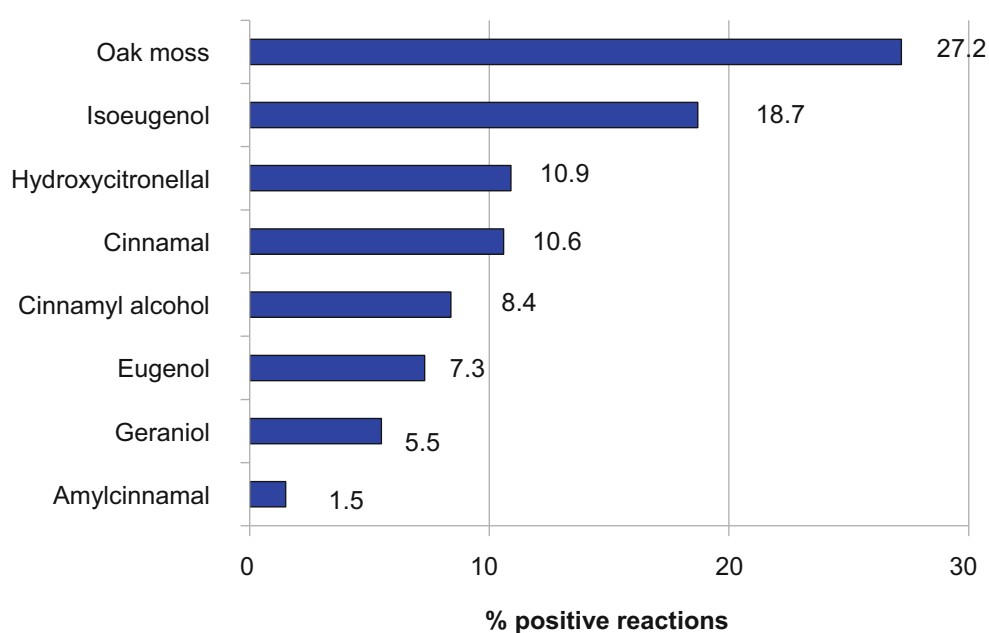


Fig. 6 Percentages of positive reactions to individual components in fragrance mix II in patients that tested positive to fragrance mix II ($n=1058$, HICC hydroxyisohexyl 3-cyclohexene carboxaldehyde, [22])

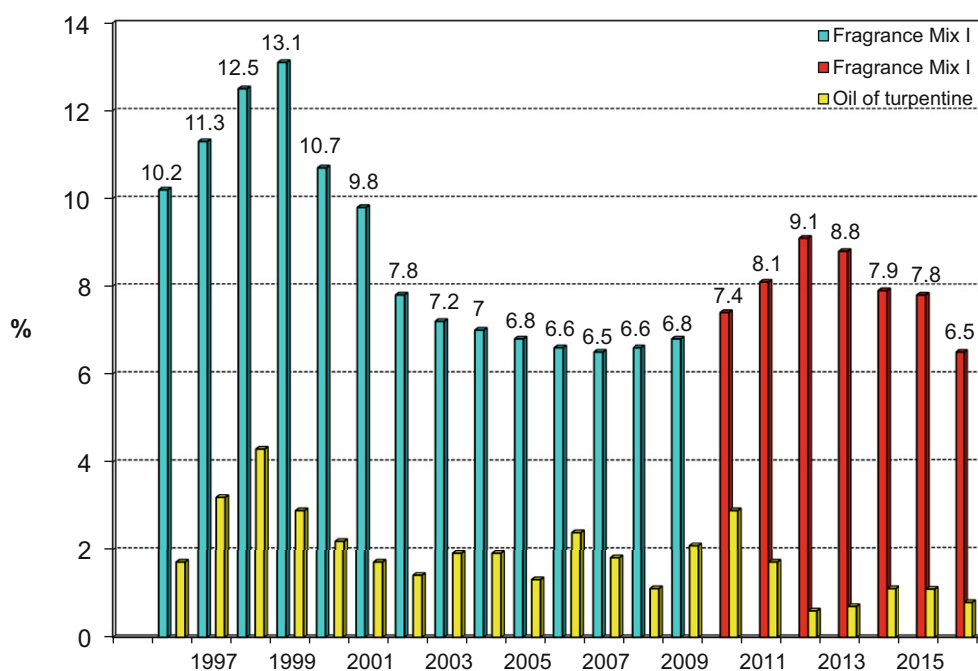
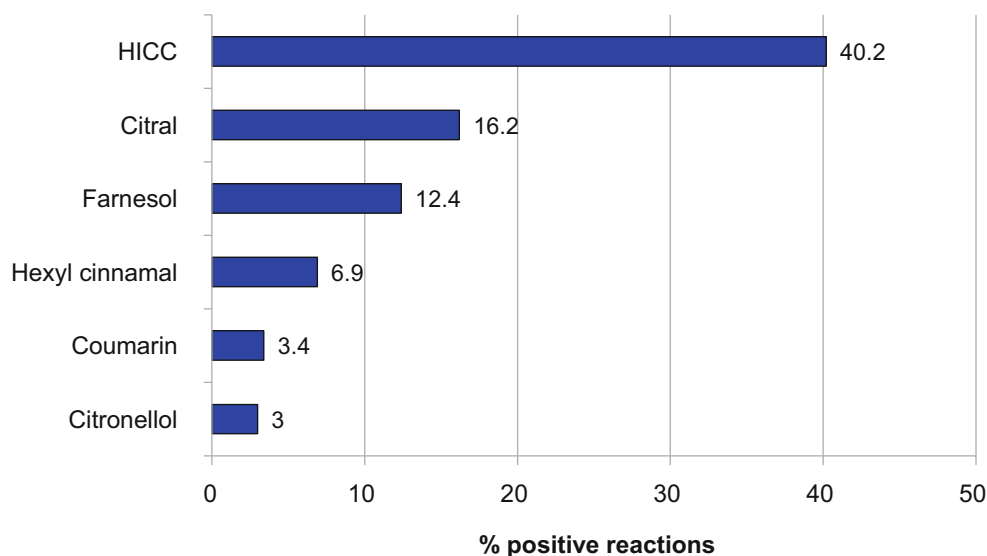


