

Fragrance- and Botanical-Related Allergy and Associated Concomitant Reactions: A Retrospective Analysis of the North American Contact Dermatitis Group Data 2007–2016

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Importance: When fragrance- and botanical-related (F/BR) allergy is identified, concomitant reaction (CR) frequencies can help direct avoidance recommendations.

Objective: This study aimed to determine the CR rates for F/BR allergens.

Design: A retrospective cross-sectional analysis of the North American Contact Dermatitis Group data 2007–2016 was conducted. Frequencies of demographics, positive reactions, strength of reactions, trends, and CR rates were calculated.

Results: A total of 5504 (22.7%) of 24,246 patients had F/BR allergic reactions. The F/BR-sensitive patients were more likely to be female, older than age 40 years, and White and have face, leg, or anal/genital dermatitis. Top allergens included fragrance mix I (FMI, 10.6%), *Myroxylon pereirae* (balsam of Peru [BOP], 8%), and fragrance mix II (FMII, 4.9%). There were increasing trends for FMI, FMII, cinnamic aldehyde, and Compositae mix and decreasing trends for BOP and propolis. When patients were positive to any F/BR allergen, they were likely to be positive to FMI, FMII, and BOP. Concomitant reactions were bidirectional between multiple fragrance allergens and propolis, colophony, and Compositae mix.

Conclusions: Concomitant reactions were identified between fragrances, between fragrances and BR allergens, and between BR allergens and fragrances. If CRs of greater than 10% suggest cross-reactivity, then all patients with fragrance sensitivity should avoid BR allergens and vice versa.

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The term *fragrance* is defined by the International Fragrance Association as “a mixture of fragrance ingredients and functional components formulated to impart an odor/flavor or for its malodor coverage/taste making.”¹ Fragrances may be derived from natural or synthetic chemicals and can be found in a vast array of consumer products including cosmetics, personal hygiene products, household products, pharmaceuticals, and foods.² Botanical-related chemicals including Compositae mix, sesquiterpene lactone mix, essential oils, colophony, and propolis are derived from trees and plants and may also be used for their fragrant properties. However, they carry additional qualities such as adhesion and tackiness as well as anti-inflammatory and antimicrobial properties, which are used in industrial, medicinal, and household products.³ Fragrance- and botanical-related (F/BR) chemicals are causative agents in allergic contact dermatitis.^{3–6}

When contact allergy is identified, patients should avoid the identified allergens and their relevant cross-reactors to attain optimal improvement. This can be achieved with use of the American Contact

Dermatitis Society's Contact Allergen Management Program⁷ or similar databases that provide alternative products that do not contain allergens or their cross-reactors. When evaluating concomitant reactions (CRs), some authors recognize a threshold of 10% or greater as significant enough to suggest cross-reactivity in which the patient should avoid products containing the patient's allergen and its cross-reactors.³ This threshold allows for balance of inclusivity (only accepting cross-reactions that are 100% certain with the risk of including products that are not safe) and exclusivity (accepting all cross-reactions with the risk of excluding almost all products leaving few alternatives).⁸ When fragrance allergy is identified and all potential cross-reactors are eliminated, product availability may be limited. Given this, there is a need for better understanding of CRs in patients with fragrance sensitivity.

There are a limited number of North American studies that review F/BR patch test results and their associated CRs. The current study was designed to analyze the demographics, clinical presentation, patch test results, and concomitant positive patch test reactions to F/BR allergens in the North American Contact Dermatitis Group (NACDG) data population.

METHODS

This retrospective study was approved by the Duke University Institutional Review Board. The NACDG includes contact dermatitis experts from the United States and Canada; NACDG methodology has been reported previously.⁹ The NACDG screening series allergens (Chemotechnique Diagnostics, Malmö, Sweden; allergEAZE, SmartPractice, Calgary, Alberta, Canada) were applied with Finn Chambers (SmartPractice) and Scanpor tape (Norgesplaster ALPHARMA AS, Vennesla, Norway). First and second readings were designated as +++ (very strong), ++ (strong), + (mild), and +/- (weak/doubtful) in accordance with NACDG criteria. For each allergen, a final interpretation was determined by each investigator and documented as allergic, unknown, irritant, or negative. Doubtful/weak (+/-) readings interpreted as negative were excluded. For this study, a positive patch test reaction is defined as a final interpretation of allergy. Relevance for positive reactions was recorded as definite, probable, possible, past, and unknown.⁹

We included the 2007–2016 NACDG F/BR allergen data. Fragrance- and botanical-related allergens that were tested simultaneously for at least 3 consecutive cycles were included in the analysis. The tested allergens varied based on NACDG testing cycle. In this study, allergens were grouped based on cycles tested and analyzed individually and in groups (Table 1). Allergens presented in group 1 were tested from 2007 to 2016. Groups 2 to 4 had shorter test periods.

The following fragrance allergens were included: fragrance mix I (FMI) 8% petrolatum (pet), fragrance mix II (FMII) 14% pet, *Myroxylon pereirae* (balsam of Peru [BOP]) 25% pet, cinnamic aldehyde 1% pet, carvone 5% pet, and benzyl alcohol 1% pet. Botanical-related allergens were colophony 20% pet, propolis 10% pet, Compositae mix 6% pet, sesquiterpene lactone mix 1% pet, *Melaleuca Alternifolia* (tea tree oil), oxidized, 5% pet, *Cananga odorata* oil

(ylang-ylang oil) 2% pet, *Lavandula angustifolia* oil (lavender oil) 2% pet, *Mentha piperita* oil (peppermint oil) 2% pet, and *Jasminum officinale* oil (jasmine oil) 2% pet.

