

Identification of the causes of an allergic reaction to a fragranced consumer product^{#†}

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ABSTRACT: Identification of substances in consumer products (more particularly fragrance allergens in cosmetics) that are responsible for cases of contact dermatitis is of key importance for the patient and also for industry so that appropriate risk management measures can be applied. This is best done by a close collaboration between the dermatologist, the manufacturer of the consumer (cosmetic) product and the fragrance supplier. This paper describes a recommended practice that has been successfully applied for many years to achieve this goal. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Around 3000 fragrance ingredients are in current use (www.ifraorg.org) and some of these may be associated with cases of contact dermatitis in consumers of cosmetics or other fragrance-containing products. In their attempts to determine what substances have caused these types of allergic reaction, dermatologists often use patch testing and in some cases will employ sophisticated and time-consuming analytical techniques in order to identify the causative allergen,^[1,2] which is beneficial to neither the patient nor the dermatologist in identification and avoidance of the contact allergen.

Via Appendix 4 to the Code of Practice of the International Fragrance Association (www.ifraorg.org), fragrance manufacturers are required to give 'full assistance to physicians in attempting to discover the causative agents of contact dermatitis'. The aim of this publication is to provide guidance in this regard, based on established practices that have been successfully used by a number of manufacturers of fragrances and cosmetic products over many years. Despite surveillance procedures such as 'Cosmetovigilance' throughout Europe,^[3] allergic reactions to cosmetic ingredients are apparently relatively rare in relation to the number of cosmetic products in the marketplace.

Dermatologists often pursue studies, despite the serious practical difficulties,[†] to establish clear relationships between cause and effect for patients with cases of contact dermatitis. Although there are many publications that implicate fragrance materials and demonstrate sensitivity to them in patients, very few mention strict procedures for establishing clinical relevance.^[4-7] A key step is to identify the substance or substances present in a recently used product that can elicit an allergic response.

[†] One of the issues linked to patch testing is the quality of the material used for patch testing compared to what is used in the marketplace. Age, storage conditions, source of the material (especially for naturals) can have a significant impact on the quality of the material, including its potential to induce or elicit skin sensitization.

The Fragrance Industry has established a project with manufacturers of patch test materials to supply them free of charge with marketed qualities of fragrance ingredients.

Previous publications provided information to improve the flow of information between dermatologists and the industry.^[8,9]

This publication intends to enlarge the scope by presenting the full extent of the systems that have been put into place by the perfumery and cosmetics industries. It aims to help dermatologists identify the fragrance ingredient(s) that may be responsible for the reactions, in cases of suspected fragrance allergy, so that appropriate risk management procedures can be put in place.

Process Description

The overall process is summarized in Figure 1. The first steps, starting with the patient's visit to a dermatologist, are already described in the paper 'Procedures for promptly supplying fragrance information the dermatologists'^[10] and will therefore be only briefly repeated here. Further information can also be found on the IFRA website in the section 'Education', subsection 'Working with dermatologists'.

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[#] This recommended practice was developed by a special task force of experts from IFRA and COLIPA

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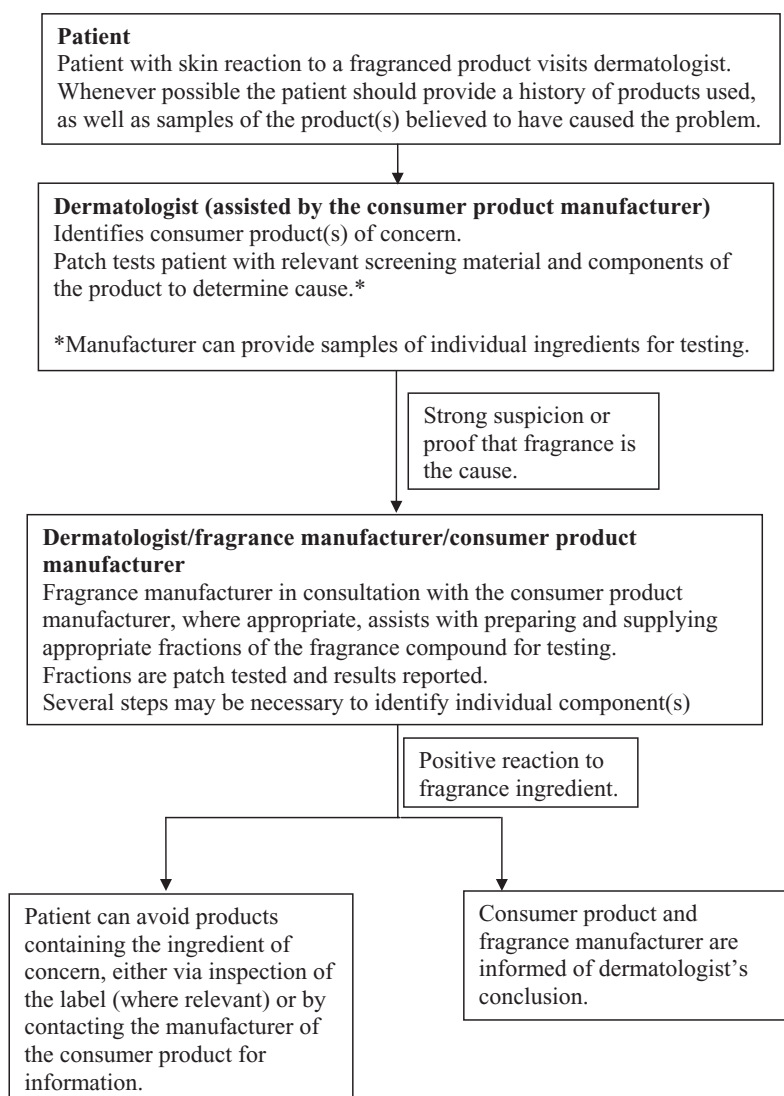