Fig. 7 Prevalence of sensitization to fragrance mix I (FM I) and turpentine oil in the Information Network of Departments of Dermatology (*Informationsverbund Dermatologischer Kliniken*, IVDK) for the period 1996–2016. Between 1996 and 2002, the turpentine oil curve ran parallel to FM I. This was explained by the increased use of essential oils (e.g., tea tree oil). In addition, turpentine oil was considered a surro-

gate marker for tea tree oil exposure [36]. The (statistically significant) decline from 2000 onwards might be explained by a reduction in the use of problematic fragrances such as oak moss and isoeugenol, while the temporary (yet significant) rise from 2010 could be explained by a relative increase in sensitizations to cinnamon derivatives (cinnamal, cinnamic alcohol, and hexyl cinnamal; [12, 22, 37, 38], IVDK 2017, unpublished)

of HICC was still 44.7% in the years 2005/2006, this dropped to 27.8% in 2013. This could be due to the reduction in concentrations used, as recommended by IFRA. During the same time period, the percentage of hexyl cinnamal rose from 2.9 to 8.9%, making it one of the more important fragrances in FM II.

The obligatory completion of a patch test is to determine clinical relevance. This characterizes the proven relationship between exposure to an allergen,

e.g., in a consumer product, and the manifest ACD caused as a result. Clinical experience has shown that strong patch test reactions are also more often clinically relevant (indicated by a positive patient history or a positive repeated open application test [ROAT]; [27, 28]). Conversely, evidence of relevance is often lacking in only weak (“+”) reactions [1, 29]. Thus, de Groot and Frosch concluded: “False-positive reactions (to the Fragrance mix) are not rare, and a single

Table 4 MOAHLFA index of cases that tested positive to fragrance mixes and individual allergens in the IVDK between 1999 and 2012 (and to FM II between 2005 and 2012)^a [12]

	Total IVDK	FM I-positive ^b	FM II-positive ^c	MPR	Turpentine	Fragrance-positive
<i>n</i>	132,384	11,345	3959	10,894	2568	21,595
% Positive	—	8.71	4.87	8.36	1.95	16.31
95% Confidence interval	—	8.55–8.86	4.73–5.02	8.21–8.52	1.88–2.03	16.1–16.5
Male	37.8	32.4	32.6	34.6	34.4	33.8
Occupational dermatitis	15	13.6	15.8	11	16.2	13
Atopic eczema	18.8	18.8	21.4	13.9	19.4	17.3
Hand dermatitis	27.6	25.8	27.8	21.8	27.1	24.7
Leg dermatitis	11.7	16	13.1	20.7	17.4	17
Face dermatitis	15.7	16.6	17.5	14.7	14.5	16
Age 40+	69.5	80.5	80.1	85.6	79.2	81.5