To determine CRs, pairwise comparisons were performed with allergens tested during the entire study period. Allergens tested during a portion of the study period were also paired, but this was limited to overlapping testing cycles. To calculate the CR frequency, allergen 1 was used as the denominator, and allergen 2 was used as the numerator.³ In addition, when F/BR allergens present in T.R.U.E. TEST (SmartPractice Denmark, Hillerød, Denmark; BOP, FMI, colophony) were simultaneously positive, the CR between these and other F/BR allergens of lower prevalence was calculated. We considered 10% or greater CR frequency to be potentially significant.^{3,8}

Patient demographics, clinical characteristics, and patch test results were summarized with frequency counts and percentages of nonmissing variables. Odds ratios (ORs) between groups with and without positive reactions, together with its 95% confidence intervals (CIs), were calculated. Trends of patch test reactions over time were analyzed with a simple linear regression model, with the following formula: Positive rate = $\beta_0 + \beta_1 \text{Time} + \epsilon$. Regression diagnostics were performed to evaluate the model assumptions and linear regression models only considered if linearity assumptions were valid. The parameter estimate represented the average increase or decrease of the percentage of positive patch test reactions with 1 test cycle increase. Concomitant positive rates together with exact 95% CIs were calculated. A 2-sided *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 24,246 patients underwent patch testing from 2007 to 2016. The demographics and clinical characteristics for the total population tested and patients with reaction to F/BR allergens are summarized in Table 2. A total of 5504 patients (22.7%) had at least 1 positive reaction to an F/BR allergen. These patients were significantly more likely to be female (OR, 1.17; 95% CI, 1.1–1.25) and White (OR, 1.28; 95% CI, 1.17–1.41) and less likely to be Black (OR, 0.65; 95% CI, 0.55–0.77) or Hispanic (OR, 0.63; 95% CI, 0.49–0.81) as compared with those without F/BR allergy. In addition, they were statistically more likely to be older than 40 years (OR, 1.47; 95% CI, 1.37–1.57); subgroup analysis revealed that patients 60 years or older (OR, 1.49; 95% CI, 1.4–1.59) were significantly more likely to have an F/BR allergy as compared with those who did not. Fragrance- and botanical-related allergic patients were more likely to have face (OR, 1.12; 95% CI, 1.03–1.21), leg (OR, 1.22; 95% CI, 1.06–1.41), or anal/genital (OR, 1.26; 95% CI, 1.04–1.52) dermatitis and less likely to have hand dermatitis (OR, 0.88; 95% CI, 0.82–0.95).

The percentage, strength, and clinical relevance of positive patch test reactions are summarized in Table 3. The top 3 F/BR allergens were FMI 8% pet (10.6%), BOP 25% pet (8%), and FMII 14% pet (4.9%). The lowest frequency allergens were carvone 5% pet (0.8%),

TABLE 1. Allergens Grouped by Test Cycles

2007–2016	2009–2016	2007–2012	2009–2014
Total No. Tested Population n = 24,197	Total No. Tested Population n = 19,156	Total No. Tested Population n = 13,628	Total No. Tested Population n = 13,566
Positive Patch Test Reactions to F/BR Allergens n = 5374	Positive Patch Test Reactions to F/BR Allergens n = 301	Positive Patch Test Reactions to F/BR Allergens n = 44	Positive Patch Test Reactions to F/BR Allergens n = 91
Colophony 20% pet FMII 14% pet BOP 25% pet Cinnamic aldehyde 1% pet FMI 8% pet Sesquiterpene lactone 1% pet Propolis 10% pet Compositae mix 6% pet Tea tree oil oxidized 5% pet Ylang-ylang oil 2% pet	Carvone 5% pet Lavender oil 2% pet Peppermint oil 2% pet	Benzyl alcohol 1% pet	Jasmine oil 2% pet

Fragrance- and botanical-related allergens are grouped based on the maximum amount of overlapping test cycles from 2007 to 2016.

BOP, balsam of Peru; FMI, fragrance mix I; FMII, fragrance mix II; F/BR, fragrance- and botanical-related; pet, petrolatum.

jasmine oil 2% pet (0.7%), sesquiterpene lactone mix 0.1% pet (0.6%), peppermint oil 2% pet (0.5%), lavender oil 2% pet (0.4%), and benzyl alcohol 1% pet (0.3%).

Trends for positive reactions to F/BR allergens are summarized in Figure 1. Of the 15 allergens tested, 4 showed increasing reaction frequencies: FMI (9.3%–11.3%), FMII (3.6%–5.3%), cinnamic aldehyde (2.4%–3.8%), and Compositae mix (1.4%–2.1%). Two allergens had decreasing frequencies: BOP (11%–7%) and propolis (4.9%–2.3%). Linear regression analysis of allergen trends only found a significant linear trend for FMII. For each test cycle, FMII reaction frequency increased by 0.45% (95% CI, 0.00%–0.90%; $P < 0.05$; data not shown). All other allergen trends did not reach statistical significance, most likely because of the limited number of time points available for analysis and nonlinear trends.

Table 4 summarizes the significant ($\geq 10\%$) CRs in both directions for F/BR allergens. Patients positive to any F/BR allergen were also likely to be positive to FMI. The greatest number of CRs occurred between cinnamic aldehyde and FMI; 82.5% of cinnamic aldehyde-positive patients also had positive reactions to FMI. The following high-frequency CRs also occurred with FMI: ylang-ylang oil/FMI (57%), lavender oil/FMI (56.3%), and jasmine oil/FMI (49.4%). In addition, for patients positive to any F/BR allergen tested, they were also likely to be positive to BOP. The highest frequency CR to BOP was with benzyl alcohol; 64.3% of benzyl alcohol-positive patients were also positive to BOP. Additional BOP CRs included ylang-ylang oil/BOP (48.6%), jasmine oil/BOP (46.1%), peppermint oil/BOP (35.6%), and propolis/BOP (32.4%). For patients positive to any F/BR allergen tested, they were also likely to be positive to FMII. In general, with the exception of lavender oil, significant CRs between F/BR allergens and FMII were less frequent than those with FMI or BOP. Fragrance mix I-positive patients had CRs with BOP (29.9%) and FMII (20.3%). In addition, FMII-positive patients had CRs with FMI (44.2%) and BOP (24.7%). Balsam of Peru-positive

patients had CRs with FMI (39.5%) and FMII (15%). Colophony-positive patients had CRs with propolis (27.1%), FMI (23.4%), BOP (22.9%), FMII (14.4%), Compositae mix (11.4%), and ylang-ylang oil (10.2%). Specific to the Compositae family of allergens, patients allergic to sesquiterpene lactone mix had CRs with Compositae mix in 56.1% of cases. Furthermore, when there were simultaneously positive reactions to BOP, FMI, and colophony, patients were also positive to FMII (47.6%, data not shown), ylang-ylang oil (30.2%, data not shown), Compositae mix (30.2%, data not shown), tea tree oil (17.5%, data not shown), jasmine oil (16.7%, data not shown), peppermint oil (16.7%, data not shown), lavender oil (8.3%, data not shown), carvone (6.3%, data not shown), sesquiterpene lactone mix (6.3%, data not shown), and benzyl alcohol (5.4%) (data not shown).

