



Dermatotoxicologic clinical solutions: clinical management of fragrance mix #1 #2 patients?

Ashley Edwards, Nicholas Blickenstaff, Garrett Coman & Howard Maibach

To cite this article: Ashley Edwards, Nicholas Blickenstaff, Garrett Coman & Howard Maibach (2015) Dermatotoxicologic clinical solutions: clinical management of fragrance mix #1 #2 patients?, Cutaneous and Ocular Toxicology, 34:2, 167-170, DOI: [10.3109/15569527.2014.926368](https://doi.org/10.3109/15569527.2014.926368)

To link to this article: <http://dx.doi.org/10.3109/15569527.2014.926368>



Published online: 25 Jun 2014.



Submit your article to this journal [↗](#)



Article views: 58



View related articles [↗](#)



View Crossmark data [↗](#)

COMMENTARY

Dermatotoxicologic clinical solutions: clinical management of fragrance mix #1 #2 patients?Ashley Edwards¹, Nicholas Blickenstaff², Garrett Coman^{2,3}, and Howard Maibach³¹Touro University, Vallejo, CA, USA, ²University of Utah School of Medicine, Salt Lake City, USA, and ³Department of Dermatology, University of California San Francisco, San Francisco, USA**Abstract**

Today's fragrances are present in more than just perfumes, having become ubiquitous in skin care products such as creams, shampoos, sun tan lotion and deodorants. While aromatics can arouse the senses, aromatic compounds applied to skin can also cause allergic contact dermatitis. This article describes diagnosis, limitations of patch testing for fragrance mix 1 and fragrance mix 2, the relevance of fragrance concentration in products, use testing of common consumer products and our current recommendations in regards to the management of fragrance contact allergy.

Keywords

Dermatitis, fragrance allergy, patch test, repeat open application test, use test

History

Received 6 January 2014

Revised 17 April 2014

Accepted 15 May 2014

Published online 19 June 2014

Introduction

Scenting our bodies with the fragrances of flowers, herbs and other plants is an ageless practice, not unique to a single culture. Today's fragrances are present in more than just perfumes, having become ubiquitous in skin care products (Table 1) such as creams, shampoos, sun tan lotion¹ and deodorants². While these fragrances can increase the appeal of consumer products, they can also lead to allergic contact dermatitis. To identify patients who may suffer from dermatitis resulting from fragrance, patch testing for common aromatic allergens was developed. Fragrance mix #1 (FM1) and fragrance mix #2 (FM2) (Table 2), composed of putative common allergens, are used as convenient screens. While some dermatologists recommend avoiding fragrances in patients with a positive patch test result, this is challenging for the patient and may be unnecessary.

This article describes diagnosis, limitations of patch testing for FM1 and FM2, the relevance of fragrance concentration in products, use testing and recommendations.

Diagnosis

The diagnosis of a fragrance contact allergy always starts with a detailed medical history. Schollhammer et al., provided a questionnaire that determined if patients had a certain,

probable or possible allergy³, outlined in Table 3. In this study, 7.4% of consecutive patch tested patients for allergic contact dermatitis provided a "certain" history of fragrance allergy. FM1 patch testing of this cohort identified 28.6–38.6% of those with a certain history of fragrance allergy, demonstrating that FM1 is not sufficient to diagnose fragrance allergy.

We note that history is unfortunately not in itself a strong predictor of allergic contact dermatitis (ACD). While most clinicians believe that nickel sensitivity would be easily diagnosed by history, Keefer observed 65% sensitivity and 96.6% specificity when comparing a history of metal allergy to nickel patch positivity⁴. Fragrance allergy can prove even more challenging than nickel to diagnose by history alone, except for that involving the axilla and deodorants/antiperspirants².

Traditionally, with the proper clinical history, patients proceed to patch testing for FM1 and FM2 in order to define the possible role of fragrance to the dermatitis.

In addition, negative reactions to FM1 and FM2 in the baseline series do not exclude the diagnosis of fragrance allergy.

