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Prevalence, concomitant reactions, and factors associated with fragrance allergy in Thailand

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Abstract

Background: Fragrances are the most common cause of cosmetic contact allergy. Up-to-date information on contact allergy frequencies and relevance aids primary and secondary preventive measures.

Objectives: To determine the prevalence, associated factors, and concomitant reactions in fragrance allergy among Thais.

Methods: This retrospective study collected data from 2012 to 2019. The patient characteristics of fragrance and nonfragrance allergy groups were compared. Concurrent positive reactions to fragrance allergens (fragrance mix [FM] I, FM II, *Myroxylon pereirae* resin and hydroxyisohexyl 3-cyclohexene carboxaldehyde) and other baseline-series allergens were analysed.

Results: Of 1032 patients, 175 (17.0%) had fragrance allergy, with 57.7% of clinical relevance. FM I showed the highest prevalence (9.4%). The associated factors were being elderly, lesions on the extremities, metal allergy history, and long dermatitis duration. Contact allergies to epoxy resin and Compositae plants were significantly associated with fragrance allergy with an odds ratio of 5.95 (95% confidence interval [CI]: 5.21-6.80) and an odds ratio of 4.42 (95% CI: 1.58-12.36), respectively. No significant associations between colophonium (previously proposed as a fragrance marker) and fragrance allergens were found.

Conclusions: The prevalence of fragrance contact allergy remains high and should be considered in old patients presenting with long-standing eczema on the extremities. Unlike reports from other countries, varied, significant, concomitant reactions were observed.

KEYWORDS

clinical relevance, Compositae mix II, concomitant patch-test reactions, fragrance allergy, fragrance mix I, fragrance mix II, hydroxyisohexyl 3-cyclohexene carboxaldehyde, *Myroxylon pereirae* resin (balsam of Peru), prevalence

1 | INTRODUCTION

Fragrances are frequent causes of allergic contact dermatitis and the most common cause of contact allergy in cosmetics.^{1,2} The prevalence of fragrance allergy has been estimated at 6% to 14% among patients

with allergic contact dermatitis and 1.7% to 4.1% among the general population.³ Moreover, it has been reported that between 61.0% and 75.7% of positive reactions to the 26 most common fragrance allergens are clinically relevant.^{4,5} Fragrances can be obtained naturally or synthetically, and they are commonly found in perfumes, cosmetics,

household products, and personal products.⁶ In addition, masking fragrances are a possible source of exposure. For instance, topical medications and cosmetics may be labelled as being fragrance free, yet they actually contain natural plant or flower extracts that are fragrances.⁷

A wide range of common risk factors have been reported to be associated with the development of a fragrance allergy. These factors include a positive history of atopy; female gender; having several lesion sites; having lesions in particular areas; increasing age; and occupation-related factors, for example, employed as a masseur, shop assistant, or physiotherapist.^{8–10} Currently, there is no extensive data regarding the associated risk factors for fragrance allergy in the Asian population; these might vary with nationality, culture, geographical location, and social factors. The assessment of a patient's exposure to fragrances and the associated clinical relevance are not always clear, and it remains one of the most challenging areas of establishing a diagnosis of allergic contact dermatitis. Different methods have been used to determine clinical relevance.⁴ Few other allergens have been reported to be associated with fragrance allergy, and the patterns of concomitant positive reactions among fragrance allergens have been identified differently by various studies.^{11,12} Identifying the pattern of concomitant allergen reactions is important as it could lead to the proper management of contact allergy patients. This study set out to determine the overall and individual prevalence of positive reactions to fragrance allergens in the baseline series, their clinical relevance, the factors associated with fragrance allergy, and the concomitant positive reactions in fragrance allergy patients.

2 | MATERIALS AND METHODS

2.1 | Study population and patch testing

This retrospective, case-control study was approved by the Siriraj Institutional Review Board (Si461/2563). Based on history taking and clinical presentations, the study patients had been suspected of having allergic contact dermatitis and were therefore patch tested by dermatologists at the Occupational and Contact Dermatitis Clinic, Siriraj Hospital. For the present research, the following clinical data were collected for the period from January 2012 to December 2019: age; gender; personal and family history of atopy; disease duration; predominant lesion site; and history of metal, cosmetic, and drug allergies. The criteria of Hanifin and Rajka were used to diagnose patients with atopic dermatitis.¹³ For analysis purposes, the study patients were classified as blue-collar workers (individuals whose occupation requires them to perform a considerable share of manual labour) and white-collar workers performing professional, managerial, or administrative work.¹⁴

Patients were included in the analysis if they had been patch tested with the hospital's baseline series, which was an adaptation of the European and the International baseline series.¹⁵ The fragrance allergens in the baseline series were fragrance mix (FM) I 8% pet., containing amyl cinnamal, cinnamyl alcohol, eugenol, hydroxycitronellal,

isoeugenol, cinnamal, geraniol, and *Evernia prunastri* extract 1% each; FM II 14% pet., containing 1% citral, 2.5% coumarin, 2.5% farnesol, 0.5% citronellol, 5% hexyl cinnamal, and 2.5% hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC); *Myroxylon pereirae* resin (balsam of Peru [BOP]) 25% pet.; and HICC 5% pet. Patients with at least one positive patch-test reaction to the fragrance allergens were classified as the fragrance allergy group. The nonfragrance allergy (control) group comprised eczema patients who were negative to the fragrance allergens.