DISCUSSION

This study evaluated NACDG F/BR allergy from 2007 to 2016. Fragrance mix I, BOP, and FMII had the highest overall frequencies, whereas carvone, jasmine oil, sesquiterpene lactone mix, peppermint oil, lavender oil, and benzyl alcohol had lower frequencies.

Demographics

Patients allergic to F/BR allergens were significantly more likely to be female as compared with those without F/BR allergy. This is not surprising because female patients may be more often exposed to products containing F/BR allergens.¹¹

Patients with F/BR allergy were significantly more likely to be older than 40. Subgroup analysis confirmed the greatest differential was in patients 60 years or older; these patients were significantly more likely to have F/BR allergy as compared with those who did not. Similarly, a UK study found that there was a steep increase in

TABLE 2. Patient Demographic and Clinical Characteristics

Characteristic	Total No. Tested Population (N = 24,246), n (%)	Positive Patch Test Reactions to F/BR Allergens		OR (95% CI)
		Yes (n = 5504), n (%)	No (n = 18,742), n (%)	
Male*	7595 (31.3)	1581 (28.7)	6014 (32.1)	0.85 (0.80–0.91)
Age >40 y*	16,350 (67.5)	4056 (73.7)	12,294 (65.7)	1.47 (1.37–1.57)
Age groups, y				
≤18	1264 (5.2)	213 (3.9)	1051 (5.6)	0.68 (0.58–0.79)
19–39	6182 (25.5)	1143 (20.8)	5039 (26.9)	0.71 (0.66–0.77)
40–59	10,041 (41.5)	2262 (41.1)	7779 (41.6)	0.98 (0.92–1.04)
≥60	6731 (27.8)	1884 (34.2)	4847 (25.9)	1.49 (1.4–1.59)
Race				
White	20,535 (85.6)	4759 (87.8)	15,776 (84.9)	1.28 (1.17–1.41)
Black	1060 (4.4)	171 (3.2)	889 (4.8)	0.65 (0.55–0.77)
Asian	1408 (5.9)	322 (5.9)	1086 (5.8)	1.02 (0.9–1.15)
Hispanic	468 (2)	73 (1.4)	395 (2.1)	0.63 (0.49–0.81)
Other	528 (2.2)	93 (1.7)	435 (2.3)	0.73 (0.58–0.91)
Primary dermatitis sites				
Hand*	5086 (21)	1066 (19.4)	4020 (21.5)	0.88 (0.82–0.95)
Scattered generalized	4644 (19.2)	1038 (18.9)	3606 (19.3)	0.98 (0.90–1.05)
Face*	3782 (15.6)	922 (16.8)	2860 (15.3)	1.12 (1.03–1.21)
Eyelids	2299 (9.5)	488 (8.9)	1811 (9.7)	0.91 (0.82–1.01)
Trunk	1475 (6.1)	340 (6.2)	1135 (6.1)	1.02 (0.9–1.16)
Leg*	1002 (4.1)	263 (4.8)	739 (3.9)	1.22 (1.06–1.41)
Arm	1145 (4.7)	254 (4.6)	891 (4.8)	0.97 (0.84–1.12)
Lips	945 (3.9)	234 (4.3)	711 (3.8)	1.13 (0.97–1.31)
Scalp	916 (3.8)	197 (3.6)	719 (3.8)	0.93 (0.79–1.09)
Foot	644 (2.7)	147 (2.7)	497 (2.7)	1.01 (0.84–1.21)
Anal/genital	547 (2.3)	147 (2.7)	400 (2.1)	1.26 (1.04–1.52)
Other	518 (2.1)	129 (2.3)	389 (2.1)	1.13 (0.93–1.39)
Neck	428 (1.8)	104 (1.9)	324 (1.7)	1.10 (0.88–1.37)
Most exposed areas	290 (1.2)	77 (1.4)	213 (1.1)	1.23 (0.95–1.6)
Ears	255 (1.1)	47 (0.9)	208 (1.1)	0.77 (0.56–1.06)
Eyes	107 (0.4)	22 (0.4)	85 (0.5)	0.88 (0.55–1.41)
Only under clothing	116 (0.5)	20 (0.4)	96 (0.5)	0.71 (0.44–1.15)
Nose	9 (0)	2 (0)	7 (0)	0.97 (0.2–4.69)
Erythroderma	11 (0)	0 (0)	11 (0.1)	0.15 (0.01–2.51)

The demographics and dermatitis sites for patients with F/BR allergy are presented.