Figure 1. Sequence for the identification of the cause of an allergic reaction to a fragranced product

The patient may already suspect one or more cosmetic products to be the cause of his/her medical condition. This may be further strengthened by the interview with the dermatologist and consideration of the history of product(s) use. It is vital that the patient brings the product(s) and its packaging to the dermatologist. Points strengthening the suspicion towards a specific product are the site of the eczema and history of exposure to the product (timing of exposure). Patch testing or repeat open application testing (ROAT) with the complete product may be indicated. A positive result would be the proof of relevance.

When the source of skin allergy has been traced to a particular suspected product, it is strongly recommended that the dermatologist contacts the manufacturer of that product.

Many manufacturers provide a contact address or phone number on their packaging. In addition, the Personal Care Products Council (PCPC) of the USA maintains a service called 'Cosmetic Industry ON CALL'. This is a joint project between the PCPC and the American Contact Dermatitis Society (ACDS), which has resulted in the publication of a directory that identifies the contact persons employed by the individual cosmetic manufacturers or distributors who can provide information on product

formulations and ingredients. Copies can be ordered from the PCPC (<http://www.personalcarecouncil.org/>).

Other associations representing producers of cosmetic products, such as COLIPA in Europe (www.colipa.com), JCIA in Japan (www.jcia.org) or ACCORD in Australia (<http://www.accord.asn.au/home>) will provide help in establishing contact to finished product manufacturers in their respective regions.

By contacting the manufacturer, the dermatologist will gain access to expert information about the product and, if necessary, to ready-prepared patch test samples of the actual raw materials used in the suspected product.

With the help of the manufacturer, the dermatologist may continue the investigation by patch testing the cosmetic product and its ingredients, in addition to any standard battery of commercially available patch test materials judged relevant to the patient's medical history.

If the diagnostic patch test reveals a skin allergy due to the fragrance compound (a mixture of fragrance ingredients found in the final cosmetic product) in the product, the investigation may begin into the fragrance's ingredient(s) responsible for the reactions.

Identifying the Ingredient(s) within a Fragrance Compound Responsible for the Reaction

Until recently the word 'parfum' indicated that a cosmetic product contained a fragrance. In Europe, since March 2005 cosmetic as well as detergent products also indicate the presence of 26 specific materials (above a certain threshold), listed with their INCI names in Table 1.^[11,12]

One of the reasons for declaring these substances on cosmetic products and detergents in Europe, besides the main purpose of consumer information, has been to assist dermatologists in determining the cause of allergies. However, several of those may be declared on a single product and not all are associated with the same likelihood of causing or eliciting reactions in consumers.^[13–22] In regions where labelling of individual fragrance ingredients is not in place, this identification may not be possible.

In order to gain detailed information about the composition of a fragrance compound, it will be necessary to contact the fragrance supplier. The identity of this supplier can be obtained from the manufacturer of the consumer product. Some of the cosmetic product manufacturers may themselves take on the task of pursuing the investigation with the help of their fragrance supplier, thus acting as an intermediary between the fragrance supplier and the dermatologist.

The expertise and knowledge regarding a specific fragrance compound from a specific manufacturer is also readily shared by the International Fragrance Association (contact details on www.ifraorg.org), which maintains a list of expert contacts within each of the different fragrance suppliers.