Patch testing was performed and interpreted in accordance with International Contact Dermatitis Research Group (ICDRG) guidelines.¹⁶ The allergens (Chemotechnique Diagnostics, Vellinge, Sweden) were applied in 8-mm aluminium Finn Chambers (SmartPractice, Phoenix, Arizona) that were placed on unaffected skin on the upper back. They were left in situ for 48 hours. Skin reactions were evaluated on day (D) 2 and D4 after placement of the patches. The percentage of positive patch test results for each allergen was defined as the sum of patients who had positive reactions at either D2 or D4 divided by the total number of patients who were patch tested for that specific allergen. A positive patch test result for an allergen group was defined as having at least one positive allergen in that group. The clinical relevance of a fragrance allergy was defined as having an existing exposure with a correlation for the presence of dermatitis. This was mainly assessed via history taking, skin examination, patch testing with personal products, and inspection of product labelling. For instance, patients with eczematous reactions from scented products or personal products with labelling stating that the product was a perfume or a fragrance were counted as having clinical relevance.

2.2 | Statistical analysis

The clinical data and percentage of positive allergens were analysed using a descriptive method. Pearson chi-square test or Fisher exact test was performed with PASW Statistics for Windows (version 18.0; SPSS, Chicago, Illinois) to analyse and compare the proportion of patients in the two groups. The risk factors found to be associated with fragrance allergy with a *P*-value of <.2 were then further quantified by a crude odds ratio (OR) and an adjusted OR. Binary logistic regression was used to estimate the crude OR, and multiple binary logistic regression was utilized to estimate the adjusted OR. A *P*-value <.05 was deemed statistically significant. The median values of the two groups were analysed using the Mann-Whitney *U* test. Pearson chi-square test or Fisher exact test was used to analyse the differences in concomitant fragrance allergy among individual fragrance allergens and concomitant allergy to other groups of allergens.

3 | RESULTS

In all, 1032 patients were patch tested with all four fragrance allergens in the baseline series between January 2012 and December 2019. The overall mean age was 43.1 ± 16.0 years (47.8 ± 18.0 years

for males, and 41.7 ± 15.0 years for females; P -value $<.001$). Females were predominant (791 [76.6%] of the patient cohort). Of the 1032 patients, 175 (17.0%) tested positive for at least one of the fragrance allergens. The prevalence of positive patch-test reactions to FM I, FM II, BOP, and HICC were 9.4%, 6.9%, 6.0%, and 3.8%, respectively (Figure 1). Clinical relevance in patients with positive reactions to the fragrances was found in 57.7% of the patients, which was significantly higher than the value for patients with negative reactions to the fragrances and positive reactions to other allergens (19.8%; $P < .001$).

Table 1 details the demographic data of the patients and the results of univariate and multivariate regression analyses of the patients with and without a fragrance allergy. The mean age of the patients with a fragrance allergy was 47.6 ± 15.1 years, which was significantly older than that for the patients with a negative patch-test reaction to fragrances (42.2 ± 16.0 years). In the multivariate analysis, the factors confirmed to be associated with a fragrance allergy were an older age (≥ 60 years, compared with <20 years; OR 4.55, CI 1.04, 19.91), having lesions on the extremities (OR 1.67, CI 1.05, 2.66), having a history of metal allergy (OR 1.44, CI 1.01–2.06), and a duration of lesions >12 months (OR 1.48, CI 1.05–2.07).

Figure 1 illustrates the patterns of patch-test reactions to fragrance allergens in the baseline series in terms of the percentages of patients who had single, double, or multiple positive patch-test

reactions to the fragrance allergens. Table 2 compares the concomitant positive patch test reactions among individual fragrance allergens in the baseline series. The OR (95% confidence interval [CI]) of having concomitant positive reactions between FM I and II was 14.10 (9.28–23.99). Concomitant positive reactions between BOP and FM I and FM II were significant: OR 8.43 (95% CI 4.81–14.77) and OR 3.27 (95% CI 1.62–6.60), respectively; however, no positive reaction also to HICC was noted. As to HICC, which is an ingredient in FM II, 30 patients reacted to both FM II and HICC, whereas 9 patients reacted to HICC alone. The ORs (95% CIs) between HICC and FM I and FM II were 15.84 (8.06–31.12) and 77.40 (34.51–173.61), respectively.