*Part of the MOAHLFA.¹⁰

CI, confidence interval; F/BR, fragrance- and botanical-related; OR, odds ratio.

the prevalence of fragrance allergy during the seventh decade in female individuals and the eighth decade in male individuals.¹¹ Explanations may include impaired skin barrier function because of asteatotic eczema on the lower legs and increased use of fragranced topical medications in this age group.¹¹

Dermatitis Sites

In the most recent NACDG publication describing 2015–2016 patch test results, the most common primary dermatitis sites for all allergens tested were the hand (22%), scattered generalized (17.8%), face (16.9%), and eyelids (9.6%)⁹; our study revealed that patients with F/BR allergy are more likely to have face, leg, or anal/genital dermatitis and less likely to have hand dermatitis. This is similar to the data from

the Information Network Departments of Dermatology that revealed that 9074 patients with a positive reaction to 1 or more fragrance or essential oil allergens were more likely to have face (18%, $P < 0.002$) and leg (14%, $P < 0.002$) dermatitis and less likely to have hand (26%, $P < 0.002$) dermatitis.⁶ In addition, in an Italian study, 400 patients were questioned on botanical product use, and 60% used botanical products. Of the reported botanical products, facial and body creams, ointments, and lotions (36%) were most frequently used, followed by facial and body cleansers (16%). The face was the most commonly reported dermatitis site (31%).¹² A European study on dermatitis body sites found that BOP and colophony were associated with allergic contact dermatitis of the legs and suggested that this may be due to use of topical agents for treatment of stasis dermatitis and lower leg ulceration.¹³ Our study showed that, in

TABLE 3. Percentage, Strength, and Clinical Relevance of Positive Patch Test Reactions to F/BR Allergens From 2007 to 2016

F/BR Allergen	n	Positive Reactions, n (%) ^a					Second Read Code, n (%) ^a					Relevance, n (%)				
		+++	++	+	+/-	Definite	Probable	Possible	Past	Unknown						
FMI 8% pet	24,197	2570 (10.6)	407 (1.38)	711 (24.1)	1292 (43.8)	516 (17.5)	44 (1.7)	790 (31.3)	1410 (55.8)	85 (3.4)	199 (7.9)					
BOP 25% pet	24,197	1942 (8)	188 (8.3)	416 (18.3)	1113 (48.9)	544 (23.9)	18 (0.9)	625 (32.7)	1063 (55.7)	60 (3.1)	144 (7.5)					
FMII 14% pet	24,197	1182 (4.9)	110 (8.1)	259 (19.1)	701 (51.7)	279 (20.6)	26 (2.2)	432 (37)	610 (52.3)	32 (2.7)	67 (5.7)					
Cinnamic aldehyde 1% pet	24,197	801 (3.3)	49 (5.6)	186 (21.2)	487 (55.5)	154 (17.6)	12 (1.5)	259 (32.8)	453 (57.4)	17 (2.2)	48 (6.1)					
Propolis, 10% pet	24,197	627 (2.6)	83 (10.6)	140 (17.8)	388 (49.4)	162 (20.6)	21 (3.4)	96 (15.7)	281 (45.9)	32 (5.2)	182 (29.7)					
Colophony 20% pet	24,197	590 (2.4)	173 (26.8)	164 (25.4)	227 (35.1)	76 (11.8)	23 (4.0)	106 (18.3)	193 (33.4)	157 (27.2)	99 (17.1)					
Compositae mix 6% pet	24,197	436 (1.8)	69 (12.6)	122 (22.3)	226 (41.4)	119 (21.8)	13 (3.0)	76 (17.7)	206 (47.9)	15 (3.5)	120 (27.9)					
Ylang-ylang oil 2% pet	24,197	286 (1.2)	60 (18.4)	85 (26.1)	123 (37.7)	55 (16.9)	3 (1.1)	51 (18.2)	177 (63.2)	8 (2.9)	41 (14.6)					
Tea tree oil, oxidized 5% pet	24,197	261 (1.1)	64 (22)	85 (29.2)	106 (36.4)	33 (11.3)	25 (9.9)	93 (36.9)	72 (28.6)	24 (9.5)	38 (15.1)					
Carvone 5% pet	19,156	150 (0.8)	13 (6.4)	34 (16.7)	101 (49.8)	51 (25.1)	0 (0)	42 (28.2)	70 (47.0)	10 (6.7)	27 (18.1)					
Jasmine oil 2% pet	13,566	91 (0.7)	11 (9.7)	23 (20.4)	43 (38.1)	34 (30.1)	0 (0)	21 (23.1)	60 (65.9)	2 (2.2)	8 (8.8)					
Sesquiterpene lactone 1% pet	24,197	155 (0.6)	60 (32.1)	44 (23.5)	51 (27.3)	31 (16.6)	3 (1.9)	53 (34.4)	59 (38.3)	5 (3.2)	34 (22.1)					
Peppermint oil 2% pet	19,156	105 (0.5)	13 (10.3)	24 (19.0)	63 (50.0)	25 (19.8)	4 (3.8)	27 (26.0)	50 (48.1)	4 (3.8)	19 (18.3)					
Lavender oil 2% pet	19,156	71 (0.4)	7 (7.8)	22 (24.4)	32 (35.6)	29 (32.2)	7 (9.9)	22 (31.0)	32 (45.1)	4 (5.6)	6 (8.5)					
Benzyl alcohol 1% pet	13,628	44 (0.3)	1 (1.5)	8 (12.1)	39 (59.1)	16 (24.2)	7 (16.3)	17 (39.5)	10 (23.3)	1 (2.3)	8 (18.6)					

^aDiscrepancies in positive reaction numbers and second read code will differ because final interpretation is a clinical decision made by the physician. BOP, balsam of Peru; FMI, fragrance mix I; FMII, fragrance mix II; F/BR, fragrance- and botanical-related; pet, petrolatum.

addition to an increased likelihood of face and leg dermatitis, patients with F/BR allergy may present with anogenital dermatitis. A study of 449 patients with anogenital dermatitis found that compared with individuals without anogenital dermatitis those with anogenital dermatitis were significantly more likely to have relevant reactions to BOP (relative risk, 1.38; 95% CI, 1.01–1.88).¹⁴ Two additional studies found that fragrance and flavorings were the most common allergens among those with anogenital involvement.^{15,16} Another study of 45 patients with fragrance allergic contact dermatitis found that 47% improved with a low balsam diet, and 31% of patients had anogenital involvement.¹⁷ These patients were suspected to have a systemic contact dermatitis from ingestion of BOP; however, to our knowledge, no formal studies have evaluated this conjecture.

Concomitant Reactions

Concomitant patch test reactions can be indicative of pseudo-cross-reactivity in which the same haptens are present within multiple allergens, true cross-reactivity due to structurally similar allergens, coreactivity in which cosensitization occurs because of the presence of multiple allergens in the same product, and independent sensitization over time from different products.¹⁸ We agree that all 4 processes could explain the CRs found in this study; however, we are unable to differentiate these types of reactions in the context of a cross-sectional study. True cross-reactivity can only be determined in a controlled laboratory setting.