Table 1. Substances that may now appear on the list of ingredients of cosmetic or detergent products

Amyl cinnamal
Amylcinnamyl alcohol
Anise alcohol
Benzyl alcohol
Benzyl benzoate
Benzyl cinnamate
Benzyl salicylate
Butylphenyl methylpropional
Cinnamal
Cinnamyl alcohol
Citral
Citronellol
Coumarin
Eugenol
<i>Evernia furfuracea</i> (treemoss) extract
<i>Evernia prunastri</i> (oakmoss) extract
Farnesol
Geraniol
Hexyl cinnamal
Hydroxycitronellal
Hydroxyisohexyl 3-cyclohexene carboxaldehyde
Isoeugenol
α -Isomethyl ionone
Limonene
Linalool
Methyl 2-octynoate

The fragrance compound supplier, often in collaboration with the cosmetic product manufacturer, will examine the fragrance compound, which may contain over 200 individual ingredients, and will provide information to the dermatologist on the presence and levels of certain ingredients. It is advised that fractions of the fragrance be prepared for testing, to help track down the causative allergen. Due to the number and diversity of fragrance ingredients, this can be a complex task and often expertise in the formulation and safety of fragrances is required. We therefore provide guidance below as a recommendation for a way to achieve this.

Guidance on Preparation of Fractions of the Fragrance

For the choice of fractions of the fragrance compound, the fragrance supplier should take into account the following: the percentage of individual ingredients in the compound and the likelihood of each to cause allergy; potential for cross-reaction of ingredients in the fragrance; the need to avoid inducing allergy during patch testing; the need to minimize false-positive and false-negative reactions; the chemical family of the ingredients; and the number of patch sites available to test. This will determine how many fractions of the fragrance need to be prepared. The fractions should be planned so as to reduce as far as practicable the number of visits required to arrive at a conclusion. These considerations are further explored below.^{††}

Identifying the Most Likely Cause(s) of Allergy

On inspection of a fragrance formula, knowledge of the percentage of each ingredient in the fragrance, the amount of fragrance in the cosmetic product and information regarding the sensitization potential of each ingredient can be brought together to make a screen for potential candidates for the cause of the allergy. Substances present at high levels that have a known sensitization potential, or those which are frequently reported in clinical studies as sources of positive patch tests, would be lead candidates in this case. Presence on the list of 26 labelled fragrance ingredients and the proximity of the substances concentration in the final consumer product to the maximum IFRA limits can be useful guides.

While the IFRA Code of Practice stipulates that ingredients should only be present at levels that do not induce allergy, the patient may have a particular sensitivity above that seen in the general population. Another possibility is that the sensitization may have been induced via a separate exposure and subsequent elicitation of the allergy is seen and attributed to the cosmetic product in question.

Potential for Cross-reaction of Ingredients

Inspection of the formula may also reveal cross-reacting ingredients that converge to a common allergen and which together may be present at a significant concentration, such that they

^{††} Differences in health care practices worldwide might have an impact of the patient's willingness to participate in all testing steps potentially necessary to identify the cause of his individual reaction. Systems that support patients to repeatedly visit the dermatologist certainly encourage patients to get tested and make informed decisions, which is in their best interest as well as in the interest of manufacturers of fragranced products.

should be tested together. For example, the possibility of so-called 'cross-reactions', either through similarities in chemical structure^[23] or due to cutaneous metabolisms which converge to give a common 'ultimate hapten',^[24] should be considered at this stage.

The Need to Avoid Inducing Allergy during Patch Testing

Repetitive patch testing at high doses can sensitize the patient to substances to which they were not originally sensitive. Although standard patch-testing procedures are not set up to detect this type of phenomenon, cases have been observed and reported^[25–27] and the phenomenon is probably more widely spread than many think.^[28,29] Care must be taken to avoid such unwanted reactions, e.g. by avoiding testing fractions at doses which are comparable to those that could sensitize or cause irritation to patients (for instance historical data from human safety testing).

The Need to Minimize False-positive and False-negative Reactions

Neither is in the interest of the patient. The dose delivered by common commercial patches containing only 1% test material can vary in the range 300–1770 $\mu\text{g}/\text{cm}^2$, whereas consumer exposure to a fragrance ingredient present at 1% in a perfume spray will not exceed applied doses of 100 $\mu\text{g}/\text{cm}^2$.^[30] The occlusion afforded by commercial patches also enhances dermal penetration compared to normal exposure to substances in cosmetics^[31] and patch testing maintains exposure for longer periods (48 h) than would normally be experienced with most cosmetic products.