The concomitant positive reactions between the fragrance allergens and the other, nonfragrance allergens in our baseline series¹⁵ were analysed (Supplementary Table SS1). Patients with positive reactions to fragrances had significantly more often positive reactions to epoxy resin and the Compositae plant allergen group (Compositae mix II and sesquiterpene lactone mix), with an OR and 95% CI of 5.95 (5.21–6.80) and 4.42 (1.58–12.36), respectively. A comparison of the individual fragrance allergens with the other allergens in the baseline series did not reveal any significant concomitant positive reactions between FM I and the other allergens. Patients who reacted to FM II showed significantly more concurrent positive reactions to the

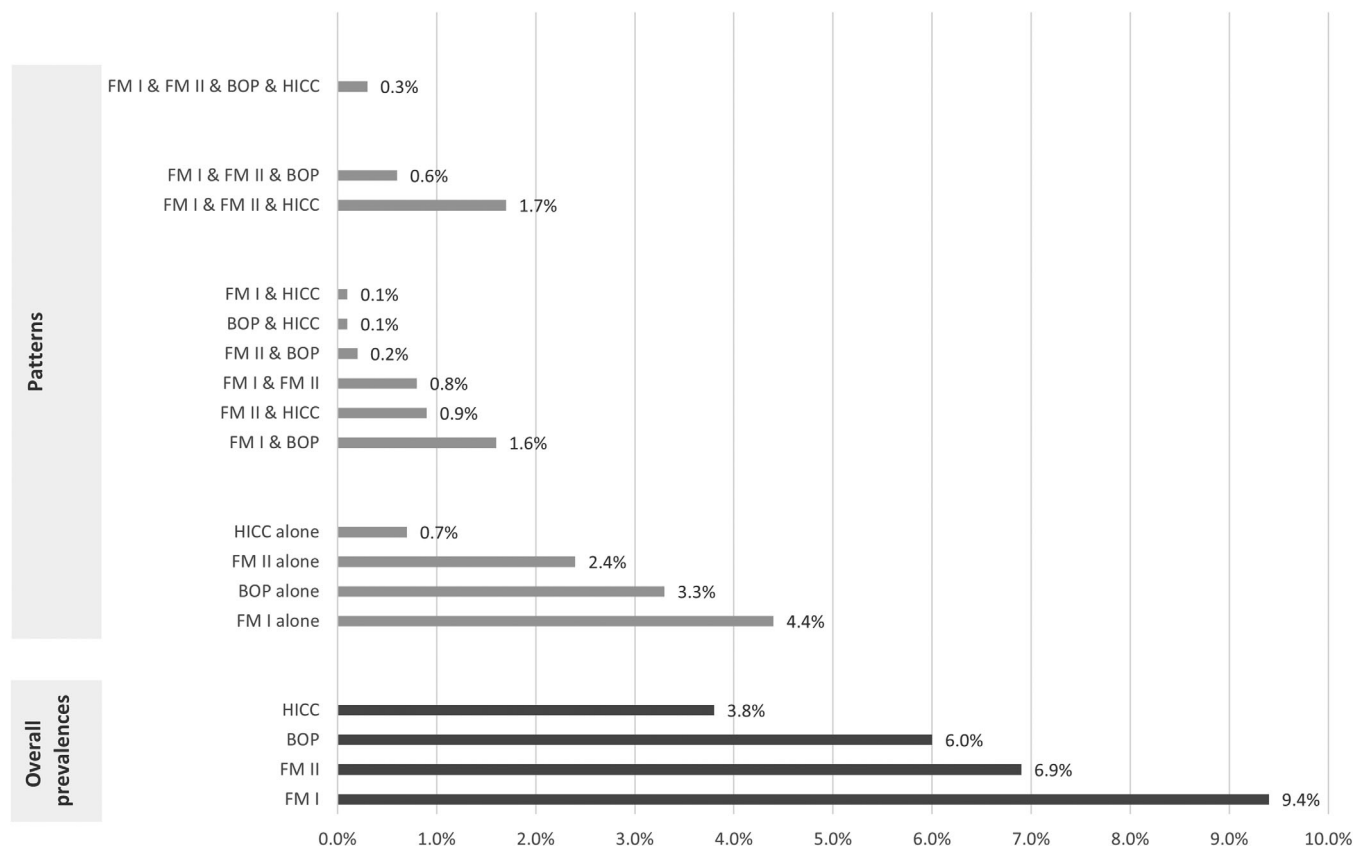


FIGURE 1 The prevalence and patterns of positive patch-test reactions to fragrance allergens in the baseline series. BOP, Myroxylon pereiraeresin (balsam of Peru); FM I, fragrance mix I; FM II, fragrance mix II; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde

TABLE 1 Demographic data of patients with positive and negative patch-test reactions to fragrances

