
Contact reactions to fragrances

Alexandra Katsarou, MD; Melina Armenaka, MD; Dimitris Kalogeromitros, MD; Vasiliki Koufou, MD; and Sofia Georgala, MD

Background: The most common reaction to fragrances is contact dermatitis, a delayed hypersensitivity reaction; however, other reactions include immediate contact reactions (contact urticaria) and photo-allergic reactions. Fragrance mix (FM) and balsam of Peru (BP) are used to screen for fragrance allergy.

Objective: To study the different types of allergic skin reactions to fragrance compounds.

Methods: Delayed hypersensitivity reactions to FM and BP were studied in 4,975 patients with suspected contact dermatitis by routine patch testing interpreted at 48 and 96 hours. In 664 of the patients, patch tests were read at 30 minutes to evaluate for immediate (wheal-and-flare) contact reactions and again at 48 and 96 hours. Photopatch tests to FM were performed in 111 patients with suspected photo-allergic dermatitis.

Results: Delayed contact reactions to FM occurred in 6.6% of females and 5.4% of males and to BP in 3.9% of females and 4.1% of males. Analysis of data over time (12 study years) showed an increased trend for reactions to fragrances, particularly in males. Sensitivity to other contact allergens (polysensitivity) was found in 62% of patients and polysensitivity presented more often with generalized contact dermatitis. The most sensitizing components of the fragrance mix that were tested in 38 patients were cinnamic alcohol, oak moss, and cinnamic aldehyde. There were 112 immediate patch test reactions to FM and 113 to BP in 664 patients. Immediate contact reactions were followed by delayed contact reactions in 13.4% of patients for FM and 8.8% for BP, representing a significant increase in the frequency of delayed contact reactions. Patients with immediate contact reactions to fragrances did not have a higher incidence of atopy (25.9%). No cases of positive photopatch test reactions to FM were seen.

Conclusion: Fragrances commonly cause both delayed and immediate patch test reactions and patients with immediate contact reactions have an increase in delayed contact reactions to the same allergen.

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INTRODUCTION

The use of fragrances is widespread and not limited to cosmetic products. Flavors used in oral hygiene products, candy, foods, and soft drinks are fragrance compounds.¹ Fragrances are also used in household products, in industry (paints, rubber, plastics, insecticides, and herbicides), in paper products, in fabric and clothes, and in topical medications.^{1,2} Fragrances may be natural (balsams, essential oils and

spices like cinnamon, clove, vanilla, and cardamon) or synthetic. Natural fragrances are usually of botanical origin and contain several hundred different chemicals. Today, synthetic chemicals are the main source of perfume composition (90%), and many synthetic fragrances are used as spices and flavors.^{1,2}

Allergic contact dermatitis, a delayed hypersensitivity reaction, is the most common and well-known adverse reaction to fragrance materials such as balsam of Peru and fragrance mix. Other adverse contact reactions include irritant dermatitis, immediate reactions (contact urticaria), and photo-dermatitis. The incidence of allergic

contact reactions to fragrances ranges worldwide from 4% to 11% for fragrance mix^{3–5} and from 1.6% to 10.8% for balsam of Peru.^{6–8} Immediate contact reactions to fragrances are less well studied. They have been reported to be frequent especially for some fragrance compounds, although the clinical relevance of these reactions are not known.^{1,9–12} Photo-allergic reactions to fragrances are not common, but have been reported in some patients with persistent light reactions.¹³

This study was performed in order to provide a better understanding of the different types of adverse reactions to fragrance substances and the frequency with which they occur.

METHODS

Delayed Hypersensitivity Reactions

A total of 4,975 patients, 2,619 females and 2,356 males, with suspected contact dermatitis were patch tested at our hospital from 1985 through 1996 with the European Standard Series that includes the fragrance mix 8% and balsam of Peru 25%. Patch testing was always performed when dermatitis was not active. Patch tests were performed according to the International Contact Dermatitis Research Group guidelines. Allergens were supplied by Hermal (Trolab) and applied to the lower back using Finn chambers (Epitest) fixed by Scanpor tape (Norges plaster). Patches were removed at 48 hours and read by a staff dermatologist 30 minutes after removal and again at 92 hours.

The frequency of positive patch tests reactions to the fragrance compounds was examined during the 12 study years, for the total group and for males versus females. Over the 12 study years, the patch test method, material manufacturer, and test concentration of fragrance compounds was the same. In addition, the method of patient refer-

From the Skin Test Laboratory, Department of Dermatology, University of Athens, "A. Sygros" Hospital, Athens, Greece.