Although it has been proposed that CRs of 10% or greater suggest cross-reactivity, strong evidence to support this is lacking.⁸ For example, patients with positive reactions to nickel sulfate 2.5% pet had a significant CR with cobalt chloride 1% pet (23.2%; 95% CI, 20.5%–25.9%) and vice versa (65.9%; 95% CI, 60.6%–70.9%) in the 2015–2016 NACDG data set,⁹ but they are known to be coreactors, not cross-reactors.¹⁹ Therefore, further evaluation of the relationship between CRs and cross-reactivity is indicated.

Screening Fragrance Markers: FMI, FMII, and BOP

Our results revealed that FMI-positive patients were also BOP positive 29.9% of the time and FMII positive 20.3% of the time. Patients who were FMII positive were also FMI positive 44.2% of the time and BOP positive 24.7% of the time. Balsam of Peru-positive patients were also FMI positive 39.5% of the time and FMII positive 15% of the time. A Swedish study of 445 fragrance-allergic patients found that 25% who were FMI positive were also FMII positive, and 51% who were FMII positive were also FMI positive.²⁰ Nardelli et al⁴ tested 3380 patients and found that 106 (30.4%) of the 349 FMI-positive patients also reacted to FMII and 106 (51.7%) of the 205 FMII-positive patients also reacted to FMI. Uter et al²¹ found that, of the 5339 fragrance-allergic patients, 1.57% tested positive to both FMI and BOP, 0.4% tested positive to both FMII and BOP, and 0.71% tested positive to both FMI and FMII. When screening for contact allergy, and when fragrance allergy is suspected, it is important to test all 3 fragrance markers in addition to fragrance supplemental testing.

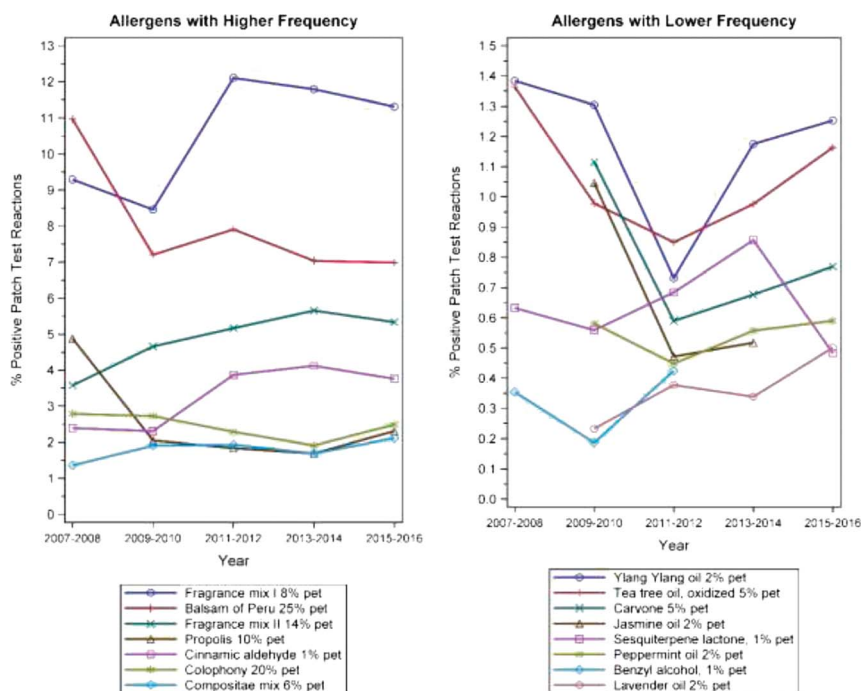


Figure 1. Fragrance- and botanical-related allergen trends.

Importance of Avoiding Fragrance in Individuals Positive to Colophony and Propolis

Our results revealed that colophony/propolis-sensitive patients were significantly more likely to also have positive reactions to FMI, FMII, or BOP. Shi et al³ performed a retrospective analysis on 4017 patients who were simultaneously tested to colophony, propolis, FMI, FMII, and BOP. Patients with positive reactions to colophony had significant CRs with BOP (23%), propolis (21%), FMI (20%), and FMII (13%), suggesting that colophony-positive patients should also avoid fragrance and propolis. They also found that patients positive to propolis had significant CRs with FMI (25%), FMII (20%), colophony (13%), and BOP (13%), suggesting that propolis-positive patients should avoid fragrance and colophony.³ These reactions may be due to pseudo-cross-reactivity rather than true cross-reactivity given the presence of common haptens such as resin acids,^{4,22,23} cinnamic compounds,^{24–26} and terpenes^{23,27,28} in the fragrance mixes, BOP, colophony, and propolis. Our study supports their findings in that it revealed similar significant CRs.

Furthermore, Shi et al³ found that the significant CRs between colophony, propolis, FMI, FMII, and BOP were unidirectional, meaning that patients allergic to the 2 fragrance mixes and BOP did not have significant CRs to colophony or propolis. This suggested that fragrance-allergic patients do not need to avoid colophony or propolis. In contrast, our study revealed a borderline significant CR between patients allergic to BOP who also tested positive to propolis (10.5%). This may be explained by the fact that BOP and propolis share many constituent chemicals.^{24–26} This study indicates that it may be important for patients allergic to BOP to also avoid allergens known to be present in propolis.