	N = 1032		Fragrance allergy				Univariate analysis		Multivariate analysis	
			Positive (N = 175) 17.0%		Negative (N = 857) 83.0%		Crude OR (95% CI)	P-value*	Adjusted OR (95% CI)	P-value*
	n	(%)	n	(%)	n	(%)				
Mean age, years $\pm$ SD	43.1 $\pm$ 16.0		47.6 $\pm$ 15.1		42.2 $\pm$ 16.0			<.01		
Age groups, years								.03		
<20	38	3.7	2	1.1	36	4.2	1	—	1	—
20-59	790	76.6	129	73.7	661	77.1	3.51 (0.84-14.77)	.09	3.19 (0.75-13.56)	.12
≥ 60	204	19.8	44	25.1	160	18.7	4.95 (1.15-21.37)	.03	4.55 (1.04-19.91)	.04
Sex										
Female	791	76.6	142	81.1	649	75.7	1.38 (0.92-2.08)	.12	1.43 (0.919-2.23)	.11
Male	241	23.4	33	18.9	208	24.3	1	—	1	—
Occupation										
White-collar worker	851	82.5	133	76.0	718	83.8	1	—	1	—
Blue-collar worker	181	17.5	42	24.0	139	16.2	1.63 (1.10-2.41)	.01	1.35 (0.90-2.03)	.15
Personal history of atopy	481	46.6	73	41.7	408	47.6	0.79 (0.57-1.09)	.15	0.75 (0.53-1.05)	.09
Atopic dermatitis	117	11.3	15	8.6	102	11.9	0.69 (0.39-1.23)	.21		
Allergic rhinitis	381	36.9	59	33.7	322	37.6	0.85 (0.60-1.19)	.34		
Allergic conjunctivitis	114	11.0	94	11.0	20	11.4	1.05 (0.63-1.75)	.86		
Asthma	45	4.4	5	2.9	40	4.7	0.60 (0.23-1.54)	.29		
Family history of atopy	371	35.9	61	34.9	310	36.2	0.94 (0.67-1.33)	.74		
Sites of lesions										
Face	495	48.0	70	40.0	425	49.6	0.68 (0.49-0.94)	.02	0.94 (0.61-1.45)	.78
Extremities	636	61.6	128	73.1	508	59.3	1.87 (1.30-2.68)	<.001	1.67 (1.05-2.66)	.03
Trunk	266	25.8	45	25.7	221	25.8	1.00 (0.69-1.45)	.98		
Generalized	383	37.1	70	40.0	313	36.5	1.16 (0.83-1.62)	.39		
History of metal allergy	356	34.5	74	42.3	282	32.9	1.49 (1.07-2.08)	.02	1.44 (1.01-2.06)	.05
History of cosmetic allergy	130	12.6	27	15.4	103	12.0	1.34 (0.84-2.11)	.22		
History of drug allergy	171	16.6	30	17.1	141	16.5		.88		
Mean disease duration, months $\pm$ SD	33.4 $\pm$ 59.4		41.1 $\pm$ 69.0		31.7 $\pm$ 57.0			.05		
Duration of lesions (N = 1019)										
≤ 12 months	620	60.8	90	51.7	530	62.7	1	—	1	—
>12 months	399	39.2	84	48.3	315	37.3	1.57 (1.13-2.18)	.01	1.48 (1.05-2.07)	.03

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

*P-value <.05 indicates statistical significance.

Compositae plant allergen group (OR 9.76, 95% CI 3.37-28.27), Compositae mix II (OR 8.14, 95% CI 2.32-28.49), and sesquiterpene lactone mix (OR 6.93, 95% CI 1.25-38.49). Patients who reacted to HICC demonstrated a significantly higher risk to react to the Compositae plant allergen group (OR 6.81, 95% CI 1.84-25.20), especially the sesquiterpene lactone mix (OR 13.35, 95% CI 2.31-75.22). Patients with a positive reaction to BOP were found to have a significantly higher risk to concomitantly react to cosmetic-related allergens (OR 1.77, 95% CI 1.02-3.05).

4 | DISCUSSION

The prevalence of fragrance allergy in the study was 17.0%, which was higher than the values reported by previous studies (ranging from 6% to 14%).³⁻⁵ The difference in the prevalence might be due to both the variations in the allergens used in baseline series and changes in exposure to allergens that have occurred in different countries over time. In Thailand, the unpleasant body odour caused by sweating in a hot, humid climate is usually of concern and has resulted in the

TABLE 2 Concomitant positive patch-test reactions among fragrance allergens in the baseline series

	FM I			FM II			BOP			HICC		
	Positive (97) n (%)	Negative n (%)	OR (95% CI)	Positive (71) n (%)	Negative n (%)	OR (95% CI)	Positive (62) n (%)	Negative n (%)	OR (95% CI)	Positive (39) n (%)	Negative n (%)	OR (95% CI)
FM I	35 (36.1)	36 (3.9)	14.10* (8.28-23.99)	35 (49.3)	62 (6.5)	14.10* (8.28-23.99)	25 (40.3)	72 (7.4)	8.43* (4.81-14.77)	22 (56.4)	75 (7.6)	15.84* (8.06-31.12)
FM II	25 (25.8)	37 (4.0)	8.43* (4.81-14.77)	11 (15.5)	51 (5.3)	3.27* (1.62-6.60)	11 (17.7)	60 (6.2)	3.27* (1.62-6.60)	30 (76.9)	41 (4.1)	77.40* (34.51-173.61)
BOP	22 (22.7)	17 (1.8)	15.84* (8.06-31.12)	30 (42.3)	9 (0.9)	77.40* (34.51-173.61)	4 (6.5)	35 (3.6)	1.84 (0.63-5.36)	4 (10.3)	58 (5.8)	1.84 (0.63-5.36)
HICC												