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rals (prior screening by a hospital dermatologist and referral to our department for suspected contact dermatitis) has not changed and the same staff dermatologists read the patch tests. The occurrence of allergic contact sensitivity to fragrance compounds alone (monosensitivity) or fragrance allergy associated with sensitivity to other contact allergens (polysensitivity) was analyzed. We also recorded the localization of dermatitis at the time of patch testing and according to the history. Localization was designated as localized to the face (including only the upper neck), hands, hand and face, or generalized dermatitis (>2 sites).

In 38 patients positive to fragrance mix 8%, further patch tests were performed with the 8 individual components of fragrance mix (cinnamic alcohol, cinnamic aldehyde, oak moss, eugenol, isoeugenol, geraniol, hydroxycitronellol, and α -amyl cinnamic aldehyde) to determine which components were most sensitizing.

Immediate Contact Reactions

In 664 patients with suspected contact dermatitis, patch tests to fragrance compounds (fragrance mix and balsam of Peru) were examined at 30 minutes and again at 48 and 92 hours. Patch test sites were occluded for 30 minutes using Finn chambers and then examined with the upper edge of the strip still in contact with the skin. After recording wheal and erythematous flare reactions, the patches were reapplied and removed definitely at 48 hours. Delayed reactions were recorded as above at 48 and 96 hours.

The frequency of immediate contact reactions at 30 minutes and the presence or absence of subsequent delayed patch test reactions was studied. In this group, the incidence of atopy was also recorded. Patients were considered atopic when they had a positive personal and family history of atopic disease, or one positive history and serum IgE levels > 200 IU/mL.¹⁴

Photo-Allergic Reactions

Fragrance mix was added to the photopatch panel in 111 patients (51 fe-

males and 60 males) that had suspected photocontact dermatitis from 1988 through 1996. For the photopatch test protocol, patch tests were applied in the usual manner in duplicate and covered with a light proof black paper.¹³ Patches were removed after 24 hours in dim light. One series was immediately covered while the other was exposed to 5 J of unfiltered radiation from UVA fluorescent tubes. The reactions were evaluated 48 hours after irradiation.

Data Analysis

The data was analyzed statistically by spss 6.1 statistical package. The "chi-squared test for trend" was used to evaluate trend in fragrance allergy across the 12 study years. The binomial test was used for comparisons between monosensitivity and polysensitivity and a two-sided test for standardized difference of binomial proportions for comparisons between the frequency of delayed patch tests reactions in immediate patch tests (+) and (−) groups. The Pearson chi-squared (χ^2) test was used for all other between-group comparisons. If a two-sided *P* value was less than .05, then the variation was considered to be significant.

RESULTS

Frequency of Delayed Contact Reactions to Fragrances

A total of 407 patients, 236 females and 171 males, had positive reactions to fragrance compounds.

Fragrance mix caused 299 positive reactions, 172 in females and 127 in males. The mean frequency of positive reactions over the study years was 6.6% in females and 5.4% in males. Analysis of trend (chi-squared test for trend) from 1985 through 1996 indicated a significantly increased trend for positive reactions in males (*P* = .0008) and an increased trend that was not significant in females (*P* = .089) (Fig 1).

Balsam of Peru caused 200 positive patch reactions, 103 in females and 97 in males. The mean frequency of positive reactions over the study years was

4.1% in females and 3.9% in males. Analysis of trend demonstrated an increase in the frequency of positive reactions to balsam of Peru from 1985 through 1996 for males (*P* < .0001) and females (*P* = .0002) (Fig 1).

Monosensitive Versus Polysensitive Allergy

Patients that only had contact allergy to fragrance compounds (fragrance mix, balsam of Peru, or both) were considered to have monosensitivity, while those that also reacted to other standard contact allergens were considered to have polysensitivity. Table 1 shows the percent of patients with monosensitivity and polysensitivity according to sex and fragrance compound. More patients with fragrance allergy had polysensitivity compared with monosensitivity. Statistical analysis showed that differences between polysensitivity and monosensitivity were significant, but were not related to sex and fragrance compound (Table 1).