MOAHLFA, (M male, O occupational, A atopic, H hand, L leg, F face, A age), FM I fragrance mix I, FM II fragrance mix II, MPR Myroxylon balsamum var. pereirae (balsam of Peru), IVDK Information Network of Departments of Dermatology (Informationsverbund dermatologischer Kliniken)

^aThe age distribution and high proportion of lower leg dermatitis among individuals sensitized to balsam of Peru (MPR) are striking. The percentage of face dermatitis (an indicator of make-up allergy) is particularly high for FM II

^bCases between 1999 and 2005

^cCases between 2005 and 2012

weak (?+ or +) reaction to the mix should not be taken as evidence for fragrance contact allergy but should be substantiated by other tests (e.g. ROAT ...)" [29].

Epidemiology

As shown by comparison of epidemiological data over longer periods and from various countries, sensitization to FM I has long ranked second after nickel in terms of frequency. According to population studies, between 1 and 2% of the general population is sensitized to substances of FM I [30–32]. Sensitizations to FM I in patients tested for suspected contact allergy rose considerably in the 1990s (Fig. 7). In the hospital cohort, older individuals (>40) are significantly more frequently affected than are younger individuals, and females more frequently than males [33, 34pp. 48–49]. In extreme cases, rates for FM were between 6% in young males and 14.4% in older females [34]. The risk for females was significantly increased by 21% and continued to rise with increasing age [12]. The populations investigated in epidemiological studies are described using the MOAHLFA index, which gives percentages for the following variables: M (male), O (occupational), A (atopic), H (hand), L (leg), F (face), and A (age>40; Table 4; [12]). Changes to one or more criteria of the MOAHLFA index (e.g., age>40) can influence the determined SF over time and need to be taken into consideration when interpreting results. For example, SFs to FM I increases significantly with age (e.g., 11.6% of 30- to 39-year-old females versus 16.1% of 70- to 79-year-olds) and are markedly higher among females compared with males [33]. The percentage of patients older than 40 years also rose over the observation period: from 62.5% in 1999 to 69.9% in 2006 ($p<0.0001$; [35]). For this reason, the frequencies determined in the IVDK are standardized according to age and gender, as shown in Fig. 7.

Although FM I includes eight different substances, a mere two substances are responsible for the vast majority of reactions, i.e., oak moss absolute and isoeugenol (see above). As the trend plot shows (Fig. 7), FM I reached its peak in 1999. Since then, the number of sensitization to substances in FM I has declined significantly—a development that has also been observed in other European countries [39].

In this context, it is important to take a more detailed look at the trend seen in terpene allergy (Fig. 7). Since turpentine oil, an important allergen in the past, was used ever more rarely for “economic reasons,” its relevance as an allergen declined drastically. Already in the early 1990s it ranked below 1%, meaning that it should in actual fact lose its place in the standard series. The rapid increase in sensitization to terpenes, a class of natural substances—an increase hitherto unseen with any other allergen—changed the situation. This rise was explained by the growing popularity of alternative natural cosmetics and remedies, i.e., this time by a fashion trend [36]. Interestingly, the sales figures for essential oils developed parallel to sensitization rates, meaning that changing exposure plausibly explains both the rise and the fall in number of sensitizations [37].

There are two potential explanations for the similarly unexpected trend in fragrance allergy:

- Since almost 50% of terpene-allergic individuals—possibly due to “exposure coupling”¹—were also allergic to the fragrance mix [36], at least part of the increase as well as the decrease in fragrance allergy could be attributed to terpene exposure, which ev-

¹ The simultaneous occurrence of several allergenic substances in products can result in multiple sensitization in one person (exposure coupling), in contrast to structural coupling, which is based on structural similarities of the allergens. Here, sensitization to a single allergen is sufficient.