Abbreviations: BOP, Myroxylon pereiarae resin (balsam of Peru); CI, confidence interval; FM I, fragrance mix I; FM II, fragrance mix II; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; OR, odds ratio.
*P-value < .001 indicates statistical significance.

widespread popularity of perfumes. Moreover, not only do people tend to prefer to use scented products, but they may also be exposed to many different indirect and less obvious sources of fragrance, such as scented candles, incense, and essential oils for aromatherapy and Thai massage. Furthermore, awareness of, and concern about, contact sensitization might be lower in Thailand than in European countries, resulting in the higher prevalence of fragrance allergy found by this study. In this study, FM I, FM II, and BOP showed individual prevalences of over 1%. They are therefore still important fragrance markers and should continue to be included in our baseline series.

The prevalence of clinical relevance to fragrance allergy in the study was 59.9%, which was slightly lower than the values found by previous studies.^{4,5} The difference might be a consequence of the diverse methods utilized to assess clinical relevance. Evaluating the clinical relevance of a positive patch-test reaction can be the most challenging part of the patch-test procedure; it relies heavily on dermatologists' skills and experience, especially in cases of fragrance allergy. Identifying the particular allergens that have contributed to the clinical manifestations in individuals with positive reactions to fragrances might not be possible. Further investigations, including repeated open application testing and chemical analysis of the personal products, might help to increase the chance of identifying clinical relevance. In this work, the patients with a positive reaction to fragrances had a significantly higher clinical relevance than those who reacted to other allergens. Because scented products are widely used and difficult to avoid, deciding on the clinical relevance of a fragrance is challenging. Presumably, each patient would be exposed to at least one scented product, which could lead to a higher chance of diagnosing a case with clinical relevance. Recently, history taking and testing with personal products have become essential for determining clinical relevance for fragrance allergy patients. Further study of the clinical relevance of fragrance allergies is needed.

Among the tested patients, the males were significantly older than the females. Although more female patients reacted to fragrances, there were no significant differences in the fragrance allergies of the genders. The multiple regression analysis revealed that the patients with a fragrance allergy were older than those without an allergy, and with statistical significance. Several earlier studies also found the same trend: that is, increasing age contributes to the development of a fragrance allergy.^{8,9,17} The factor with the highest impact on the development of an allergy was an age of 60 years or older, which could reflect the effect of cumulative exposure to allergens over time.^{4,5} Sensitization to fragrance allergens can develop much earlier in life. For example, it may develop in infancy from exposure to products incorporating masking fragrances that are marketed to babies. In early adulthood, individuals will increase their exposure to fragrances if they embark on a career in industries requiring frequent hand washing with products containing fragrances, such as in the hair and beauty, cleaning, or nursing industries.¹⁷ Moreover, the use of cosmetic products (soaps, shampoos, shaving creams, and the like) could be a major cause of sensitization, given that fragrances are added to most of these products. Even if they are labelled "unscented", this does not mean that the products are indeed

fragrance free. People from all walks of life and all ages are exposed to cosmetic (personal care) products.¹⁸

Lesions on the extremities, including the axillae, were significantly related to fragrance allergy. Deodorants, scented creams, and lotions—which are leave-on products—were believed to be the sources of exposure in the patients. Moreover, the insides of the elbows and the back of the knees—naturally warm and moist areas—are the right spots to dab perfumes. Although fragrances are known as common culprits of facial dermatitis, there was no association between facial lesions and fragrance allergy in this study. Another study in Thailand also demonstrated that fragrances did not influence facial allergic contact dermatitis because metals and preservatives were two most common causes of lesions on the face.¹⁹ Our study also found that a history of metal allergy was associated with fragrance allergy. Further analysis found that there was an association between positive reactions to BOP and metals in the patients. It could be a coincidence due to the high prevalence of both metal and fragrance contact allergies. Although there was a tendency that there might be a different prevalence of fragrance contact allergy between blue-collar and white-collar workers from univariate analysis, it was not significant in multivariate analysis. Thus, occupations categorized by social images was not a significant factor in experiencing fragrance contact allergy, which might be because the chances of exposure to common fragrances between two groups were comparable. As to the duration of disease, avoiding exposure to fragrances in the environment has always been problematic. Clinical dermatitis will be continually triggered and not subside until the causative agents are identified and avoided.²⁰ Therefore, a disease duration of more than 12 months was another significantly associated factor for fragrance allergy found by this study.