Sites of Allergic Contact Dermatitis

The distribution sites of allergic contact dermatitis for patients with monosensitivity and polysensitivity are shown in Figure 2. In order of frequency, dermatitis in patients with sensitivity only to fragrance compounds was on the hands, generalized, on the face, and involving the hands and face. Patients with polysensitivity more frequently showed dermatitis that was generalized (39% versus 25.5%) or localized to the face (23.2% versus 17%). Comparisons between the two groups using Pearson's χ^2 test, demonstrated that hand dermatitis was significantly increased in monosensitive compared with polysensitive allergy (*P* = .0001), and generalized dermatitis was significantly increased in polysensitive compared with monosensitive allergy (*P* = .005).

Fragrance Mix Components

The results of patch testing to the individual fragrance mix components is shown in Table 2. Positive reactions were most common to cinnamic alcohol (16 reactions), oak moss (14 reactions), and cinnamic aldehyde (12 re-

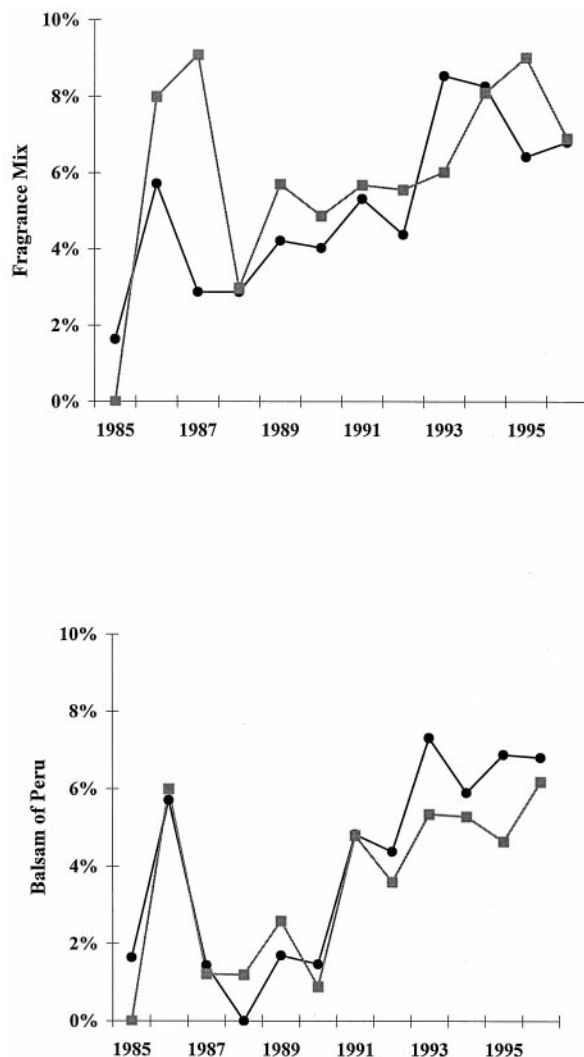


Figure 1. Percent of patients with positive patch test reactions to fragrance mix and balsam of Peru from 1985–1996. Statistical data represents trend (chi-squared test for trend). Top graph: —●— men ($P = .0008$) and —□— women ($P = .0890$). Bottom graph: —●— men ($P < .0001$) and —□— women ($P = .0002$).

actions). Six patients with positive reactions to fragrance mix did not react to any of the individual components.

Immediate Contact Reactions to Fragrances

The 664 patients evaluated for immediate patch test reactions had a total of 112 immediate patch test reactions to fragrance mix and 113 immediate patch test reactions to balsam of Peru. Fifteen (+) immediate patch test (IPT) reactions to fragrance mix (13.4%) were followed by a (+) delayed patch

test (DPT) reaction to the same compound and 10 (+) IPT reactions to balsam of Peru (8.8%) were followed by a (+) DPT reaction. There were 552 (–) IPT reactions to fragrance mix, and 24 (4.3%) were followed by a (+) DPT reaction; of the 551 (–) IPT reactions to Balsam of Peru, 8 (1.4%) were combined with a (+) DPT reaction. Delayed patch test reactions were significantly increased in patients with a (+) IPT compared with (–) IPT reaction ($P < .003$ for fragrance mix and

$P = .002$ for balsam of Peru). Those patients with immediate patch test reactions to fragrance compounds had a higher frequency of delayed patch test reactions to the same allergen as compared with patients with (–) immediate patch tests and as compared with the total patients patch tested (Fig 3).