Patch testing

Testing with FM1 is common practice when dermatitis is suspected to be from a fragrance. Nardelli et al., show that 9.6% of patients investigated for contact allergy reacted positively to FM1 and 6% to FM2⁵. Of those with suspected fragrance induced dermatitis, sensitivity for FM1 was shown to be 27.2% and 8.7–21.5% for FM2⁶. In addition, Larsen et al. report false negatives to be 33%, suggesting neither FM1 or FM2 alone to be sufficient screening tools⁷.

Address for correspondence: Garrett Coman, University of Utah School of Medicine, Salt Lake City, USA; Dermatology, University of California San Francisco, 90 Medical Center Way, Box 0989, San Francisco 94143-0989, USA. E-mail: garrett.coman@hsc.utah.edu

Table 1. Cosmetic product groups associated with fragrance allergy.

Product category
Unspecified stay-on products
Deodorant
Scented lotion
Unspecified rinse-off products
Fine fragrances
Shampoo
Liquid soap
Aftershave
Lipstick
Sun lotion
Hairstyling product
Shaving foam
Mascara
Hair dye
Eye shadow
Makeup cream

Adapted from Heisterberg et al. 2011.

Table 2. Summary of compounds tested by fragrance mix #1 and #2.

Constituent
Evernia prunastri (Oak moss)
Isoeugenol
Cinnamyl alcohol
Eugenol
Cinnamal
Geraniol
α -Amylcinnamal
Hydroxycitronellal
HICC
Farnesol
Citral
Hexyl cinnamal
Citronellol
Coumarin

HICC = hydroxyisohexyl 3-cyclohexene carboxaldehyde.
Adapted from Nardelli et al. 2013.

Table 3. Categorizing suspected allergic contact dermatitis patients based on recollection of adverse reactions to perfumes or perfumed products.

Category	Description
Certain	Has reacted with an itching dermatitis to at least one denominated fine perfume or aftershave and has reacted to other perfumed products.
Probable	Has reacted to one or more perfumed products (e.g. deodorant), but a certain perfume has not been identified as the cause of a clinical reaction.
Possible	Has reacted to various cosmetic products with and without perfume; materials other than fragrance constituents may be the cause of the reaction.
None	Has never reacted to a perfumed material.

Intuitively 2+ and 3+ patch test reactions should be more likely to be repeatable (retest) and of clinical relevance. Documenting this beguiling assumption requires additional use test studies such as the repeat open application test (ROAT) or provocative use test (PUT) as performed by Andersen et al.¹³.

Table 4. 26 specific fragrance constituents declared on cosmetics in the EU.

Constituent	Fragrance mix (if applicable)
<i>Evernia prunastri</i>	FM 1
Isoeugenol	FM 1
Cinnamyl alcohol	FM 1
Eugenol	FM 1
Cinnamal	FM 1
Geraniol	FM 1
Amyl cinnamal	FM 1
Hydroxycitronellal	FM 1
HICC	FM 2
Farnesol	FM 2
Citral	FM 2
Hexyl cinnamal	FM 2
Citronellol	FM 2
Coumarin	FM 2
Butylphenyl methylpropional	
<i>Evernia furfuracea</i>	
Linalool	
Benzyl salicylate	
Benzyl alcohol	
Anise alcohol	
Benzyl cinnamate	
Amylcinnamyl alcohol	
Limonene	
Alpha-isomethyl ionone	
Benzyl benzoate	
Methyl 2-octynoate	
Sorbitan sesquioleate	

Adapted from Heisterberg et al. 2011.

Limitations include patients reacting negatively when tested for the individual constituents of FM1, but positively to the mixture⁸. This may be due to false positive reactions to the mix, lowered allergen threshold, false negative reactions to individual constituents or the existence of a compound allergy⁵. Reaction to the mixture, and not individual constituents, further complicates the meaning of a positive FM1 patch test. Schnuch et al. noted that 46% of FM1 positives failed to react to its components, suggesting that these represent false positive responses⁸.