Table 5 Sensitization risk, calculated on the basis of INCI declaration and sensitization frequencies

INCI name	Sensitization frequency in % (absolute)	Relative sensitization frequency in %	Ingredients: product declaration (number)	Relative ingredients declaration in %	SEQ
Tree moss (<i>Evernia furfuracea</i>)	5.27	23.6	50	0.32	73.16
Oak moss absolute (<i>Evernia prunastri</i>)	3.03	12.5	44	0.28	44.03
Methyl 2-octynoate (Methyl heptene carbonate)	0.16	0.7	7	0.05	15.5
Cinnamal	1.04	4.3	67	0.43	9.95
Isoeugenol	2.01	8.3	132	0.85	9.75
HICC ^a	3.65	15.1	606	3.91	3.86
Farnesol	0.98	4	191	1.23	3.25
Anise alcohol	0.05	0.3	15	0.1	3.1
Cinnamyl alcohol	0.9	3.7	233	1.5	2.46
Benzyl cinnamate	0.16	0.7	59	0.38	1.84
Hydroxycitronellal	1.06	4.4	458	2.95	1.49
Eugenol	0.74	3	486	3.14	0.96
Citral	1.06	4.4	755	4.87	0.9
Amyl cinnamal	0.21	0.9	199	1.28	0.7
Butylphenyl methylpropional (Lilial [®])	0.7	2.9	1018	6.57	0.44
Hexyl cinnamal	0.5	2.1	867	5.59	0.38
Coumarin	0.33	1.3	711	4.59	0.28
Geraniol	0.42	1.7	1271	8.2	0.21
Benzyl salicylate	0.21	0.9	780	5.03	0.18
Benzyl alcohol	0.16	0.7	605	3.9	0.18
Citronellol	0.23	0.9	1348	8.7	0.1
Linalool	0.32	1.3	2123	13.7	0.09
Alpha-Isomethyl ionone (gamma-methyl ionone)	0.11	0.4	805	5.19	0.08
D,L-limonene	0.16	0.7	2048	13.21	0.05
Benzyl benzoate	0	0	608	3.92	0
Amylcinnamyl alcohol ^b	0.32	1.3	14	0.09	14.39

INCI International Nomenclature of Cosmetic Ingredients, SEQ sensitization exposure quotient (sensitization risk)

^aHICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde (e. g., Lyrall[®])

^bThe unexpectedly high SEQ for amylocinnamyl alcohol could be based on an overestimation of primary sensitization rates due to cross-reactions to other cinnamom derivatives

idently followed current and rapidly changing fashion trends.

- Furthermore, the recommended application concentration for isoeugenol (in products intended for skin contact) has been reduced to 0.02% by IFRA (<http://www.ifraorg.org>). Chemical analyses of perfumes revealed that, up to 2003, both the concentration and the frequency of use of problematic fragrances such as isoeugenol or oak moss had declined [2].

This downward trend in fragrance allergies, as evidenced for FM I, did not continue over the years. Following consolidation, a significant rise was seen once again, reaching a peak in 2012 [12]. This may be explained by an increase in sensitizations to cinnamon derivatives (cinnamaldehyde, [cinnamal], cinnamic alcohol, cinnamyl alcohol, and hexyl cinnamal; see above). This explanation is supported by observations from England, according to which oak moss and isoeugenol were no longer the most frequent fragrance allergens, but rather cinnamyl alcohol [38]. It

must be borne in mind that cinnamal and cinnamyl alcohol can be converted into each other by alcohol dehydrogenases during metabolism. Ultimately, however, the emergence of this trend remains unexplained, particularly since a significant decline back to the baseline level has been seen in recent years (Fig. 7).

Nevertheless, fragrance allergy (expressed by the indicators FM I, FM II, balsam of Peru, and turpentine with an overall sensitization frequency of >16% of the patients tested; Table 4, line 3) is still relevant to public health, which requires constant trend monitoring in order to initiate appropriate measures if necessary.

The risk of fragrance allergy

It is important to bear in mind with regard to all findings of clinical epidemiology that the identified sensitization prevalences also depend on the level of exposure to allergens. Although it has been repeatedly shown that FM substances are found in different categories of consumer goods [2], it is precisely

the substances of less significance in allergy (geraniol, limonene, and linalool) that are used in large quantities, while those substances that are important in allergy, such as oak moss, isoeugenol, and cinnamal, are used significantly less. This means that the level of exposure does not tally with the rate of allergies.