Atopic Predisposition and Immediate Patch Tests Reactions

The frequency of atopy among patients with positive immediate patch test reactions to fragrances (25.9%) was not significantly different than in patients with negative immediate reactions (25.4%).

Photo Patch Test Reactions

None of the patients with suspected photo-allergic dermatitis had a positive photopatch test reaction to fragrance mix.

DISCUSSION

This study shows that fragrances are an important cause of delayed hypersensitivity reactions and of many cases of generalized allergic contact dermatitis. Fragrances can also produce an immediate wheal-and-flare reaction within 20 to 30 minutes after application of the patch test allergen that resolves in 2 hours. The mechanisms involved in immediate contact reactions are not fully understood and their clinical relevance is uncertain.^{10–12} Some patients complain of redness, itching, and tingling within 5 to 10 minutes of application of cosmetics and this may be attributed to immediate contact reactions of the skin.¹⁵ The most interesting finding in this study is that patients with immediate contact reactions to fragrances had an increased frequency of delayed contact reactions. On the contrary, fragrances were not found to be an important cause of photo-allergic reactions.

Allergic contact dermatitis is a delayed, cell-mediated hypersensitivity reaction (Gell and Coombs type IV allergic reaction) that is confirmed by patch testing. The mechanism of this reaction has been well studied and primarily involves Langerhans cells and sensitized CD4 helper T-cells.¹⁶ Mast cells are not considered to play a major

Table 1. Monosensitivity (MS = reactions to fragrance compounds only) and Polysensitivity (PS = reactions to fragrances plus other standard allergens) According to Sex and Fragrance Compound

Fragrance Compound	(+) Delayed Patch Test Reactions					
	Males (N = 171)		Females (N = 236)		Total Patients (N = 407)	
	MS	PS	MS	PS	MS	PS
Fragrance Mix	29	50	52	81	81	102
Balsam of Peru	20	28	23	41	43	69
Both compounds	16	28	13	26	29	54
Total*	65	106	88	148	153	254

* Data are based on all patients patch test positive over 12 study years.

Differences between total MS and PS were significant using the binomial test, $P = .002$ for males, $P < .001$ for females and total patients. All other between group comparisons were not significant.

role in delayed hypersensitivity reactions, although a “fleeting” role early in the evolution of contact dermatitis has been reported.¹⁶ The incidence of allergic contact dermatitis to fragrances was found to have an increasing trend over the study years, 1985 through 1996, especially in males and these findings are in agreement with many other reports.^{8,17–19} Although fragrance allergy appears to be increasing in our population, it is at low levels as compared with other countries.³ Increase in fragrance allergy, particularly to in men, may be partly attributed to shaving methods, because shaving with a razor increases the penetration of fragrances that are applied to the skin from soaps, shaving foams, and after-shave lotions.²⁰

The interpretation of trend analysis is influenced by various factors, such as referral patterns for testing, reimbursement charges, and changes in test procedure or test materials. In this study that extended from 1985 through 1996, the above factors were the same, except for the addition of SSO to the test materials. Since 1984, the fragrance mix in the European Standard Series was finally formulated at a concentration of 1% for each component (fragrance mix 8%) in order to avoid irritant reactions.³ With this concentration, however, false-negative reactions can be seen.^{1,21} The same year, the emulsifier sorbitol sesquioleate (SSO) 5% was added to fragrance mix and was shown to enhance the bioavailability of the test material.^{21,22} Later, 1%