To further increase sensitivity, Heisterberg et al. recommend using four screening markers; FM1, FM2, *Myroxylon pereirae* (balsam of Peru) and hydroxyisohexyl 3-cyclohexene carboxaldehyde. They recommend testing for 26 specific fragrance constituents (Table 4) to increase sensitivity¹. Recently, additional allergens have been commercialized, including hydroperoxides of linalool, hydroperoxides of limonene and a new perfume mix⁹. In addition to screening allergens, testing with the patient's own products can be helpful.

If a patient tests positive to FM1 or FM2, some providers will advise the patient to avoid all FM1 and FM2 fragrance compounds. This is challenging because product ingredients are not always listed. Other providers advise their patients to eliminate exposure to all fragrances. This is not a simple task when considering the pervasive use of fragrance in products. It may be possible to find a fragrance-free body lotion, but few brands produce fragrance-free versions of all product lines.

Table 5. IFRA categorization of products for determining acceptable exposure level.

Category	Products
Category 1	Lip products, toys and waxes for mechanical hair removal
Category 2	Deodorants, antiperspirants and fragranced bracelets
Category 3	Aftershave, eye products, facial creams, tampons, baby creams and body paint for children

Products are categorized based Sensitization Assessment Factors (SAFs) and consumer product exposure. Adapted from <http://www.ifraorg.org>, as of 15 Oct 2013.

Concentration of fragrances

Consideration of fragrance concentration and its impact on dermatitis adds another layer of complexity when managing fragrance-allergic patients. The International Fragrance Research Association (IFRA) publishes safe guidelines on fragrance use. Based on research, the IFRA Code of practice includes 186 standards that either restrict or prohibit the use of selected fragrance materials for all types of applications. Producers of fragranced cosmetics and household products are expected to comply with IFRA standards¹⁰. The European Commission’s Scientific Committee on Consumer Safety has published an update to their opinion on fragrance allergens in cosmetic products, and based on the clinical experience alone, they now have 82 substances in fragrances that can be classified as established contact allergens in humans (54 single chemicals and 28 natural extracts)¹¹. In addition to regulating specific fragrance compounds, IFRA sets acceptable fragrance exposure levels. Allowable concentrations are determined by quantitative risk assessment of factors such as volume of use, dermal exposure and structural alerts for dermal sensitization. Three broad categories organize products by exposure level (Table 5). As the IFRA has learned more about fragrances, recommended concentrations of fragrances continues to decrease. This suggests fragrance concentration is relevant to dermatitis; however, the tolerated level is unlikely to be discerned by patch testing alone.

Use testing/ROAT

IFRA regulations underscore the importance of fragrance concentration. Understanding time–dose relationship is important information for patients to integrate into their daily use or abstinence from scented products. Svedman et al. described patients who were tested in three-week ROATs equal to or below the IFRA concentration standard for eugenol, a weak sensitizer. A typical use test (ROAT) consists of once to twice daily application of the product to a convenient anatomic site, such as the cubital fossa, for up to 28 days. At those levels, eugenol did not induce reactions in eugenol patch test positive volunteers¹². The time to react for a ROAT has been shown to vary based on individual sensitivity and exposure concentrations, up to weeks later¹³. Additional use test studies with fragrances will be welcomed.

Table 6. Recommendations.

1. Discontinue use for 8–12 weeks
2. Test to individual fragrances
3. Consider use testing – when patient is motivated to use a specific product
4. Attempt to identify product(s) that might be clinically relevant (deodorants/antiperspirants are prime targets)