Compositae

Compositae is a large family of plants comprising numerous different species of flowers, herbs, vegetables, and weeds including daisy, sunflower, and chrysanthemum.²⁹ Many of these plants contain multiple sesquiterpene lactones, which are thought to be sensitizing constituents.²⁹ Some studies have suggested using sesquiterpene lactone mix to screen for Compositae allergy^{30,31}; others have found that sesquiterpene lactone mix does not adequately screen for Compositae sensitization.^{29,32} Our study showed that 56.1% of sesquiterpene lactone mix-allergic patients had positive reactions to Compositae mix, whereas 20% of Compositae-allergic patients had positive reactions to sesquiterpene lactone mix. This suggests that Compositae allergy would have been missed in 43.9% of cases if sesquiterpene lactone mix was used alone as a screening agent for Compositae allergy. Therefore, Compositae mix should be tested in addition to sesquiterpene lactone mix when screening for botanical-related allergy. Furthermore, many studies have shown an association between Compositae sensitization and positivity to fragrance or colophony.^{28,31,33} Similarly, we identified significant CRs between Compositae-allergic patients and fragrance mixes, essential oils, propolis, and colophony; these are likely due to pseudo-cross-reactivity as these allergens share similar haptens.^{4,28} Our data found that less than 20% of patients positive to sesquiterpene lactone mix had reactions to fragrances, and less than 28% of patients positive to Compositae mix had reactions to fragrances. Our study indicates that it may be important for patients allergic to Compositae mix or sesquiterpene lactone mix to also avoid fragrance haptens known to be present in FMI, FMII, BOP, essential oils, and chemicals present in propolis and colophony.

TABLE 4. Concomitant Reactions ($\geq 10\%$)

Allergen 1	Allergen 2	Allergen 1, n	Allergen 2, n	CR Frequency (Allergen 2/Allergen 1), %	95% CI, %
Cinnamic aldehyde 1% pet*	FMI 8% pet	801	661	82.5	79.7–85.1
Cinnamic aldehyde 1% pet	BOP 25% pet	801	165	20.6	17.9–23.6
Cinnamic aldehyde 1% pet	FMII 14% pet	801	122	15.2	12.8–17.9
Benzyl alcohol 1% pet†	BOP 25% pet	42	27	64.3	48–78.5
Benzyl alcohol 1% pet	FMI 8% pet	42	13	31.0	17.6–47.1
Benzyl alcohol 1% pet	Ylang-ylang oil 2% pet	42	6	14.3	5.4–28.5
Benzyl alcohol 1% pet	Propolis 10% pet	42	5	11.9	4–25.6
Benzyl alcohol 1% pet	FMII 14% pet	42	5	11.9	4–25.6
Benzyl alcohol 1% pet	Jasmine oil 2% pet	26	3	11.5	2.5–30.2
Ylang-ylang oil 2% pet *	FMI 8% pet	286	163	57	51–62.8
Ylang-ylang oil 2% pet	BOP 25% pet	286	139	48.6	42.7–54.6
Ylang-ylang oil 2% pet	Compositae mix 6% pet	286	92	32.2	26.8–37.9
Ylang-ylang oil 2% pet	FMII 14% pet	286	90	31.5	26.1–37.2
Ylang-ylang oil 2% pet	Propolis 10% pet	286	78	27.3	22.2–32.8
Ylang-ylang oil 2% pet	Jasmine oil 2% pet	146	32	21.9	15.5–29.5
Ylang-ylang oil 2% pet	Peppermint oil 2% pet	216	46	21.3	16–27.4
Ylang-ylang oil 2% pet	Colophony 20% pet	286	60	21	16.4–26.2
Ylang-ylang oil 2% pet	Tea tree oil oxidized 5% pet	286	48	16.8	12.6–21.6
Ylang-ylang oil 2% pet	Lavender oil 2% pet	216	25	11.6	7.6–16.6
Ylang-ylang oil 2% pet	Cinnamic aldehyde 1% pet	286	33	11.5	8.1–15.8
Lavender oil 2% pet‡	FMI 8% pet	71	40	56.3	44.1–68.1
Lavender oil 2% pet	FMII 14% pet	71	29	40.8	29.3–53.2
Lavender oil 2% pet	Ylang-ylang oil 2% pet	71	25	35.2	24.2–47.5
Lavender oil 2% pet	BOP 25% pet	71	19	26.8	16.9–38.6
Lavender oil 2% pet	Jasmine oil 2% pet	43	11	25.6	13.5–41.2
Lavender oil 2% pet	Tea tree oil oxidized 5% pet	71	18	25.4	15.8–37.1
Lavender oil 2% pet	Compositae mix 6% pet	71	16	22.5	13.5–34
Lavender oil 2% pet	Cinnamic aldehyde 1% pet	71	15	21.1	12.3–32.4
Lavender oil 2% pet	Propolis 10% pet	71	12	16.9	9.1–27.7
Lavender oil 2% pet	Peppermint oil 2% pet	71	12	16.9	9.1–27.7
Lavender oil 2% pet	Colophony 20% pet	71	10	14.1	7–24.4
Lavender oil 2% pet	Carvone 5% pet	71	8	11.3	5–21
Sesquiterpene lactone mix 1% pet*	Compositae mix 6% pet	155	87	56.1	47.9–64.1
Sesquiterpene lactone mix 1% pet	FMI 8% pet	155	31	20	14–27.2
Sesquiterpene lactone mix 1% pet	BOP 25% pet	155	25	16.1	10.7–22.9
Sesquiterpene lactone mix 1% pet	FMII 14% pet	155	19	12.3	7.5–18.5
Sesquiterpene lactone mix 1% pet	Colophony 20% pet	155	16	10.3	6–16.2
Jasmine oil 2% pet§	FMI 8% pet	89	44	49.4	38.7–60.3
Jasmine oil 2% pet	BOP 25% pet	89	41	46.1	35.4–57
Jasmine oil 2% pet	Ylang-ylang oil 2% pet	89	32	36	26.1–46.8
Jasmine oil 2% pet	Compositae mix 6% pet	89	27	30.3	21–41
Jasmine oil 2% pet	Propolis 10% pet	89	23	25.8	17.1–36.2
Jasmine oil 2% pet	Peppermint oil 2% pet	91	23	25.3	16.8–35.5
Jasmine oil 2% pet	FMII 14% pet	89	21	23.6	15.2–33.8
Jasmine oil 2% pet	Tea tree oil oxidized 5% pet	89	15	16.9	9.8–26.3
Jasmine oil 2% pet	Colophony 20% pet	89	14	15.7	8.9–25
Jasmine oil 2% pet	Lavender oil 2% pet	91	11	12.1	6.2–20.6
Peppermint oil 2% pet‡	Ylang-ylang oil 2% pet	104	46	44.2	34.5–54.3
Peppermint oil 2% pet	Compositae mix 6% pet	104	44	42.3	32.7–52.4
Peppermint oil 2% pet	FMI 8% pet	104	41	39.4	30–49.5