Hence, patch testing already maximizes exposure to the test material compared to that arising from consumer use of cosmetics. This should be considered in selecting concentrations of different fractions and substances. It is possible that a patient may be weakly allergic to some substances at a sub-clinical level (i.e. the patient can still safely use products containing these and they are not responsible for the contact dermatitis experienced by the patient), but over-exposure to the substance in the patch test will elicit an allergic response that could mislead and divert attention away from the true causative allergen.^[32]

It is recommended that individual ingredients present at a high level in the formula, and with a known sensitization potential or associated with reported cases of human allergy, are tested at least at the concentration found in the final product, diluted in the relevant solvent (usually the solvent used in the fragrance preparation).

Fractionation by Chemical Family of the Ingredients

Due to the number of potential steps and visits required to the dermatologist in this process, it is recommended to use this approach only when inspection of the formula does not indicate any clearly likely causes.

The percentage of individual ingredients in the product and their likelihood to cause allergy must be evaluated as indicated above. On this basis, fractions should be constituted as far as possible such that each fraction contains only one major suspected causative agent. Substances that are potential cross-reactors would be placed in the same fraction. When the fragrance contains a high level of one or maybe two substances

known to be frequent clinical elicitors or with clear sensitization potential as described above, it would be more expedient to test the suspect substances separately in a 'fraction' of their own with the rest of the formula as a second fraction as a first step.

Fragrances may contain over 200 ingredients and these ingredients within the fragrance can, after taking account of the above-mentioned considerations, be assigned to fractions on the basis of their chemical class. This approach, although sometimes time-consuming, has been used successfully on a number of occasions to identify the eliciting allergens that were responsible for particular cases of cosmetic-related allergic contact dermatitis.^[33]

As a general rule, unless the fragrance is exceptionally deficient in one of the major classes, it should be possible to create fractions according to the following possible classes:

1. Esters.
2. Alcohols.
3. Aldehydes, Schiff bases and acetals.
4. Ketones and oximes.
5. Phenols.
6. Ethers.
7. Hydrocarbons.
8. Otherwise not assigned, e.g. naturals or purchased specialty bases containing no 'principal component(s)' of one of the above classes.

Naturals and specialty bases known to contain a 'principle component' (a judgemental decision based on concentration and notoriety of this component as an 'elicitor') are placed in the appropriate chemical class. For instance, clove oil is placed in phenols, due to eugenol. Lemon oil is added to the hydrocarbon or aldehyde fraction, depending on its relative limonene and citral levels.

As a general rule, no single fraction should contain less than 10% of ingredients from the original fragrance and the percentages of these ingredients in each fraction should be roughly equivalent. These should be diluted in the relevant solvent (usually the solvent used in the fragrance preparation).

Once a fraction is shown to be the cause of allergy, this can be further split for retesting to find the potential cause of allergy.

Number of Patch Sites Available to Test

There is a limit to the number of patches that can be applied to a patient's skin. The dermatologist may also want to simultaneously test other materials on the same patient. It is therefore advantageous to create fractions in a way that combines as many potential 'culprits' as possible.

To summarize the approach recommended: first, ingredients with a known sensitization potential present at high levels should be highlighted for patch testing. Inspection of the formula may also reveal cross-reacting ingredients that converge to a common allergen and which together may be present at significant concentration and should also be tested together. Where the likely causes are not readily identifiable then fractionation by chemical class can be used. To avoid false-positives and -negatives, dilution should be made to reflect the concentrations found in the final product and in the relevant solvent (usually the solvent used in the fragrance preparation).

Conclusions

This recommended practice aims at identifying the true causes of allergy and for describing procedures that can be used to identify substances in fragrances that may be responsible for cases of allergic contact dermatitis arising from the use of fragrance-containing consumer products. As such, it provides guidance to cosmetic and fragrance manufacturers on the practical aspect and benefits of sharing information and samples with dermatologists and on preparation of appropriate samples for the investigation.

The benefit to the consumer is that, through the measures provided by the medical community and supported by the industry, if the test procedure is successful in elucidating the cause of allergy, he/she will be able to make an informed decision by avoiding products that contain the material identified as problematic, instead of having to generally avoid all fragranced products.

For the procedure to fully benefit the community, it will require increasingly closer cooperation between industry and the medical profession. It is the experience of the industry today that very few cases of perfume allergy are directly reported to the industry's vigilance systems and few requests are received for help in in-depth investigations. A cooperative system with a more effective feedback could help guide and refine industry initiatives and the restrictive measures that it must take and would enhance the success rate of medical diagnoses and ultimately improve the well-being of the patients.

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