Concomitant positive reactions and polysensitization to the fragrance allergens were also frequently found.^{21,22} As illustrated in Figure 1, most patients reacted to only one allergen; however, many of the tested patients had positive reactions to more than one allergen. The pattern of reactions showed that this group of patients seemed to mostly react to FM I and FM II, including HICC. It was expected that the OR of having concomitant reactions to FM II and HICC would yield the highest value among the fragrance allergens in our baseline series (Table 2). HICC 2.5% pet. has been included in FM II for decades, whereas HICC 5% pet. was only introduced to our baseline patch test series in 2011 in order to detect cases of HICC allergy that might otherwise be missed.⁹ Of the patients who reacted to FM II, 42.3% showed positive reactions to HICC, whereas 76.9% of those who had a positive reaction to HICC also reacted to FM II. It can be assumed that nearly half of the positive reactions to FM II were caused by HICC, and about one-quarter of the HICC allergies would have been missed if HICC 5% pet. had not been tested. Interestingly, recent studies have proposed that patch testing with HICC might not be needed due to the overall low prevalence of positive reactions to HICC 5% pet. alone.^{23,24} Our study found that 0.9% of the tested patients reacted to HICC without having a reaction to FM II; this result was three times the corresponding share reported by the ICDRG (0.3%).²³ It might be that allergen exposure levels differ from

one country to another, with HICC possibly being used more frequently in products in Thailand. Although routine patch testing with additional HICC 5% pet. is no longer recommended by the ICDRG,²³ HICC 5% demonstrated a very high prevalence relative to the frequencies reported for other countries.²³ Patch-test screening with HICC 5% in our clinic should therefore be observed over an extended period before it is decided whether to remove it from our baseline series. This example supports the position that each patch test centre should monitor and regularly review the allergens in its baseline series to ensure the best outcomes for patients.

In this study, there was an association between contact allergy to epoxy resin and overall fragrances; unlike other reports, however, no association between epoxy resin and FM I was found.^{12,25} Amyl cinnamal and isoeugenol were FM I ingredients that showed significant association with epoxy resin.²⁵ In Thailand, fragrance contact allergy would be missed if 26 individual fragrance allergens were not tested, including cinnamal-related fragrances.²⁶ Therefore, getting more FM I allergy cases from additional patch testing with the ingredients might reveal a significant association with epoxy resin. However, the association might have been a coincidence for unclear explanations²⁵; further investigation is required to clarify the reasons. In addition, although an association of contact allergy between fragrances and the Compositae allergen has been established,¹¹ the results of this study not only confirmed that they were associated but also demonstrated that FM II was the most significantly associated allergen. The risks of having concomitant positive reactions between FM II (especially HICC) and Compositae mix II and sesquiterpene lactone mix were significantly high. Contact allergy to Compositae plant allergens could also be caused by the ingredients in cosmetic products, herbal teas, and spices.^{27–29} Therefore, co-sensitization should be a matter of concern. Colophonium, which is produced from the oleoresin of pine trees, was proposed to be a fragrance marker, as shown by its association with fragrance allergy.^{11,30} However, it must be pointed out that the usage of colophonium is mostly unrelated to fragrances.³⁰ Interestingly, this study found that there were no significant associations between the reactions to colophonium and fragrances. The association may be elusive because the results might differ between countries, and from time to time.³¹ Therefore, given the results of this study, colophonium is not an appropriate fragrance marker for our region.

The patients who reacted to BOP showed to have a significantly higher risk of having concurrent reactions to cosmetic-related allergens. These patients had the lowest risk of reacting to other fragrance allergens (Table 2). The sources of exposure to BOP in cosmetic products could differ from those for other fragrances. Crude BOP is widely used in topical pharmaceutical preparations, but it is not currently used in perfumery following its ban by the International Fragrance Association.^{32,33} Nevertheless, some cosmetic products might still contain BOP as a nonfragrance ingredient; however, this is very unlikely as its sensitizing properties have been well established for many years.³² The main culprit sources of BOP nowadays include topical pharmaceuticals, some cosmetic products, and certain foods.³² In Thailand, patients could be exposed to BOP through their diets: many

spices and curry ingredients—which have been found to demonstrate a significant association with contact allergy—are common in the local food.³⁴ A further source of BOP is the popular topical heat-rub marketed as "Tiger Balm".³²

In conclusion, special attention should be given to the diagnosis of a fragrance contact allergy if a patient matches the following profile: being elderly, the presence of lesions on the extremities, and a long disease duration. Compositae plant allergy showed a significant association with fragrance allergy, especially to the HICC in FM II. Concomitant patch-test reactions in fragrance contact allergy patients were varied in different populations, which might have resulted from a variety of sources of exposure in different regions and different periods.

CONFLICT OF INTEREST

The authors have no conflicts of interest or financial support to declare.

AUTHOR CONTRIBUTIONS

Norramon Charoenpipatsin: Data curation; formal analysis; methodology; writing-original draft. **Thanisorn Sukakul:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; visualization; writing-original draft; writing-review and editing. **Cecilia Svedman:** Supervision; validation; writing-review and editing. **Waranya Boonchai:** Supervision; validation; writing-review and editing.

