

An Update on Fragrance Contact Dermatitis

Luca Schneller-Pavelescu, MD^{1,*}

Gemma Ochando-Ibernón, MD²

Juan Francisco Silvestre-Salvador, MD¹

Address

^{*1}Department of Dermatology, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Hospital General Universitario de Alicante, Pintor Baeza 11 St, 03010, Alicante, Spain
Email: luicapavelescu@gmail.com

²Department of Dermatology, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

Published online: 23 January 2019

© Springer Nature Switzerland AG 2019

This article is part of the Topical Collection on *Contact Dermatitis*

Keywords Allergic contact dermatitis · Fragrances · Baseline series · Haptens · Fragrance mix · Fragrance markers

Abstract

Background Fragrances are a group of substances present in many cosmetic products, which are one of the most common sources of allergic contact dermatitis (ACD) in Europe. Their widespread distribution, the presence of these substances as combinations, their ability to transform into more reactive substances, and the relatively recent regulations regarding these products are the main reasons for this high prevalence. In the last few years, advances on knowledge about haptens in fragrances have made possible to discover new allergens, to state that current fragrance markers are not enough to detect most of fragrance ACD cases and to know the products that should be patched and their concentrations. In this review, we revise the mechanisms of sensitization to allergens that are not represented in baseline series and the concentrations at which they should be used, which should be included in specific series and the usefulness of baseline and fragrance specific series.

Purpose of review To revise the most recent advances in knowledge about fragrance contact dermatitis, especially about sensitization mechanisms and effectivity of fragrance markers in baseline series and fragrances in essential oils.

Recent findings Fragrance allergic contact dermatitis (ACD) is one of the most common sources of ACD only preceded by nickel sulfate. Many studies have shown that fragrance mix (FM)I, FMII, and colophonium, fragrance markers in baseline series, are not enough to screen for cases of ACD to fragrances. Some fragrances use limonene and linalool hydroperoxides, which have shown a high prevalence of sensitization and have been proposed as new allergens to include in the European Baseline Series, while other fragrances like

Evernia furfuracea, which have also shown a high prevalence of sensitization, will not be included. Essential oils are obtained by distillation process and are widely used. In some cases, their allergenic components are not known. Co-sensitization to other fragrance components is frequent and they should be patch tested if allergic contact dermatitis to fragrances or cosmetics is suspected.

Summary A more extensive group of fragrance markers should be included in the European Baseline Series, with at least limonene and linalool hydroperoxides and *Evernia furfuracea*. The use of products containing fragrances is very common and people sensitized to one of these substances should be suspected of multiple co-sensitizations.

Introduction

Fragrances are a group of more than 2500 substances present in many cosmetic products, most frequently deodorants, scented lotions, fine fragrances, shampoos and soaps [1]. These substances are one of the most common sources of allergic contact dermatitis (ACD), reaching a prevalence of almost 4% in general European population [2] and becoming the second most frequent cause of contact allergy after nickel sulfate [3], before others [4].

The causes of this high prevalence are repeated exposure due to their widespread distribution, the presence of these substances as combinations, which favors chemical interactions between them and irritating skin reactions, their ability to transform into more reactive substances through oxidation processes, and the

relatively recent regulations regarding these products, so that several still appear at unknown concentrations under “perfumes” label [5–8].

In the last few years, changes in cosmetic products legislation and advances on knowledge about haptens in fragrances have made possible to discover new allergens, to state that current fragrance markers are not enough to detect most of fragrance ACD cases, and to know the products that should be patched and their concentrations. In this review, we revise the mechanisms of sensitization, allergens that are not represented in baseline series and the concentrations at which they should be used, which ones should be included in specific series and the usefulness of baseline and fragrance specific series.

Sensitization mechanisms

Fragrances have been described as moderate sensitizers according to in vitro tests [9]. ACD to fragrances, as to other substances, consists of a type IV delayed-type hypersensitivity response to these antigens [10]. These are usually small molecules that need to attach to a carrier protein in order to be able to trigger an immune response. Depending on their ability to attach to proteins, fragrances are categorized as haptens, prehapens, or prohaptens.

