

Delayed-Type Hypersensitivity to Fragrance Materials in a Select North American Population

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Background: In published reports from Europe, 3- and 4-(4-hydroxy-4-methylpentyl)cyclohexene-1-carboxaldehyde (HMPCC) (Lyrall) has been described as a common cause of allergic contact dermatitis (ACD). In Europe, the rates of reaction to HMPCC among patients undergoing patch testing for suspected ACD have varied from 1.2 to 17.0%, depending on the country. Data on the incidence of sensitivity to HMPCC among North Americans with suspected ACD have not been reported.

Objectives: The goals of this study were (1) to assess the incidence of delayed-type hypersensitivity reactions to HMPCC among patients undergoing patch testing for evaluation of eczematous dermatitis at six centers throughout North America; (2) to determine the most appropriate concentration of HMPCC to use in performing patch tests; and (3) to compare and contrast the incidence rates for HMPCC hypersensitivity to those for other fragrance materials screened with the North American Contact Dermatitis Group (NACDG) screening tray, which includes fragrance mix, *Myroxilon pereirae* (balsam of Peru), cinnamic aldehyde, ylang ylang oil, jasmine absolute, and tea tree oil.

Methods: This report represents the prospective multicenter data on patients tested with the fragrance-related allergens on the NACDG standard screening tray and with HMPCC at 5%, 1.5%, and 0.5% concentrations in petrolatum. Statistical analyses were performed with Student's *t*-test (two tailed) and the chi-square test.

Results: Data from 1,603 patients evaluated at five US sites and one Canadian site were analyzed. Most patients (87.8%) were Caucasian. The majority (67%) were women, and 26.2% had a history consistent with atopic dermatitis. The patients ranged in age from 1 to 88 years, and the mean $\pm$ standard deviation was 46.3 ± 16.5 years. *Myroxilon pereirae* (balsam of Peru) and fragrance mix were the most frequent patch-test-positive fragrance allergens (6.6% and 5.9%, respectively). Cinnamic aldehyde (1.7%), ylang ylang oil (0.6%), jasmine absolute (0.4%), HMPCC (0.4% for 5% HMPCC, 0.3% for 1.5% HMPCC, and 0.2% for 0.5% HMPCC), and tea tree oil (0.3%) less frequently yielded positive reactions. Men were more likely than women to be allergic to cinnamic aldehyde. Women were more likely than men to be allergic to jasmine absolute. Atopic patients were no more likely to react to fragrance materials than were nonatopic patients. Patients who reacted to jasmine absolute tended to be older than the general population whereas those who reacted to tea tree oil tended to be younger than the general population. There were no other demographic differences between patients who reacted to a given fragrance material and the entire population studied. Testing with fragrance mix and balsam of Peru failed to identify the majority of patients in this study who were found to be sensitized to jasmine absolute, HMPCC, or tea tree oil.

Conclusion: HMPCC is an uncommon allergen in the North American population. We recommend testing with 5% HMPCC in petrolatum for those patients suspected of having a fragrance allergy.

PATCH-TEST REACTIONS TO FRAGRANCE MATERIALS are common in North America.^{1,2} The fragrance mix used in standard screening allergen trays has only eight constituents, and testing with it does not identify

all fragrance-allergic individuals. De Groot and colleagues³ estimated that about 15% of fragrance-allergic patients are not identified by patch-testing with the fragrance mix. In a worldwide multicenter study, Larsen and colleagues⁴ found that testing with fragrance mix correctly identified 85.6% of patients who had responses to the 31 individual fragrance ingredients tested. If ylang ylang oil, narcissus oil, and sandalwood oil had been added to the screening series, 94.2% of responses would have been detected in this study.⁴ Clearly, additional, noncross-reacting fragrance materials are present in the environment, and allergic responses to these go undetected even when fragrance mix is supplemented as described above.