DATA AVAILABILITY STATEMENT

The data is available on request. Please contact the corresponding author by sending email to Professor Waranya Boonchai at waranya.boonchai@gmail.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Supplementary Table 1. Concomitant positive patch-test reactions between fragrances and other allergens in the baseline series

	All fragrances			FM I			FM II			BOP			HICC		
	Neg N (%)	Pos N (%)	P-value (OR [95% CI])	Neg N (%)	Pos N (%)	P-value (OR [95% CI])	Neg N (%)	Pos N (%)	P-value (OR [95% CI])	Neg N (%)	Pos N (%)	P-value (OR [95% CI])	Neg N (%)	Pos N (%)	P-value (OR [95% CI])
Overall prevalence	857	175		935	97		961	91		97	62		993	39	
I. Metals	264 (30.8)	57 (32.6)	0.65	286 (30.6)	35 (36.1)	0.27	302 (31.4)	19 (26.8)	0.41	294 (30.3)	27 (43.5)	0.03 (1.77 [1.05 – 2.99])	309 (31.1)	12 (30.8)	0.96
Nickel sulphate	199 (23.2)	42 (24.0)	0.82	215 (26.0)	23.0 (26.8)	0.40	229 (23.8)	12 (16.9)	0.18	223 (23.0)	18 (29.0)	0.28	236 (23.8)	5 (12.8)	0.11
Potassium dichromate	80 (9.3)	13 (7.4)	0.42	83 (8.9)	10 (10.3)	0.64	85 (8.8)	8 (11.3)	0.49	89 (9.2)	4 (6.5)	0.33	86 (8.7)	7 (17.9)	0.08
Cobalt (II) chloride	73 (8.5)	18 (10.3)	0.45	79 (8.4)	12 (12.4)	0.20	86 (8.9)	5 (7.0)	0.59	80 (8.2)	11 (17.7)	0.01 (2.40 [1.20 – 4.79])	88 (8.9)	3 (7.7)	> .99
II. Cosmetic-related	202 (23.6)	37 (21.1)	0.49	224 (24.0)	15 (15.5)	0.06	225 (23.4)	14 (19.7)	0.48	218 (22.5)	21 (33.9)	0.04 (1.77 [1.02 – 3.05])	232 (23.4)	7 (17.9)	0.43
Preservatives	160 (18.7)	27 (15.4)	0.31	175 (18.7)	12 (12.4)	0.12	177 (18.4)	10 (14.1)	0.36	171 (17.6)	16 (25.8)	0.11	182 (18.3)	5 (12.8)	0.38
Methylisothiazolinone	100 (11.7)	14 (8.0)	0.28	108 (11.6)	6 (6.2)	0.11	108 (11.2)	6 (8.5)	0.15	108 (11.1)	6 (9.7)	0.85	110 (11.1)	4 (10.3)	0.93
Methylisothiazolinone/methylchloroisothiazolinone	75 (8.8)	14 (8.0)	0.75	83 (8.9)	6 (6.2)	0.37	85 (8.8)	4 (5.6)	0.35	81 (8.4)	8 (12.9)	0.22	87 (8.8)	2 (5.1)	0.57
Methyldibromoglutaronitrile	22 (2.6)	8 (4.6)	0.15	24 (2.6)	6 (6.2)	0.06	27 (2.8)	3 (4.2)	0.46	24 (2.5)	6 (9.7)	0.01 (4.22 [1.66 – 10.75])	28 (2.8)	2 (5.1)	0.32
Paraben mix	22 (2.6)	2 (1.1)	0.41	24 (2.6)	0 (0)	0.16	23 (2.4)	1 (1.4)	> .99	23 (2.4)	1 (1.6)	> .99	24 (2.4)	0 (0)	> .99
Formaldehyde	13 (1.5)	1 (0.6)	0.49	14 (1.5)	0 (0)	0.63	13 (1.4)	1 (1.4)	> .99	13 (1.3)	1 (1.6)	0.58	14 (1.4)	0 (0)	> .99
Diazolidinyl urea	9 (1.1)	1 (0.6)	> .99	10 (1.1)	0 (0)	0.61	10 (1.0)	0 (0)	> .99	9 (0.9)	1 (1.6)	0.46	10 (1.0)	0 (0)	> .99
Quaternium 15	12	2	> .99	13	1	> .99	14	0	0.62	12	2	0.20	14	0	> .99