Haptens have the property to interact with proteins without any modification in their structure as they have electrophilic functional groups in their structures, which allow them to react and bind to nucleophilic groups present in proteins. Usually, fragrances do not present these electrophilic groups and they need a previous reaction in order to be able to interact with proteins [8]. These reactions transform these moderate sensitizers into more powerful ones.

On one hand, these can be oxidation processes with environmental air or solar radiation. Air oxidation consists of the process of the loss of a hydrogen atom and the addition of oxygen, forming a peroxy radical. These peroxy radicals are usually formed on allylic position, places of the molecule where stable radicals can be formed. Once the molecule has formed a hydroperoxide, it can further add oxygen to its structure, forming aldehydes and epoxides, as secondary oxidation products. Substances that need a previous air oxidation process, before reaching the ability to interact with proteins, are called prehapens. All hydroperoxides, aldehydes, and epoxides represent a much more reactive form of the original molecule, and they can interact with carrier proteins, being able to trigger an immunologic response [11]. Geraniol, cinnamyl alcohol, and α -terpinene are fragrances whose main sensitizers are aldehydes and epoxides [12–14] while main sensitizers of limonene, linalool, and linalyl acetate are their hydroperoxides, which have a sensitizing potency fivefold to tenfold times higher [7]. Some attempts to prevent these air oxidation reactions have been made, like introducing antioxidant substances as butylated hydroxytoluene in products with fragrances. Nevertheless, it implies the risk of sensitization and ACD episodes to these substances [15].

On the other hand, fragrances can transform in haptens through enzymatic transformation. These substances receive the name of prohaptens. Reactions can be classified into two groups: phase I reactions, which consist of introducing hydrophilic groups into the molecule, and phase II reactions, where the molecules are conjugated to make them water-soluble. Different phase I (cytochrome P450, monoamine oxidase, hydrolytic enzymes) and phase II (sulfotransferases, acyltransferases) enzymes can be found in the skin [16], which transform fragrances that act as prohaptens: α -terpinene [17], cinnamyl alcohol [18], eugenol, isoeugenol [19], and geraniol [14].

As can be noted, several of these substances can acquire their sensitizing ability through both of the mechanisms described like α -terpinene, geraniol, and cinnamyl alcohol. Special care must be taken with patients sensitized to these fragrances as crossed reactions between aldehydes and alcohols have been described [20].

Allergens not represented in baseline series

Fragrances of mandatory labeling according to the EU Cosmetics Directive

According to the EU Cosmetics Directive, 26 specific fragrance ingredients (Table 1), which are the causes of allergic contact dermatitis, must be declared on the ingredient list of cosmetic products sold on the European market if the concentrations exceed 10 ppm in leave-on products or 100 ppm in rinse-off products. Other fragrances must appear as “aroma,” “fragrance,” or “perfume” [21].

Some of the fragrances shown in Table 1 constitute the screening markers fragrance mixes I and II, which form part of the European Baseline. Nonetheless, other fragrances such as *Evernia furfuracea*, limonene, and linalool have clinical relevance, even though they are not routinely tested.

Table 1. The 26 individual fragrance ingredients of mandatory labelling according to EU Cosmetic Directive

<i>Evernia furfuracea</i>
<i>Evernia prunastri</i> ^a
Cinnamal ^a
Isoeugenol ^a
Cinnamyl alcohol ^a
Hydroxycitronellal ^a
Eugenol ^a
Amyl cinnamal ^a
Geraniol ^a
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) ^b
Hexyl cinnamal ^b
Farnesol ^b
Citral ^b
Coumarin ^b
Citronellol ^b
Butylphenyl methylpropional
Benzyl salicylate
Benzyl alcohol
Anise alcohol
Benzyl cinnamate
Amylcinnamyl alcohol
Linalool
Limonene
Alpha-isomethyl ionone
Benzyl benzoate
Methyl 2-octynoate

^aFragrance ingredients constituting fragrance mix I^bFragrance ingredients constituting fragrance mix II