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Fenn reported that in 1989, 3- and 4-(4-hydroxy-4-methylpentyl)cyclohexene-1-carboxaldehyde (HMPCC) (Lyrall, International Flavors & Fragrances Inc., Union Beach, NJ) was among the 25 most widely used fragrances in the United States.⁵ In a multicenter European study, the incidence of positive patch-test reactions to HMPCC was reported to range from 1.2% (in London) to 17.0% (in Leuven) among patients undergoing patch testing for eczematous dermatitis.⁶ Despite the high incidence rates reported from Europe, there have been no reports of allergic contact dermatitis from HMPCC in North America. However, it must be realized that HMPCC is not part of the fragrance mix in the TRUE Test system (Mekos Laboratories A/S, Hillerød, Denmark) approved by the Food and Drug Administration. Furthermore, even the North American Contact Dermatitis Group (NACDG, whose screening tray includes fragrance mix, *Myroxylon pereirae* [balsam of Peru], cinnamic aldehyde, jasmine absolute, ylang ylang oil, and tea tree oil) has not routinely screened for cutaneous hypersensitivity to HMPCC. Therefore, it is unknown whether this widely used fragrance ingredient is in fact a common sensitizer in the North American population. This report details the prevalence of delayed-type hypersensitivity to the fragrance ingredients found on the NACDG screening tray and to HMPCC among patients who are undergoing patch tests for the evaluation of suspected allergic contact dermatitis at six centers in the United States and Canada.

Materials and Methods

Patients

Individuals with an eczematous dermatitis who were undergoing patch tests for diagnostic purposes were tested with the NACDG screening tray (Chemotechnique Diagnostics AB, Malmö, Sweden) and to three dilutions of 99.7% pure HMPCC. The HMPCC used was a 1:1 mixture of Lyrall and Kovanol (Takasago, Rockleigh, NJ). This HMPCC mixture was obtained gratis from International Flavors & Fragrances in concentrations of 5.0%, 1.5%, and 0.5% in petrolatum (United States Pharmacopeia [USP]) that contained 0.2% butylated hydroxytoluene (BHT) as an antioxidant. These concentrations were chosen on the basis of the following: (1) data (from European centers) suggesting that the 5% concentration was an adequate screening concentration that did not induce sensitization⁶⁻¹¹; (2) concern that the 5% concentration could potentially be irritant and the desire to use lower concentrations simultaneously to assess potential irritant effects; and (3) data revealing that

50% of HMPCC-allergic individuals in one study reacted to patch-test concentrations of .066% HMPCC in ethanol.¹²

Patch Tests

Patients were patch-tested in a uniform manner as previously described.¹³ They returned for patch-test evaluation at 48 hours after the initial application and for a second evaluation 4 to 7 days after the initial application. Results were assigned scores of 1 to 6, based on reaction morphology as previously described.¹³ Patients were considered allergic to a fragrance material if they had a +, ++, or +++ reaction. Included were data on patients tested between January 1, 2003, and December 31, 2003, at the following medical centers: the University of Kansas Medical Center, Kansas City, KS; the University of Louisville, Louisville, KY; McGill University, Montreal, PQ, Canada; St. Luke's-Roosevelt Medical Center, New York, NY; Hershey Medical Center, Hershey, PA; and Oregon Health Sciences University, Portland, OR.

Relevance and Statistics

The relevance of the allergic reaction to the patient's present clinical condition was also determined and was given a score of 1 to 6 as previously described.¹⁴ In this study, a relevance score of 1 (definite), 2 (probable), 3 (possible), or 4 (past) was considered clinically relevant. In addition, the site of the patient's dermatitis, the final diagnosis, and any underlying atopic diathesis was recorded, as were the patient's age, gender, and ethnicity. Statistical analyses were performed with Student's *t*-test (two tailed) and the chi-square test.

Results

A total of 1,603 patients (81 in Kansas City, 460 in Louisville, 443 in Montreal, 276 in New York, 253 in Hershey, and 90 in Portland) were evaluated. The demographic data for the population studied are delineated in Table 1. Caucasians were significantly ($p < .01$) overrepresented as compared with other ethnic groups, based on the composite index of the racial distribution of the metropolitan areas involved in this study. This was true even when these numbers were adjusted for the number of patients entered from each metropolitan area. However, the demographics did not significantly differ from those of the typical patient population seen by members of the NACDG.