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TABLE 4. (Continued)

Allergen 1	Allergen 2	Allergen 1, n	Allergen 2, n	CR Frequency (Allergen 2/Allergen 1), %	95% CI, %
Peppermint oil 2% pet	BOP 25% pet	104	37	35.6	26.4–45.6
Peppermint oil 2% pet	Jasmine oil 2% pet	72	23	31.9	21.4–44
Peppermint oil 2% pet	Propolis 10% pet	104	33	31.7	23–41.6
Peppermint oil 2% pet	FMI 14% pet	104	26	25	17–34.5
Peppermint oil 2% pet	Colophony 20% pet	104	24	23.1	15.4–32.4
Peppermint oil 2% pet	Tea tree oil oxidized 5% pet	104	17	16.3	9.8–24.9
Peppermint oil 2% pet	Cinnamic aldehyde 1% pet	104	13	12.5	6.8–20.4
Peppermint oil 2% pet	Lavender oil 2% pet	105	12	11.4	6.1–19.1
FMI 14% pet*	FMI 8% pet	1182	522	44.2	41.3–47.1
FMI 14% pet	BOP 25% pet	1182	292	24.7	22.3–27.3
FMI 14% pet	Cinnamic aldehyde 1% pet	1182	122	10.3	8.7–12.2
BOP 25% pet*	FMI 8% pet	1942	768	39.5	37.4–41.8
BOP 25% pet	FMI 14% pet	1942	292	15	13.5–16.7
BOP 25% pet	Propolis 10% pet	1942	203	10.5	9.1–11.9
Carvone 5% pet‡	FMI 8% pet	148	51	34.5	26.9–42.7
Carvone 5% pet	BOP 25% pet	148	34	23	16.5–30.6
Carvone 5% pet	FMI 14% pet	148	22	14.9	9.6–21.6
Carvone 5% pet	Cinnamic aldehyde 1% pet	148	19	12.8	7.9–19.3
Propolis 10% pet*	BOP 25% pet	627	203	32.4	28.7–36.2
Propolis 10% pet	FMI 8% pet	627	177	28.2	24.7–31.9
Propolis 10% pet	Colophony 20% pet	627	160	25.5	22.2–29.1
Propolis 10% pet	FMI 14% pet	627	96	15.3	12.6–18.4
Propolis 10% pet	Compositae mix 6% pet	627	96	15.3	12.6–18.4
Propolis 10% pet	Ylang-ylang oil 2% pet	627	78	12.4	10–15.3
FMI 8% pet*	BOP 25% pet	2570	768	29.9	28.1–31.7
FMI 8% pet	Cinnamic aldehyde 1% pet	2570	661	25.7	24–27.5
FMI 8% pet	FMI 14% pet	2570	522	20.3	18.8–21.9
Tea tree oil oxidized 5% pet*	FMI 8% pet	261	77	29.5	24–35.4
Tea tree oil oxidized 5% pet	BOP 25% pet	261	67	25.7	20.5–31.4
Tea tree oil oxidized 5% pet	FMI 14% pet	261	60	23	18–28.6
Tea tree oil oxidized 5% pet	Ylang-ylang oil 2% pet	261	48	18.4	13.9–23.6
Tea tree oil oxidized 5% pet	Compositae mix 6% pet	261	41	15.7	11.5–20.7
Tea tree oil oxidized 5% pet	Colophony 20% pet	261	38	14.6	10.5–19.4
Tea tree oil oxidized 5% pet	Jasmine oil 2% pet	127	15	11.8	6.8–18.7
Tea tree oil oxidized 5% pet	Propolis 10% pet	261	27	10.3	6.9–14.7
Compositae mix 6% pet*	FMI 8% pet	436	121	27.8	23.6–32.2
Compositae mix 6% pet	BOP 25% pet	436	112	25.7	21.7–30.1
Compositae mix 6% pet	Propolis 10% pet	436	96	22	18.2–26.2
Compositae mix 6% pet	Ylang-ylang oil 2% pet	436	92	21.1	17.4–25.2
Compositae mix 6% pet	Sesquiterpene lactone mix 1% pet	436	87	20	16.3–24
Compositae mix 6% pet	FMI 14% pet	436	80	18.3	14.8–22.3
Compositae mix 6% pet	Colophony 20% pet	436	67	15.4	12.1–19.1
Compositae mix 6% pet	Jasmine oil 2% pet	249	27	10.8	7.3–15.4
Compositae mix 6% pet	Peppermint oil 2% pet	367	44	12	8.9–15.8
Colophony 20% pet*	Propolis 10% pet	590	160	27.1	23.6–30.9
Colophony 20% pet	FMI 8% pet	590	138	23.4	20–27
Colophony 20% pet	BOP 25% pet	590	135	22.9	19.6–26.5

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TABLE 4. (Continued)

Allergen 1	Allergen 2	Allergen 1, n	Allergen 2, n	CR Frequency (Allergen 2/Allergen 1), %	95% CI, %
Colophony 20% pet	FMII 14% pet	590	85	14.4	11.7–17.5
Colophony 20% pet	Compositae mix 6% pet	590	67	11.4	8.9–14.2
Colophony 20% pet	Ylang-ylang oil 2% pet	590	60	10.2	7.9–12.9
≥10% CRs	≥20% CRs	≥30% CRs	≥40% CRs		

The significant (>10%) CRs between F/BR allergens are presented. CRs are shaded from higher frequency (dark blue) to lower frequency (light blue). Additional CRs occurred, but only significant reactions were included.

*This allergen was tested from 2007 to 2016.

†This allergen was tested from 2007 to 2012.

‡This allergen was tested from 2009 to 2016.

§This allergen was tested from 2009 to 2014.