Evernia furfuracea (tree moss) is a moss that grows on pine and fir trees. Its extract is used in the fragrance industry, mainly in personal care products, men's cosmetics, fine fragrances, and deodorants, and has been identified as a contact allergen [7, 22]. *E. furfuracea* extract is usually patch tested in 1% pet. Studies consistently report a prevalence of > 1% and place *E. furfuracea* extract as one of the most important individual fragrance allergens found on testing the 26 individual fragrances named in ingredient labeling [1, 23–27]. The majority of the cases of contact allergy to *E. furfuracea* are not detected by screening with either fragrance mix I and/or colophonium [28]. For this reason, the European Society of Contact Dermatitis has proposed to patch test all patients with *E. furfuracea* during 1 year to study its potential inclusion in the baseline series.

Limonene and linalool are common fragrance terpenes widely used in cosmetics such as creams and deodorants and hygiene and household products. In addition, they are also constituents of some essential oils. After air exposure, they oxidize and become hydroperoxides, which have an important sensitizing potential [7, 29, 30].

The prevalence of sensitization to limonene and linalool hydroperoxides has been estimated around 5–6% in some multicentric studies [31, 32]. Some patients are co-sensitized to both hydroperoxides, as well as to other fragrances and preservatives present in hygiene products and cosmetics. This would suggest simultaneous exposure to different fragrances in products of frequent use [33].

The European Environmental Contact Dermatitis Research Group has recently recommended adding limonene and linalool hydroperoxides to the European Baseline Series. They recommend testing linalool hydroperoxide 1% and 0.5% pet. and limonene hydroperoxide 0.3% and 0.2% pet. to aid in the interpretation of frequent irritant and doubtful patch test reactions [34].

Methyl 2-octynoate has been reported to produce active sensitization in various subjects during patch testing [1, 35]. Therefore, we believe patch testing with this compound should be considered only in selected patients when suspicion is high.

In conclusion, the single fragrances most often causing contact allergy are the natural extract *E. furfuracea* and the hydroperoxides of limonene and linalool. Only 30–50% of the sensitized patients are detected when patch tested with fragrance mixes I and II [36].

The mandatory labeling of the 26 individual fragrance ingredients on cosmetic products has been of great importance to determine the clinical relevance of a positive patch test reaction and to assist patient avoidance of the sensitizer. We believe that this directive should also apply to household products, as they also contain many of these allergens.

Essential oils

Essential oils are complex substances usually obtained by steam distillation of plant materials. These compounds are widely used in the flavor, food, fragrance, cosmetic, and pharmaceutical industries in many applications. Pure oils are usually applied to the skin for alleged therapeutic actions.

Most reactions are caused by the application of pure oils or high-concentration products. Nearly 80 essential oils have been reported to cause contact allergy. Cosmetics, toothpaste, and topical pharmaceutical preparations containing essential oils have been reported to cause allergic contact dermatitis [37–39]. Occupational contact dermatitis may occur frequently in professionals performing massages or aromatherapists.

Essential oils should be patch tested in any patient suspected of contact allergy to these oils because of their history and clinical features, such as hand dermatitis in aromatherapists, in masseurs or workers of the fragrance industry, and in patients that have applied essential oils to their skin. Patch testing with essential oils should also be suggested when there are positive reactions to fragrance mixes, *Myroxylon pereirae*, or patient's products that contain them. It is preferable to patch test the patient's product itself, as the composition may vary

strongly. Testing 2 to 5% in petrolatum is adequate for most essential oils. Proper assessment of the relevance is of great importance. It is common to observe co-reaction to other essential oils, FMI, FMII, *Myroxylon pereirae*, and individual or combined fragrance chemicals [40]. Laurel, turpentine, orange, tea tree, citronella, ylang-ylang, sandalwood, clove, and costus root showed greater than 2% positive patch test reactions [40].

Tea tree oil is the volatile oil obtained by distillation from the leaves and terminal branchlets of tea tree *Melaleuca alternifolia*, a tree native to Australia. It has been perceived as an effective remedy for many skin conditions, such as eczema, acne, wounds, burns, herpes simplex, or molluscum contagiosum. Contact dermatitis caused by tea tree oil has been frequently described, including cases of occupational contact dermatitis. Co-reactivity with turpentine oil, fragrance mix I, *Myroxylon pereirae*, and colophonium has been observed [41].