The prevalence rates of delayed-type hypersensitivity reactions to the various fragrance ingredients are delineated in Table 2. As expected, *Myroxylon pereirae* and fragrance

Table 1. Demographic Data on All Patients Evaluated for Fragrance Allergy

Gender	Female: 1,076 (67.1%) Male: 527 (32.9%)
Race	Caucasian: 1,404 (87.8%) African American: 79 (4.9%) Asian: 56 (3.5%) Hispanic: 34 (2.1%) Other or N/R: 27 (1.6%)
Age	Range: 1–88 yr Median: 46 yr Mean $\pm$ SD: 46.3 $\pm$ 16.5 yr
History of atopic eczema	420 (26.2%)

N/R = not recorded.

mix accounted for most of the observed hypersensitivity reactions. The prevalence of hypersensitivity to HMPCC at all concentrations was as low as or lower than those of all the other fragrance materials tested, with the exception of tea tree oil. Possible, probable, or definite relevance of the allergic reaction was found in the majority of cases for each of the tested fragrance allergens.

Among the 105 patients who had positive reactions to *Myroxilon pereirae*, 41 (39.0%) also had positive reactions to fragrance mix. Among the 94 patients who reacted to fragrance mix, 41 (43.6%) also reacted to *Myroxilon pereirae*. There were no demographic differences between patients who reacted to both fragrance mix and *Myroxilon pereirae* and those who reacted only to one of these two.

Among the 27 patients who reacted to cinnamic aldehyde, 22 (81.5%) also reacted to fragrance mix and 14 (51.9%) reacted to *Myroxilon pereirae*. Although ylang ylang oil is not present in fragrance mix and theoretically

should not cross-react with *Myroxilon pereirae*, 6 (54.5%) of the 11 individuals who reacted to ylang ylang oil also reacted to both fragrance mix and *Myroxilon pereirae*. Two (28.8%) of the patients who reacted to HMPCC at 5% also reacted to both fragrance mix and *Myroxilon pereirae*, and 1 (14.3%) of these 7 patients reacted only to fragrance mix. Finally, 1 of 7 (14.3%) and 1 of 5 (20%) of patients who reacted to jasmine absolute and tea tree oil, respectively, also reacted to both fragrance mix and *Myroxilon pereirae*.

The demographic data for patients who had at least one positive patch-test reaction to any of the concentrations of HMPCC are shown in Table 3. Of the four patients whose HMPCC reactions were considered possibly relevant, two reacted to all concentrations tested, one reacted to the 5% and 1.5% concentrations, and one reacted only to the 5% concentration. Of patients whose reactions to HMPCC were thought to be of past relevance, one reacted to all concentrations, and another reacted only to the 5% concentration. For two patients, the relevance of the HMPCC reaction was unknown; one of these patients reacted to both the 5% and 1.5% concentrations (but not the 0.5% concentration) of HMPCC, and the other reacted only to the 1.5% concentration of HMPCC.

When the demographic data for individuals who reacted to specific fragrances were compared with the data for nonreactors, it was found that men were significantly more likely to react to cinnamic aldehyde than were women ($p = .03$) and had a strong trend (although not significant) for reactivity to HMPCC ($p = .06$). Although more women reacted to jasmine absolute on a percentage basis than did men, this difference failed to reach statistical significance ($p = .06$). Age-related effects were also

Table 2. Prevalence and Relevance of Positive Allergic Reactions to Fragrance Materials

Allergen	DTH* (%)	Relevance of Positive Reactions (%)				
		Definite	Probable	Possible	Past	Unknown
<i>Myroxilon pereirae</i>	105 (6.6)	3 (2.9)	24 (22.9)	43 (41.0)	7 (6.7)	28 (26.7)
Fragrance mix	94 (5.9)	5 (5.3)	27 (28.7)	38 (40.4)	8 (8.5)	16 (17.0)
Cinnamic aldehyde	27 (1.7)	1 (3.7)	5 (18.5)	14 (51.9)	2 (7.4)	5 (18.5)
Ylang ylang oil	11 (0.7)	0	0	7 (63.6)	0	4 (36.4)
Jasmine absolute	7 (0.4)	0	1 (14.3)	4 (57.1)	1 (14.3)	1 (14.3)
Tea tree oil	5 (0.3)	0	1 (20.0)	3 (60.0)	0	1 (20.0)
HMPCC, 5.0%	7 (0.4)	0	0	4 (57.1)	2 (28.6)	1 (14.3)
HMPCC, 1.5%	6 (0.3)	0	0	3 (50.0)	1 (16.7)	2 (33.3)
HMPCC, 0.5%	3 (0.2)	0	0	2 (66.7)	1 (33.3)	0

DTH = delayed-type hypersensitivity; HMPCC = 3- and 4-(4-hydroxy-4-methylpentyl)cyclohexene-1-carboxaldehyde.