BOP, balsam of Peru; CI, confidence interval; CR, concomitant reaction; FMI, fragrance mix I; FMII, fragrance mix II; pet, petrolatum.

Essential Oils

Essential oils can contain anywhere from 100 to 500 chemicals, of which 2 to 5 components together can constitute greater than 50% to 60% of the oil.³⁴ Our study showed that of the 4 essential oils (ylang-ylang oil, lavender oil, peppermint oil, tea tree oil) and 1 absolute (jasmine) tested—all had significant CRs with FMI, FMII, BOP, propolis, and colophony. Similarly, in a European study by Uter et al,³⁵ of the 637 patients allergic to at least 1 essential oil tested, 55% had a CR with FMI, and 35% had a CR with FMII.

Of the essential oils/absolute tested by the NACDG, ylang-ylang oil, lavender oil, and jasmine oil share linalool as a major allergenic constituent, whereas ylang-ylang oil, lavender oil, and peppermint oil share caryophyllene as a major allergenic constituent. Tea tree oil does not share a major allergenic constituent with the other essential oils tested and had lower significant CRs with jasmine oil (11.8%) and ylang-ylang oil (18.4%). It is possible that the CRs identified for ylang-ylang oil, lavender oil, jasmine oil, and peppermint oil may be due to pseudo-cross-reactivity, whereas CRs associated with tea tree oil are due to either coreactivity or to independent sensitization.¹⁸

Peppermint oil is an essential oil obtained from the herbaceous, rhizomatous perennial plant, *Mentha x piperita* L, and is used in many cosmetic, personal hygiene, food, and pharmaceutical products.^{36,37} The major allergenic constituent is likely menthol; however, other allergenic constituents include but are not limited to the following: linalyl acetate, linalool, piperitenone oxide, carvone, myrcene, α -pinene, limonene, pulegone, and caryophyllene.^{37,38} Although studies have shown CRs between essential oils and F/BR allergens,^{35,39} limited publications^{28,40–42} have shown F/BR CRs specifically with peppermint oil. Our study revealed that the prevalence of peppermint oil positive reaction is low (0.5%); however, there were numerous significant CRs between peppermint oil and FMI, FMII, BOP, cinnamic aldehyde, colophony, propolis, Compositae mix, tea tree oil, ylang-ylang oil, lavender oil, and jasmine absolute. Many of these allergens contain haptens, which are also present in peppermint oil: jasmine absolute (linalool and caryophyllene), lavender

oil (linalool and caryophyllene), ylang-ylang oil (linalool and caryophyllene), tea tree oil (carvone, limonene, myrcene), and Compositae mix (β -caryophyllene). These reactions are likely secondary to pseudo-cross-reactivity. Others such as propolis,⁴⁰ cinnamic aldehyde,⁴³ and colophony⁴⁴ may be present in the same products with peppermint oil; therefore, these CRs may be due to coreactivity. Our study indicates that it may be important for patients with a positive reaction to peppermint oil to also exclude fragrance haptens known to be present in FMI, FMII, BOP, cinnamic aldehyde, Compositae family, tea tree oil, ylang-ylang oil, lavender oil, and jasmine oil, as well as haptens known to be present in colophony and propolis.

T.R.U.E. TEST Detection of F/BR Allergens

T.R.U.E. TEST (SmartPractice Denmark) is a ready-to-use patch test system, which contains 35 allergens (with 1 negative control) preloaded into hydrophilic gels, coated on a water impermeable sheet of polyester, dried to a thin film, and incorporated into adhesive panels for direct patient application.⁴⁵ The NACDG conducts patch testing using comprehensive testing techniques, with allergens dispersed predominantly in pet or water and placed onto Finn Chambers.⁴⁶

When comparing T.R.U.E. TEST F/BR with NACDG F/BR, only BOP, FMI, and colophony are screened by both. Parthenolide, a botanical-related allergen, was tested by the NACDG 2013–2016 and is present in the T.R.U.E. TEST, but it did not meet the inclusion criteria for this study.

Suneja and Belsito⁴⁶ found that in comparison with the Finn Chamber patch test method, T.R.U.E. TEST missed relevant contact allergy to FMI 50% of the time, BOP 55.6% of the time, and colophony 33.3% of the time. In comparison, the Finn Chamber method missed relevant positive reactions to FMI 7.1% of the time and did not miss any relevant positive reactions to BOP or colophony.⁴⁶ Other studies have shown the Finn Chamber or similar methods to be superior in detecting F/BR allergy.^{47–51}

In this study, in the setting of simultaneously positive reactions to BOP, FMI, and colophony, we identified CRs to benzyl alcohol, sesquiterpene lactone mix, carvone, lavender oil, peppermint oil, jasmine oil, tea tree oil, Compositae mix, ylang-ylang oil, and FMII. These additional allergens would have been missed by T.R.U.E. TEST without additional supplemental testing.

Limitations

This study is retrospective and cross-sectional. When interpreting results of CRs, we were not able to differentiate reactions as pseudo-cross-reactions, true cross-reactions, coreactions, or independent reactions. We chose to use the American Contact Dermatitis Society's Contact Allergen Management Program threshold of 10% to determine significance of CRs. However, it is unclear whether this threshold suggests allergens with CRs of 10% or greater should be considered cross-reactors or whether a higher threshold is warranted. Individual physician patch test reading, relevance, and other variables are based on clinical judgment. Variation in patient characteristics or exposure to allergens may be region dependent. These data represent a largely referral patient population and may not be representative of the general patch test or dermatology population.

CONCLUSIONS

During 2007–2016, positive reactions to FMI, BOP, and FMII were most prevalent (>4.8%), whereas carvone, jasmine oil, sesquiterpene lactone mix, peppermint oil, lavender oil, and benzyl alcohol were all less than 1%. Multiple F/BR CRs were identified. It has been suggested that CRs of 10% or greater suggest cross-reactivity,⁸ and in this study population, application of this concept would result in essentially all patients with fragrance sensitivity avoiding all botanical-related allergens and vice versa. Further evaluation of the relationship between CRs and cross-reactivity is indicated.

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