Sandalwood oil has three different variants that originate from East India, Australia, and New Caledonia, is obtained by distillation of the stem and stump wood and roots, and is used in the production of soaps powder and creams, as well as for medicinal purposes. There have been cases of pigmented cosmetic dermatitis in Asian women and cases of photocontact allergy [42]. In patients suspected of contact dermatitis, there is a prevalence of positivity to sandalwood oil among 0.1 to 2.4% [24, 43, 44].

Ylang-Ylang oil is the essential oil from the flowers of the homonymous tree (*Cananga odorata*), native to Malaysia and Indonesia. It is obtained by fractional distillation and is used for the production of fine fragrances, but also soap, skin lotions, and detergents, as well as flavoring. In folk medicine, it has been used for infections and skin diseases. It is a frequent sensitizer in Japan and has been related to pigmented cosmetic dermatitis [42]. In groups of patients suspected of contact dermatitis, a prevalence of 0.7 to 2.6% positive patch tests have been reported [44]. Co-reactivity to benzyl salicylate and geraniol has been observed [42].

Patch test series and fragrances

Fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde in baseline series

Before 2005, the only fragrance marker included in the European Baseline Series was fragrance mix I (FMI), which consists of a mix of *Evernia prunastri*, isoeugenol, cinnamal, cinnamyl alcohol, hydroxycitronellal, eugenol, geraniol, and α -amylcinnamal. Some authors also included *Myroxylon pereirae* (25% pet.) and colophonium (20% pet.) as fragrance markers, despite the fact that in a strict way, they are not [45•]. In 2005, it was stated that between 33 and 43% of ACD episodes caused by fragrances were not being detected by patching MFI [4, 46], and a suggestion of including a new mixture and marker was emitted. The new mixture was fragrance mix II (FMII), which contains six of the 14 fragrances causing most of the ACD to these substances: hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC or Lyrall®), citral, farnesol, coumarin, citronellol, and α -hexyl cinnamal [47]. Due to its wide presence in household products [48], a recommendation to include HICC, as a fragrance marker, at double concentration than in FMII was also emitted [47]. Finally, in 2008, FMII and HICC

were included in European Baseline Series [49]. In the last 10 years, only 14 fragrances from the 26 that are required to be labeled if present at a concentration of ≥ 10 ppm in leave-on cosmetics or ≥ 100 ppm in rinse-off cosmetics have been represented in European Baseline Series [50]. Recently, the European Baseline Series have been updated, recommending to include linalool hydroperoxide 0.5% and 1% pet. and limonene hydroperoxide 0.2% and 0.3% pet. But still, some of the most common fragrance sensitizers like *Evernia furfuracea* or *Evernia prunastri* are not included in baseline series or fragrance mixes [25, 34], while other ACD tests, such as TrueTest®, still only include only FMI as a fragrance marker.

FMII is the second fragrance marker more frequently found positive in patch testing (4.5%), after FMI (6.0%), and followed by *M. pereirae* (2.8%), HICC (2.4%), and colophonium (2.1%) [4]. The most common sensitizers from fragrance mix II are HICC (2.5% pet.) followed by citral or farnesol [20, 51]. It has been estimated that almost 3% of the patients who are patched with FMI and FMII present a positive response only to the second one [52]. More than 70% of the positive results of FMII have been categorized as clinically relevant, and it has been described that FMII contributes to detecting up to 26% of patients with fragrance contact allergy, which would not have been detected only with FMI, colophonium, and *M. pereirae* [4].

Due to its widespread distribution and false-negative responses to the concentration included in FMII, HICC 5% pet. has been also included in the European Baseline Series [51]. Nevertheless, further studies reported that only between 10 and 13% of patients with ACD to HICC are not detected with the concentration included in baseline series and conclude that this may be a difference that does not justify the inclusion of HICC at double concentration in the baseline series and recommend to patch it only in order to confirm positive responses to FMII [53]. The high prevalence of positive responses to HICC can be explained by its common use in household products, where it can be found in up to 30% of them [22], and in cosmetics, where this percentage rises up to 72% [54]. As a result, several European and international agencies have recommended limiting the concentration of HICC in all of these products, but legislation changes have still not been made.