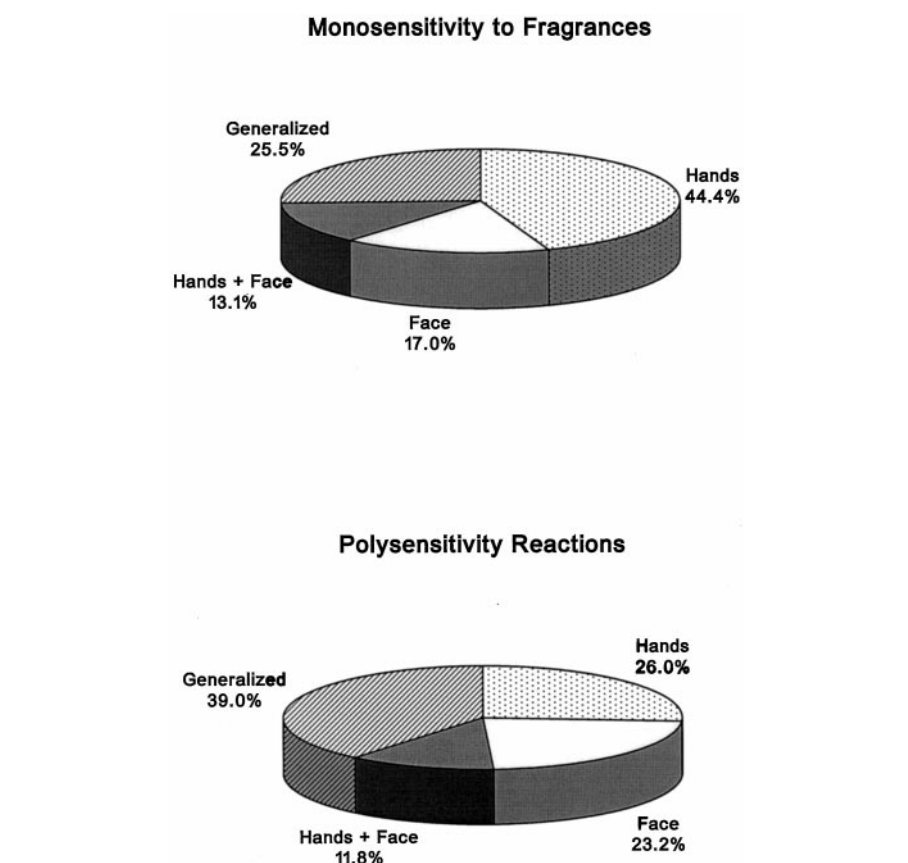


Figure 2. Sites of allergic contact dermatitis in monosensitivity to fragrances (sensitivity to fragrance compounds) and polysensitivity (sensitivity to fragrances and other contact allergens). Face also includes upper neck. Comparisons demonstrate that hand dermatitis in monosensitive patients was significantly increased ($P = .0001$) and generalized dermatitis was significantly increased in polysensitive patients ($P = .005$).

SSO was added to the standard series in order to identify whether SSO caused allergic patch test reactions.³ In our department, SSO has been added

to the standard patch test series from 1994, and until the end of the study in 1996, only 2 patients were seen with positive reactions to both SSO and fra-

Table 2. Delayed Patch Test Reactions to 8 Components of Fragrance Mix in 38 Patients*

Substance	% Concentration	No. Positive Reactions (%)
Fragrance mix	8	38
Cinnamic alcohol	1	16 (42.1)
Oak moss	1	14 (36.8)
Cinnamic aldehyde	1	12 (31.6)
Isoeugenol	1	9 (23.7)
Eugenol	1	7 (18.4)
Hydroxycitronellol	1	7 (18.4)
Geraniol	1	5 (13.2)
α -amyl cinnamic aldehyde	1	3 (7.9)

* Six of the 38 patients did not react to any of the individual components tested.

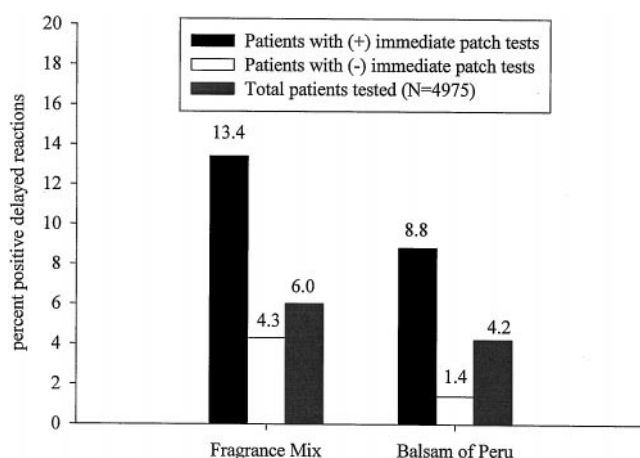


Figure 3. Percent positive delayed patch test reactions to fragrance mix and balsam of Peru in patients with (+) immediate patch test reactions (black bar), (-) immediate patch test reactions (white bar) and the total patients patch tested (grey bar). See text for data analysis.

grance mix—a reaction probably caused by SSO allergy. The addition of SSO as an emulsifier, therefore, does not appear to influence the frequency of fragrance allergy.