*As defined by an allergic patch-test reaction of grade 1, 2, or 3.

Table 3. Demographic Data from Patients with Positive Patch-Test Reactions to HMPCC

Age (yr)	Gender	Race	Hay Fever	Eczema	Asthma	Sites	Final Diagnosis	Patch-Test Interpretation			Relevance
								HMPCC 5.0%	HMPCC 1.5%	HMPCC 0.5%	
51	M	C	No	No	No	Trunk, anogenital	Allergic	1	6	6	3
66	M	C	No	No	No	Face	Allergic, seborrheic	1	1	1	3
46	F	C	Yes	Yes	Yes	Feet	Allergic	1	6	6	4
60	M	C	No	No	No	Scalp, feet	Allergic	1	1	1	4
33	M	C	Yes	No	No	Arms, legs	Allergic, irritant	1	1	6	5
68	F	C	No	No	No	Face	Allergic	2	1	6	3
47	F	C	No	Yes	Yes	Generalized	Allergic, atopic	3	2	1	3
51	M	C	No	No	No	Anogenital	Allergic	6	1	6	5

C = Caucasian; F = female; HMPCC = 3- and 4-(4-hydroxy-4-methylpentyl)cyclohexene-1-carboxaldehyde; M = male.

seen: older patients were more likely to react to jasmine absolute ($p = .04$), and younger patients more likely to react to tea tree oil ($p = .03$). Of note, individuals with a history of atopic eczema were no more likely to react to fragrances than were their nonatopic counterparts. There were no other demographic differences between those patients who reacted to a given fragrance material and the entire population studied.

Discussion

The percentage of our patients who reacted to various fragrance ingredients was, for all fragrance allergens tested, lower than that historically seen by the NACDG. In this study, 6.6% of patients reacted to balsam of Peru, and 5.9% reacted to fragrance mix. The most recent data from the NACDG for the 2001–2002 study period indicate that the percentages of patients allergic to balsam of Peru and fragrance mix were 11.6% and 10.4%, respectively.² In this study, 1.7% of the population was allergic to cinnamic aldehyde, a percentage lower than the last reported 2-year (1998–2000) prevalence rate of 3.6% for patients evaluated by the NACDG.¹ Finally, 0.7% of our patients reacted to ylang ylang oil, and 0.4% reacted to jasmine absolute, which contrasts with the 1.1% and 0.7% of the 2001–2002 NACDG population² who reacted to these allergens, respectively. Prior data regarding the prevalence of allergy to tea tree oil are not available.

The reason (or reasons) for the discrepancy between the reactivity rates found in this study and those of the historical NACDG data is (or are) unclear. However, it must be kept in mind that only 6 of the 14 study centers in the NACDG contributed data to this study. Furthermore, the above historical NACDG data for all of the fragrance

allergens comes from the 2001–2002 study period, with the exception of the data for cinnamic aldehyde, which was last tested by the NACDG from 1998 to 2000. Preliminary data from the NACDG 2003–2004 study period, which would include the period during which these data were collected, suggest that the rates of reactivity to fragrance allergens may have declined slightly from those found by prior studies; however, these rates are not as low as the rates observed in this study.

As might be expected in the case of allergens as ubiquitous as fragrances, allergic reactions to each fragrance material had past or present relevance in the majority of cases (ranging from 63% [for ylang ylang oil] to 85% [for jasmine absolute]). However, in the majority of these cases, relevance was considered possible, which means that the patients had been exposed (in an area of the body corresponding to the dermatitis) to a material containing unknown fragrances. A study in which 15 patients with hand eczema thought to be possibly related to fragrance exposure and whose dermatitis was not elicited in a 4-week immersion study that used appropriate dilutions of the fragrances to which they had previously reacted suggests that “possible relevance” may be overestimated.¹⁵