Specific fragrance series

In order to confirm ACD to fragrances, some specific series have been developed (Chemotechnique®, Vellinge, Sweden; MartiTor, Barcelona, Spain). There has been debated in the last years about the moment to patch these series. While some groups supported doing it after a detailed anamnesis, only in patients with a high-degree suspicion, in order to avoid false-positive results that would miscarry the management of these patients, others sustain that the sensitivity of anamnesis to detect these cases is way too low due to the high prevalence of fragrance sensitizing and that specific series should be systematically patched [55•].

Retrospective and prospective investigations about the sensitivity of FMI and FMII to predict fragrance allergy show that between 18 and 31% of patients with a positive result to any allergen in the fragrance series did not react to any of the fragrance mixes [26, 27]. By including other fragrance markers from baseline series, as colophonium and HICC, between 16 and 34% of patients with ACD

to fragrances would not be detected [1, 26]. A conclusion that can be extracted from the available bibliography is that patching only baseline series fragrance markers (FMI, FMII, *M. pereirae*, and colophonium) may not be enough. This hypothesis has recently been sustained by another group who found that sensitivity to detect fragrance allergy was 25.7% through anamnesis and 40.8% for European Baseline Series fragrance markers [55•]. In order to increase the sensitivity of fragrance patches, it should be taken into account that these patches should not be prepared in advance, as they are volatile allergens [56].

Recent data published from a multicenter study from Spain shows that only 65% of patients with a positive reaction to one of the fragrance markers from baseline series are patched with specific fragrance series. As co-sensitization to multiple fragrances is usually found in these patients, specific fragrance series usually detect sensitization to fragrances which are not present in fragrance markers. This study also concludes that fragrances in FMI should be present at double concentration in a specific series, in order to avoid a high rate of false-negative results [57].

Different attempts have been made in order to try to increase the sensitivity of fragrance patches. Some authors propose patching all 26 individual fragrances for which labeling is mandatory in the European Union as allergens in baseline series [26]. Others suggest patching, at least, those more commonly related to positive results: oxidized terpenes, limonene, linalool, and essential oils [29, 58]. Thus, our group agrees that fragrance screening still needs to be improved, by including other representative fragrances and essential oils, like *Evernia furfuracea*, oils of *Melaleuca alternifolia*, and *Santalum album* [59•]. Nonetheless, due to the ubiquitous distribution of these substances, and the problems that can be caused by the recommendation of avoiding one of them, we still think that fragrance patching should be guided by a proper anamnesis.

Conclusion

Allergy to fragrances has become one of the most frequent causes of ACD. Available tools to detect these cases have proven to be insufficient, as many fragrances have shown a higher sensitization prevalence than other substances represented in European Baseline Series. Recently, it has been recommended to include limonene and linalool hydroperoxides in baseline series. Experience with them could be decisive to include other fragrances or essential oils in the future. Co-sensitization must be taken into account in patients sensitized to fragrances and they should be patch tested with specific series if allergic contact dermatitis to fragrances or cosmetics is suspected.