We found that fragrance allergy was more frequently associated with polysensitivity than monosensitivity, however the sex-distribution of polysensitive and monosensitive allergy was similar. Polysensitive contact allergy most often presented with generalized dermatitis, followed by dermatitis on the hands and the face, while in monosensitive allergy the hands were most frequently affected. The localization of dermatitis at these sites in fragrance allergy can be explained by contact with fragranced cosmetics, perfumed household products, and food flavor-

ings.^{1,23} Polysensitive contact allergy, especially with multiple very strong reactions, can be seen with hyperirritability of the skin. Skin hyperirritability, also referred to as “excited skin syndrome” or “angry back syndrome,” is considered responsible for false-positive reactions of allergic or irritant origin.²⁴ This is minimized by performing patch tests when dermatitis is not active and by repeating individual test allergens when there are doubts.²⁴ At our hospital, we also stop patch testing during the summer months of July and August, because we have noticed, in the past, an increase in cases of angry back syndrome.

The frequency of delayed contact reactions to the individual components of fragrance mix varies widely.^{1,3,25}

Most delayed contact reactions to the fragrance mix appear to be caused by the components oak moss, isoeugenol, and cinnamic aldehyde.²³ In our patients, reactions were most frequent with cinnamic alcohol, oak moss, and cinnamic aldehyde. Of the 38 patients with positive delayed contact reactions to fragrance mix, six patients did not react to any of the components of fragrance mix. This phenomenon is known to occur.¹ False-negative reactions to the individual components of fragrance mix could be due to their low concentrations. Also, the presence of other chemicals influences the sensitizing potential of the mix¹ and two or more ingredients in the mix may interact to form “new allergens” (compound allergy).²²

Numerous studies demonstrate that patch test allergens can produce immediate contact reactions (contact urticaria).^{9–11,15,26,27} Contact urticaria is an immediate reaction characterized by a wheal-and-flare response that occurs on intact skin within minutes after contact with certain substances. Based on proposed mechanisms, immunologic contact urticaria and non-immunologic contact urticaria are described.⁹ Immunologic contact urticaria is IgE dependent, requires prior exposure to the allergen, and can become generalized (generalized urticaria, anaphylaxis), while non-immunologic contact urticaria remains localized to the site of contact and is incapable of becoming systemic. IgE-mediated contact urticaria has been described with latex, antibiotics, food and animal products, and a variety of chemicals (reviewed in 9). The mechanisms involved in non-immunologic immediate contact reactions are poorly understood, but are believed to involve a non-IgE histamine liberating effect, or release of other vasoactive mediators.^{1,9–12} Non-immunologic contact urticaria is inhibited by topical or per os non-steroidal anti-inflammatory drugs and ultraviolet light.^{9,28–30} In a recent study, non-immunologic contact urticaria and acute skin irritation were not found to be closely related phenomena.³¹

Immediate contact reactions have been previously demonstrated with fragrance compounds (balsam of Peru, cinnamic aldehyde, fragrance mix) and usually are non-immunologic.^{1,9-11,26,27} In this study, 664 patients were investigated for immediate contact reactions to fragrances and the results showed that fragrance mix caused 113 immediate patch test reactions and balsam of Peru 112. Most worthy of attention is that for the first time an increase in the frequency of delayed (type IV) reactions was shown in those patients with immediate contact reactions. Our findings suggest that allergen-specific immune responses may in fact be involved in immediate contact reactions and this is supported by a previous study in which immediate patch test reactions were associated with allergen-specific T-cell responses.³² Although "non-immunologic" contact urticaria may not be IgE dependent, it is not clear that it is non-immunologic.

The presence of atopy in patients with immediate patch test reactions to fragrances (25.9%) was not different compared with patients with negative immediate reactions (25.4%) and this observation is in agreement with other reports.^{10,11,33} The prevalence of atopy in our highly selected population, referred for evaluation of dermatitis, is somewhat higher than that quoted for the general population (2% to 20%).^{14,34} About 30% of "normal" persons are reported to have a family history of atopic disorders in their immediate relatives.³⁴

In conclusion, fragrances are an important cause of immediate and delayed contact skin reactions in both sexes. Immediate contact reactions are associated with delayed contact reactions to the same allergen in a minority of cases. The presence of immediate reactions is associated with a significant increase in delayed hypersensitivity reactions.

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- Requests for reprints should be addressed to:*
Alexandra Katsarou, MD
Assistant Professor of Dermatology
A. Sygros Hospital
5 Ionos Dragoumi St
Athens, 161 21
Greece
-