In order to describe the allergy risk, i.e., the dependence of allergy frequency on exposure, an attempt was made to describe exposure using two indicators: The percentage frequency with which allergens were labeled on the ingredients list of product packaging (statistics of the CVUA Karlsruhe, Germany, on over 5000 products for 2007–2009) and the volume of fragrances used (in tonnes; data for Europe for 2008) as reported by IFRA. The *relative* frequency of use was calculated from these data as follows [40]: (1) The total quantity of all fragrances used (the sum of all volumes of single fragrances) was set at 100% and the share of the total volume was determined for the actual individual volumes for each fragrance; (b2) the total number of all fragrance declarations was set at 100% and the share of labeling per fragrance calculated (Table 5, column 5).

The frequency of sensitization per fragrance was calculated from the IVDK data for the period 2007–2009 (Table 5, column 3). As an estimate of the risk of sensitization, the sensitization exposure quotient (SEQ) was calculated as the quotient of the relative SF and the relative exposure frequency for each fragrance. Thus, the SEQ yields the relative sensitization risk of a fragrance in relation to other fragrances (Table 5, column 6).

These sensitization frequencies (Table 5, column 2) correspond with those calculated in other European studies. Three groups emerge as a result of these findings:

- Group I (frequent allergens, in decreasing order of frequency): tree moss, HICC, oak moss, isoeugenol, hydroxycitronellal, citral, cinnamal, farnesol, and cinnamyl alcohol.
- Group II (rare allergens): amyl cinnamal, benzyl salicylate, methyl 2-octynoate (methyl heptene carbonate), benzyl cinnamate, benzyl alcohol, limonene, α -isomethyl ionone, anise alcohol, and benzyl benzoate.
- Group III (less frequent but not negligible): eugenol, butylphenyl methylpropional (Lilial®), hexyl cinnamal, geraniol, coumarin, amylcinnamyl alcohol, linalool, and citronellol.

The sensitization risk for substances with $SEQ < 0.1$ (Table 5, column 6), e.g., linalool, limonene, α -isomethyl ionone, and benzyl benzoate, is all but negligible. These substances show extremely high EC3 values in the LLNA, indicating very low sensitization potency. (The EC3 value indicates the concentration at which a three-fold increase in lymphocyte stimulation in the LLNA is achieved.)

The highest risk of sensitization is seen with oak moss, tree moss, methyl 2-octynoate, cinnamal, and isoeugenol. These substances also proved to be (extremely) potent sensitizers in the LLNA ($EC3 < 1$). Thus, there is a good correlation between the sensitizing potency measured in animal experiments and the SEQ as a measure of risk for humans.

However, one must bear in mind that the risk cannot be directly derived from the sensitization potency, since the risk is a function of potency *and* exposure. As such, extremely low levels of highly potent allergens can pose a low risk, while high levels of only moderately potent allergens, or the use of moderately potent allergens on skin areas at particular risk, can pose a high risk. For example, the relatively high SEQ for farnesol can scarcely be explained by its EC3 value ($>4\%$), but rather by its frequent use in deodorants, since the skin barrier in the axillary region is comparatively low due to the relatively thin and strongly hydrated skin.

Although a moderate EC3 value was determined for HICC (EC3: 17.1%), it is second in the frequency statistics and sixth in the risk statistics. The previously relatively high risk of sensitization to HICC is probably due to excessively high levels in products [41]: $>1\%$ in the past, up to 0.2% from 2007. From 2009, levels of up to 0.02% were classified as safe (www.ifraorg.org).

High sensitization frequencies, irrespective of potency and risk, should always be seen as a warning signal (sentinel health events in a monitoring system) requiring investigation and preventive measures. However, frequency and risk diverge in some cases, particularly if frequency statistics give little cause for concern, yet the SEQ proves to be high, as with benzyl cinnamate, anise alcohol, and especially methyl 2-octynoate (methyl heptene carbonate).

The overall conclusion is that there is no such thing as “fragrance allergy,” but that each fragrance needs to undergo a differentiated evaluation in its own right. A detailed risk assessment concludes that there are problematic fragrances that need to be subject to concentration limits in products. These include oak moss and tree moss with high chloroatranol content, methyl 2-octynoate, hexyl cinnamal, and isoeugenol. But there are also unproblematic fragrances that do not require regulation, such as limonene and linalool, which are used in large quantities and are considered weak allergens at most. However, the content of oxidation products, which have been identified as comparatively potent allergens, should be limited.

Conflict of interest A. Schnuch and P. Griem declare that they have no competing interests.

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