Compliance with Ethical Standards

Conflict of Interest

Luca Schneller-Pavelescu declares that he has no conflict of interest. Gemma Ochando-Ibernón declares that she has no conflict of interest. Juan Francisco Silvestre-Salvador has received grants as advisor and speaker for Novartis.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Heisterberg MV, Menne T, Johansen JD. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis*. 2011;65:266–75.
2. Diepgen TL, Ofenloch R, Bruze M, Cazzaniga S, Coenraads PJ, Elsner P, et al. Prevalence of fragrance contact allergy in the general population of five European countries: a cross-sectional study. *Br J Dermatol*. 2015;173:1411–9.
3. Schnuch A, Uter W, Geier J, Gefeller O. Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug-utilization research (CE-DUR) approach. *Contact Dermatitis*. 2002;47:32–9.
4. Heisterberg MV, Andersen KE, Avnstorp C, Kristensen B, Kristensen O, Kaaber K, et al. Fragrance mix II in the baseline series contributes significantly to detection of fragrance allergy. *Contact Dermatitis*. 2010;63:270–6.
5. Paramasivan P, Lai C, Pickard C, Ardern-Jones M, Healy E, Friedmann PS. Repeated low-dose skin exposure is an effective sensitizing stimulus, a factor to be taken into account in predicting sensitization risk. *Br J Dermatol*. 2010;162:594–7.
6. Bonefeld CM, Nielsen MM, Rubin IMC, Vennegaard MT, Dabelsteen S, Giménez-Arnau E, et al. Enhanced sensitization and elicitation responses caused by mixtures of common fragrance allergens. *Contact Dermatitis*. 2011;65:336–42.
7. Uter W, Yazar K, Kratz EM, Mildau G, Liden C. Coupled exposure to ingredients of cosmetic products: I. Fragrances. *Contact Dermatitis*. 2013;69:335–41.
8. Karlberg AT, Bergstrom MA, Borje A, Luthman K, Nilsson JLG. Allergic contact dermatitis—formation, structural requirements, and reactivity of skin sensitizers. *Chem Res Toxicol*. 2008;21:53–69.
9. Liden C, Yazar K, Johansen JD, Karlberg AT, Uter W, White IR. Comparative sensitizing potencies of fragrances, preservatives, and hair dyes. *Contact Dermatitis*. 2016;75:265–75.
10. Kaplan DH, Igyarto BZ, Gaspari AA. Early immune events in the induction of allergic contact dermatitis. *Nat Rev Immunol*. 2012;12:114–24.
11. Brared Christensson J, Matura M, Backtorp C, Borje A, Nilsson JLG, Karlberg AT. Hydroperoxides form specific antigens in contact allergy. *Contact Dermatitis*. 2006;55:230–7.
12. Niklasson IB, Delaine T, Islam MN, Karlsson R, Luthman K, Karlberg AT. Cinnamyl alcohol oxidizes rapidly upon air exposure. *Contact Dermatitis*. 2013;68:129–38.
13. Rudback J, Bergstrom MA, Borje A, Nilsson U, Karlberg AT. alpha-Terpinene, an antioxidant in tea tree oil, autoxidizes rapidly to skin allergens on air exposure. *Chem Res Toxicol*. 2012;25:713–21.
14. Hagvall L, Backtorp C, Svensson S, Nyman G, Borje A, Karlberg AT. Fragrance compound geraniol forms contact allergens on air exposure. Identification and quantification of oxidation products and effect on skin sensitization. *Chem Res Toxicol*. 2007;20:807–14.
15. Karlberg AT, Borje A, Duus Johansen J, et al. Activation of non-sensitizing or low-sensitizing fragrance substances into potent sensitizers - prehaptenes and prohaptenes. *Contact Dermatitis*. 2013;69:323–34.
16. Smith C, Hotchkiss S. Enzymes and mechanisms of xenobiotic metabolism. In: allergic contact dermatitis chemical and metabolic mechanisms. London and New York, Taylor and Francis; 2001. p. 89–117.
17. Bergstrom MA, Luthman K, Nilsson JLG, Karlberg AT. Conjugated dienes as prohaptenes in contact allergy: in vivo and in vitro studies of structure-activity relationships, sensitizing capacity, and metabolic activation. *Chem Res Toxicol*. 2006;19:760–9.
18. Basketter DA. Skin sensitization to cinnamic alcohol: the role of skin metabolism. *Acta Derm Venereol*. 1992;72:264–5.
19. Melles D, Vielhaber T, Baumann A, Zazzeroni R, Karst U. In chemico evaluation of skin metabolism: investigation of eugenol and isoeugenol by electrochemistry coupled to liquid chromatography and mass spectrometry. *J Chromatogr B Anal Technol Biomed Life Sci*. 2013;913–914:106–12.
20. Schnuch A, Uter W, Geier J, Lessmann H, Frosch PJ. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis*. 2007;57:1–10.
21. European Commission. Consolidated version of Cosmetics Directive 76/768/EEC, Cosmetic Restriction III/