Recommendations

If contact dermatitis from a fragrance is suspected, the fragranced product should be discontinued for 8–12 weeks. At that point, patch testing for common aromatic allergens included in FM1 and FM2 should be attempted to identify clinically relevant fragrances. Dermatologic offices equipped with more complete fragrance batteries (Tables 2 and 4) permit identification of additional fragrance allergens. In Europe, if the concentration of the 26 known fragrance allergens exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product, they must be listed on the label. With the allergens listed on products, it gives the patient more freedom in choosing products¹⁴. If a patient is motivated to use a specific product after the period of abstinence, a ROAT can be performed to ascertain if there is an acceptable exposure concentration. As noted above, this consists of once to twice daily applications of the product for up to 28 days, typically to the cubital fossa. Identification of the offending fragrance and a ROAT to understand appropriate concentration may allow the patient to resume use of the fragranced product in a safe manner (Table 6). Botanicals cover a broad arena of related and unrelated chemicals to which a consumer is exposed. Although widely used over centuries in Europe and Asia, full chemical disclosures are limited. Scheman et al. provide an assessment of fragrance chemicals in natural products¹⁵. Until complete chemical characterization and labeling, we advise fragrance allergic contact dermatitis patients to use caution in the interim. When the patient is highly emotionally motivated to continue their use of the product, the four-week use test (ROAT/PUT) provides a degree of practicality. Taken together, much remains to be learned about the clinical relevance of a positive fragrance mix patch test. The recent use test observation of Svedman et al. provides one link to understanding practical patient centric tolerated fragrance levels. Banning lifelong fragrance use is practiced – but often cumbersome for the patient. With the exception of overt dermatitis from fine fragrances/toilet water and axillary dermatitis from deodorant/antiperspirant, clinical relevance is often not obvious.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Heisterberg MV, Menné 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;65:266–275.
2. Heisterberg MV, Menné T, Andersen KE, et al. Deodorants are the leading cause of allergic contact dermatitis to fragrance ingredients. Contact Dermatitis 2011;64:258–264.
 3. Schollhammer L, Andersen KE, Mortz CG. The diagnostic value of patch tests with two fragrance mix I preparations for detection of clinically relevant perfume allergy. Contact Dermatitis 2012;66:350–352.
 4. Kieffer M. Nickel sensitivity: relationship between history and patch test reaction. Contact Dermatitis 1979;5:398–401.
 5. Nardelli A, Carbonez A, Drieghe J, Goossens A. Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and *Myroxylon pereirae* and colophonium, over a 21-year period. Contact Dermatitis 2013;68:307–313.
 6. Frosch PJ, Pirker C, Rastogi SC, 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;52:207–215.
 7. Larsen W, Nakayama H, Fischer T, et al. A study of new fragrance mixtures. Am J Contact Dermat Off J Am Contact Dermat Soc 1998;9:202–206.
 8. Schnuch A, Geier J, Uter W, Frosch PJ. Another look at allergies to fragrances: frequencies of sensitisation to the fragrance mix and its constituents. Exog Dermatol 2002;1:231–237.
 9. Patch Test Products and Reference Manual 2014. 2014. Available from: [http://www.chemotechnique.se/ckfinder/userfiles/files/Patch%20Test%20Products%20and%20Reference%20Manual%202014%20-%20For%20digital%20distribution\(1\).pdf](http://www.chemotechnique.se/ckfinder/userfiles/files/Patch%20Test%20Products%20and%20Reference%20Manual%202014%20-%20For%20digital%20distribution(1).pdf) [last accessed 15 Nov 2013].
 10. IFRA RIFM QRA Information Booklet Version 6.0. International Fragrance Association; 2011. Available from: <http://www.ifraor-g.org> [last accessed 15 Oct 2013].
 11. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety (SCCS); 2012. Available from: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf [last accessed 16 April 2014].
 12. Svedman C, Engfeldt M, Api AM, et al. Does the new standard for eugenol designed to protect against contact sensitization protect those sensitized from elicitation of the reaction? Dermat Contact Atopic Occup Drug 2012;23:32–38.
 13. Andersen KE, Johansen JD, Bruze M, et al. The time-dose-response relationship for elicitation of contact dermatitis in isoeugenol allergic individuals. Toxicol Appl Pharmacol 2001;170:166–171.
 14. Buckley DA. Fragrance ingredient labelling in products on sale in the U.K. Br J Dermatol 2007;157:295–300.
 15. Scheman A, Scheman N, Rakowski E-M. European directive fragrances in natural products. Dermatitis 2014;25:51–55.