The age-related trends seen in this study are interesting; however, these observations are based on a small number of individuals and require verification in larger numbers of patients. That younger patients were more likely to be allergic to tea tree oil probably has more to do with tea tree oil’s use as a botanical ingredient than with its use as a fragrance. Nonetheless, the low rate of reactivity to tea tree oil that we observed in this study suggests, as has been noted by others,¹⁶ that this allergen is an uncommon cause of dermatitis. The increased reactivity to jasmine absolute among older patients may relate to their greater

use of fine fragrances although there are few data to support this speculation.¹⁷ In a multicenter study of 167 volunteers with fragrance allergy, individuals older than 40 years were more likely to react to sandela, Majantol (Symrise GmbH & Co., Holzminden, Germany), and galbanum; however, response to jasmine absolute was not evaluated.⁴

The influences of gender and atopic status on fragrance allergy have been previously reported.⁴ As was reported by Larsen and colleagues, men were more likely than women to exhibit positive responses to cinnamic aldehyde.⁴ The increased incidence of allergic reactions to cinnamic aldehyde among men suggests that this fragrance may be used more frequently or in higher concentrations in products designed for the male market although this could not be verified by the industry (Dr. Matthias Vey, Scientific Director, International Fragrance Association, Brussels, Belgium, personal communication, April 11, 2005). Larsen and colleagues reported a higher-than-expected incidence of atopic eczema among their fragrance-allergic patients⁴; however, we could not duplicate this finding. The lack of association between atopic eczema and fragrance allergy is interesting and has been previously observed in a study of 658 patients presenting with hand eczema.⁷

The incidence of delayed-type hypersensitivity to HMPCC in our population (0.4%) was significantly lower than that observed in Europe. There are no data from North America with which to compare these numbers. Overall, testing with 5%, 1.5%, and 0.5% HMPCC resulted in no observed irritant reactions. The 5% preparation would appear to be best for screening patients. As noted in another study,⁶ patch testing at lower concentrations may miss relevant reactions. Among the 7 patients who reacted to 5% HMPCC, 3 reacted to the 1.5% and 0.5% concentrations, 2 reacted only to the 1.5% concentration and not to the 0.5% concentration, and 2 failed to react to lower dilutions.

Overall, no predominant area of the body was likely to be affected by allergic reactions to HMPCC. Of interest, as opposed to the data from Europe, where significant numbers of individuals have become sensitized to HMPCC (from deodorants) in the axillae,^{9,11,18,19} none of our HMPCC-allergic patients had axillary dermatitis. In one study, 53% of 73 deodorants randomly selected from the European marketplace had an HMPCC content of 1 to 1,874 parts per million.²⁰

The difference between the 1-year prevalence rate of cutaneous hypersensitivity to HMPCC in the North American population and that in the European population has a number of potential explanations. However, we do not believe that the addition of 0.2% BHT as an antioxidant

Table 4. Concentration of HMPCC in Hydroalcoholic and Underarm Products

Region	Number of Products	Ten Highest Concentrations (% Range)	97.5 Percentile Concentration (%)
Europe	834	12.00–20.00	8.67
United States	66	2.80–6.25	4.89

Data courtesy of Dr. Matthias Vey, Scientific Director, International Fragrance Association, Brussels, Belgium.

HMPCC = 3- and 4-(4-hydroxy-4-methylpentyl)cyclohexene-1-carboxaldehyde.

contributed to the lower numbers, because one would not expect oxidative by-products of HMPCC (an aldehyde) to have enhanced allergenicity as has been observed for the monoterpenes linalool²¹ and d-limonene.²² Data provided by the International Fragrance Association (Table 4) would suggest that differences in the product types that contain HMPCC and the concentrations of HMPCC used likely account for a significant part of the difference seen between the European countries and the United States. This points to the need for ongoing studies to evaluate risk ratios for the induction of sensitization to fragrance materials, studies that take into account not only the concentration of the material applied per unit area of skin but also the type of skin (eg, abraded from shaving) and area of the body (eg, axillae) to which the product is likely to be applied.^{12,23–25}

Among the seven patients who reacted to HMPCC, three (42.9%) also reacted to fragrance mix. This proportion is consistent with a prior report in which 24 of 50 HMPCC-positive patients reacted to fragrance mix.⁶ The failure of testing with fragrance mix to detect the majority of patients who are allergic to HMPCC illustrates the need to test individuals who are suspected of having fragrance reactions to more than the standard fragrance mix. However, given the apparent low incidence of HMPCC in the North American population, we recommend testing with 5% HMPCC in petrolatum only when the specific allergy is highly suspected rather than incorporating this allergen in a standard series (as has been done in Germany).⁹

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