- 1,79, 2009. Available at: http://ec.europa.eu/enterprise/cosmetics/html/consolidated_dir.htm. Accessed Dec 2010.
 22. Buckley DA. Fragrance ingredient labelling in products on sale in the U.K. *Br J Dermatol*. 2007;157:295–300.
 23. Pongpaiboj K, Puangpet P, Thaiwat S, McFadden JP. Should *Evernia furfuracea* be included in a baseline screening series of contact allergens? *Contact Dermatitis*. 2016;74:257–8.
 24. Uter W, Schmidt E, Geier J, Lessmann H, Schnuch A, Frosch P. Contact allergy to essential oils: current patch test results (2000–2008) from the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis*. 2010;63:277–83.
 25. van Oosten EJ, Schuttelaar MLA, Coenraads PJ. Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. *Contact Dermatitis*. 2009;61:217–23.
 26. Mann J, McFadden JP, White JML, White IR, Banerjee P. Baseline series fragrance markers fail to predict contact allergy. *Contact Dermatitis*. 2014;70:276–81.
 27. Vejanurug P, Tresukosol P, Sajjachareonpong P, Puangpet P. Fragrance allergy could be missed without patch testing with 26 individual fragrance allergens. *Contact Dermatitis*. 2016;74:230–5.
 28. Uter W, Schmidt E, Lessmann H, Schnuch A. Contact sensitization to tree moss (*Evernia furfuracea* extract, INCI) is heterogeneous. *Contact Dermatitis*. 2012;67:36–41.
 29. Audrain H, Kenward C, Lovell CR, et al. Allergy to oxidized limonene and linalool is frequent in the U.K. *Br J Dermatol*. 2014;171:292–7.
 30. Rudback J, Islam MN, Borje A, Nilsson UI, Karlberg AT. Essential oils can contain allergenic hydroperoxides at eliciting levels, regardless of handling and storage. *Contact Dermatitis*. 2015;73:253–4.
 31. Deza G, Garcia-Bravo B, Silvestre JF, et al. Contact sensitization to limonene and linalool hydroperoxides in Spain: a GEIDAC prospective study. *Contact Dermatitis*. 2017;76:74–80.
 32. Brared Christensson J, Andersen KE, Bruze M, et al. An international multicentre study on the allergenic activity of air-oxidized R-limonene. *Contact Dermatitis*. 2013;68:214–23.
 33. Brared Christensson J, Karlberg AT, Andersen KE, et al. Oxidized limonene and oxidized linalool - concomitant contact allergy to common fragrance terpenes. *Contact Dermatitis*. 2016;74:273–80.
 34. Wilkinson M, Goncalo M, Aerts O et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis*. 2018;80:1–4.
 35. Heisterberg MV, Vigan M, Johansen JD. Active sensitization and contact allergy to methyl 2-octynoate. *Contact Dermatitis*. 2010;62:97–101.
 36. Bennike NH, Zachariae C, Johansen JD. Non-mix fragrances are top sensitizers in consecutive dermatitis patients - a cross-sectional study of the 26 EU-labelled fragrance allergens. *Contact Dermatitis*. 2017;77:270–9.
 37. Lauriola MM, De Bitonto A, Sena P. Allergic contact dermatitis due to cinnamon oil in galenic vaginal suppositories. *Acta Derm Venereol*. 2010;90:187–8.
 38. Nardelli A, D'Hooghe E, Drieghe J, Dooms M, Goossens A. Allergic contact dermatitis from fragrance components in specific topical pharmaceutical products in Belgium. *Contact Dermatitis*. 2009;60:303–13.
 39. Clayton R, Orton D. Contact allergy to spearmint oil in a patient with oral lichen planus. *Contact Dermatitis*. 2004;51:314–5.
 40. de Groot AC, Schmidt E. Essential oils, part IV: contact allergy. *Dermatitis*. 2016;27:170–5.
 41. de Groot AC, Schmidt E. Tea tree oil: contact allergy and chemical composition. *Contact Dermatitis*. 2016;75:129–43.
 42. de Groot AC, Schmidt E. Essential oils, part VI: sandalwood oil, ylang-ylang oil, and jasmine absolute. *Dermatitis*. 2017;28:14–21.
 43. Frosch PJ, Johansen JD, Menné T, et al. Further important sensitizers in patients sensitive to fragrances. *Contact Dermatitis*. 2003;47:279–87.
 44. Wetter DA, Yiannias JA, Prakash AV, Davis MDP, Farmer SA, el-Azhary RA. Results of patch testing to personal care product allergens in a standard series and a supplemental cosmetic series: an analysis of 945 patients from the Mayo Clinic Contact Dermatitis Group, 2000–2007. *J Am Acad Dermatol*. 2010;63:789–98.
 45. Frosch PJ, Duus Johansen J, Schuttelaar MLA, et al. Patch test results with fragrance markers of the baseline series - analysis of the European Surveillance System on Contact Allergies (ESSCA) network 2009–2012. *Contact Dermatitis*. 2015;73:163–7.
- This study provides a thorough description of fragrance contact dermatitis in European countries.
46. Larsen W, Nakayama H, Fischer T, Elsner P, Frosch P, Burrows D, et al. A study of new fragrance mixtures. *Am J Contact Dermat*. 1998;9:202–6.
 47. Frosch PJ, Pirker C, Rastogi SC, Andersen KE, Bruze M, Svedman C, et al. Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. *Contact Dermatitis*. 2005;52:207–15.
 48. Frosch PJ, Johansen JD, Menne T, Rastogi SC, Bruze M, Andersen KE, et al. Lyril is an important sensitizer in patients sensitive to fragrances. *Br J Dermatol*. 1999;141:1076–83.
 49. Bruze M, Andersen KE, Goossens A. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyril) in the European baseline patch test series. *Contact Dermatitis*. 2008;58:129–33.
 50. Bruze M, Svedman C, Andersen KE, Bruynzeel D, Goossens A, Johansen JD, et al. Patch test concentrations (doses in mg/cm²) for the 12 non-mix fragrance substances regulated by European legislation. *Contact Dermatitis*. 2012;66:131–6.
 51. Frosch PJ, Rastogi SC, Pirker C, Brinkmeier T, Andersen KE, Bruze M, et al. Patch testing with a new fragrance