	(1.4)	(1.1)		(1.4)	(1.0)		(1.5)	(0)		(1.2)	(3.2)		(1.4)	(0)	
Imidazolidinyl urea	12 (1.4)	0 (0)	0.24	12 (1.3)	0 (0)	0.62	12 (1.2)	0 (0)	> .99	12 (1.2)	0 (0)	> .99	12 (1.2)	0 (0)	> .99
Other cosmetics															
p-Phenylenediamine	47 (5.5)	12 (6.9)	0.48	54 (5.8)	5 (5.2)	0.80	53 (5.5)	6 (8.5)	0.30	52 (5.4)	7 (11.3)	0.05	57 (5.7)	2 (5.1)	> .99
Lanolin alcohol	11 (1.3)	1 (0.6)	0.70	12 (1.3)	0 (0)	0.62	12 (1.2)	0 (0)	> .99	12 (1.2)	0 (0)	> .99	11 (1.1)	1 (2.6)	0.37
III. Rubbers	82 (9.6)	13 (7.4)	0.37	81 (9.3)	8 (8.2)	0.73	89 (9.3)	6 (8.5)	0.82	90 (9.3)	5 (8.1)	0.75	92 (9.3)	3 (7.7)	> .99
Carba mix	59 (6.9)	8 (4.6)	0.26	62 (6.6)	5 (5.2)	0.57	64 (6.7)	3 (4.2)	0.62	64 (6.6)	3 (4.8)	0.79	65 (6.5)	2 (5.1)	> .99
Thiuram mix	14 (1.6)	3 (1.7)	> .99	15 (1.6)	2 (2.1)	0.67	14 (1.5)	3 (4.2)	0.11	17 (1.8)	0 (0)	0.62	16 (1.6)	1 (2.6)	0.48
Mercaptobenzothiazole	9 (1.1)	1 (0.6)	> .99	10 (1.1)	0 (0)	0.61	10 (1.0)	0 (0)	> .99	9 (0.9)	1 (1.6)	0.46	10 (1.0)	0 (0)	> .99
Mercapto mix	7 (0.8)	2 (1.1)	0.65	8 (0.9)	1 (1.0)	0.59	9 (0.9)	0 (0)	> .99	7 (0.7)	2 (3.2)	0.10	9 (0.9)	0 (0)	> .99
N-isopropyl-N-phenyl-4-phenylenediamine	7 (0.8)	0 (0)	0.61	7 (0.7)	0 (0)	> .99	7 (0.7)	0 (0)	> .99	7 (0.7)	0 (0)	> .99	7 (0.7)	0 (0)	> .99
IV. Resins	49 (5.7)	9 (5.1)	0.76	52 (5.6)	6 (6.2)	0.80	56 (5.8)	2 (2.8)	0.42	56 (5.8)	2 (3.2)	0.57	57 (5.7)	1 (2.6)	0.72
Colophonium	38 (4.4)	7 (4.0)	0.80	40 (4.3)	5 (5.2)	0.69	44 (4.6)	1 (1.4)	0.36	44 (4.5)	1 (1.6)	0.52	44 (4.4)	1 (2.6)	> .99
4-tert-butylphenol formaldehyde resin	12 (1.4)	0 (0)	0.24	12 (1.3)	0 (0)	0.62	12 (1.2)	0 (0)	> .99	12 (1.2)	0 (0)	> .99	12 (1.2)	0 (0)	> .99
Epoxy resin	0 (0)	2 (1.1)	0.03 (5.95 [5.21 – 6.80])	1 (0.1)	1 (1.0)	0.18	1 (0.1)	1 (1.4)	0.13	1 (0.1)	1 (1.6)	0.12	2 (0.2)	0 (0)	> .99
Toluenesulfonamide formaldehyde resin	2 (0.2)	1 (0.6)	0.43	2 (0.2)	1 (1.1)	0.24	3 (0.3)	0 (0)	> .99	3 (0.3)	0 (0)	> .99	3 (0.3)	0 (0)	> .99
V. Topical medications	19 (2.2)	3 (1.7)	> .99	20 (2.1)	2 (2.1)	> .99	21 (2.2)	1 (1.4)	> .99	21 (2.2)	1 (1.6)	> .99	21 (2.1)	1 (2.6)	0.58
Neomycin sulphate	15 (1.8)	3 (1.7)	> .99	16 (1.7)	2 (2.1)	0.68	17 (1.8)	1 (1.4)	> .99	17 (1.8)	1 (1.6)	> .99	17 (1.7)	1 (2.6)	0.50
Budesonide	2 (0.2)	0 (0)	> .99	2 (0.2)	0 (0)	> .99	2 (0.2)	0 (0)	> .99	2 (0.2)	0 (0)	> .99	2 (0.2)	0 (0)	> .99
Tixocortal-21-pivalate	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99
Hydrocortisone-17-butyrate	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99	1 (0.1)	0 (0)	> .99
VI. Plants	8 (0.9)	7 (4.0)	< .01 (4.42 [1.58 – 12.36])	13 (1.4)	2 (2.1)	0.64	9 (0.9)	6 (8.5)	< .01 (9.76 [3.37 – 28.27])	15 (1.5)	0 (0)	> .99	12 (1.2)	3 (7.7)	0.02 (6.81 [1.84 – 25.20])
Compositae mix II	7 (0.8)	4 (2.3)	0.09	9 (1.0)	2 (2.1)	0.28	7 (0.7)	4 (5.6)	< .01 (8.14 [2.32 –	11 (1.1)	0 (0)	> .99	10 (1.0)	1 (2.6)	0.35

									28.4 9))						
Sesquiterpene lactone mix	3 (0.4)	3 (1.7)	0.07	6 (0.6)	0 (0)	> .99	4 (0.4)	2 (2.8)	0.01 (6.93 [1.25 – 38.4 9))	6 (0.6)	0 (0)	> .99	4 (0.4)	2 (5.1)	0.02 (13.3 5 [2.37 – 75.2 2))

Abbreviations: BOP, *Myroxylon pereirae* resin (balsam of Peru); CI, confidence interval; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; FM I, fragrance mix I; FM II, fragrance mix II; OR, odds ratio
P-value < .05 indicates statistical significance; ORs are reported when *P*-value < .05.