- mix - reactivity to the individual constituents and chemical detection in relevant cosmetic products. *Contact Dermatitis*. 2005;52:216–25.
52. Krauthelm A, Uter W, Frosch P, Schnuch A, Geier J. Patch testing with fragrance mix II: results of the IVDK 2005-2008. *Contact Dermatitis*. 2010;63:262–9.
 53. Isaksson M, Inerot A, Liden C, et al. Multicentre patch testing with fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde by the Swedish Contact Dermatitis Research Group. *Contact Dermatitis*. 2014;70:187–9.
 54. Rastogi SC, Johansen JD, Bossi R. Selected important fragrance sensitizers in perfumes—current exposures. *Contact Dermatitis*. 2007;56:201–4.
 55. • Ung CY, White JML, White IR, Banerjee P, McFadden JP. Patch testing with the European baseline series fragrance markers: a 2016 update. *Br J Dermatol*. 2018;178:776–8.
- This study states that current fragrance markers in the European Baseline Series are not enough to detect fragrance sensitization.
56. Buckley DA. Advance preparation of some patch test series should be avoided. *Br J Dermatol*. 2012;167:708–9.
 57. Silvestre JF, Mercader P, González-Pérez R et al. Sensitization to fragrances in Spain: a 5-year multicentre study (2011-2015). *Contact Dermatitis*. 2018;80:94–100.
 58. Warshaw EM, Zug KA, Belsito DV, et al. Positive patch-test reactions to essential oils in consecutive patients from North America and Central Europe. *Dermatitis*. 2017;28:246–52.
 59. • Wilkinson M, Gallo R, Goossens A, et al. A proposal to create an extension to the European baseline series. *Contact Dermatitis*. 2018;78:101–8.
- This article states that limonene and linalool hydroperoxides should be included in European baseline series.