Multicentre patch testing with fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde by the Swedish Contact Dermatitis Research Group

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Fragrance mix 2 (FM 2) has been shown to be a useful marker of fragrance contact allergy in addition to the old fragrance mix, with contact allergy frequencies up to 5% when tested in many national baseline patch test series (1–3). Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) is one of the six fragrance substances in this FM 2, and the most common sensitizer, with contact allergy rates up to 3% when tested in consecutive dermatitis patients (4–8). The present study was initiated to investigate the rates of contact allergy to FM 2 and HICC in a Swedish dermatitis population, and to determine how common are simultaneous allergic reactions between the two. A recommendation to include FM 2 and HICC in the European baseline series was published in 2008 (9). Six centres representing the Swedish Contact Dermatitis Research Group included FM 2 and HICC in their baseline series from 2006 until 2012, to identify the contact allergy rate in the tested population and to investigate possible simultaneous allergic reactions between the two.

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Conflict of interests: Magnus Bruze is a member of Rexpan, an expert panel of the Research Institute of Fragrance Materials (RIFM). Carola Lidén was a member of the EC Scientific Committee on Consumer Safety (SCCS) working group on sensitization and fragrances (2009–2013), and the EC Scientific Committee on Consumer Products (SCCP) (2004–2009).

Materials and Results

Six dermatology clinics took part in the study, in which the majority of the members of the Swedish Contact Dermatitis Research Group participated. Participating centres were in Malmö, Lund, Gothenburg, Örebro, Stockholm, and Umeå. In Malmö, Lund, Gothenburg, and Stockholm, the study period was from 1 July 2006 to 31 December 2011; in Örebro, it was from 1 January 2007 to 31 December 2011; and in Umeå, it was from 1 October 2006 to 31 December 2011. In total, 6629 women and 3381 men were tested. In all departments, the test preparations were purchased from Chemotechnique Diagnostics (Vellinge, Sweden), that is, FM 2 14.0% pet. (wt/wt) containing 2.5% HICC, and HICC 5.0% pet (wt/wt). Tests were performed with Finn Chambers® (diameter, 8 mm) (Epitest Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennesla, Norway) in all centres. The patch testing personnel placed 20 mg of each pet. test preparation into each Finn Chamber®

Table 1. Number of patients who were patch test-positive to fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) in six dermatology departments in Sweden

	Number of patients tested with the baseline series			Positive to FM 2 (%)			Positive to both FM 2 and HICC (%)			Positive to FM 2 only (%)			Positive to HICC (%)			Positive to HICC only (%)		
	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F
Malmö*	3508	1256	2252	113 (3.2)	31	82	46 (1.3)	13	33	67 (1.9)	18	49	55 (1.6)	14	41	9 (0.3)	6	3
Lund*	1325	354	971	83 (6.3)	22	61	41 (3.1)	10	31	42 (3.2)	12	30	46 (3.5)	11	35	5 (0.4)	1	4
Gothenburg*	2638	849	1789	56 (2.1)	15	41	26 (1.0)	7	19	30 (1.1)	8	22	29 (1.1)	7	22	3 (0.1)	0	3
Stockholm*	1008	408	600	39 (3.9)	2	37	15 (1.5)	0	15	24 (2.4)	2	22	17 (1.7)	2	15	2 (0.2)	1	1
Örebro†	780	270	510	30 (3.8)	9	21	13 (1.7)	5	8	17 (2.2)	4	13	15 (1.9)	6	9	2 (0.3)	1	1
Umeå‡	751	244	507	16 (2.1)	2	14	7 (0.9)	1	6	9 (1.2)	1	8	9 (1.2)	1	8	2 (0.3)	0	2
All centres	10.010	3381 (33.8)	6629 (66.2)	337 (3.4)	81 (2.4)	256 (3.9)	148 (1.5)	36	112	189 (1.9)	45	144	171 (1.7)	41 (1.2)	130 (2.0)	23 (0.2)	9	14

M, males; F, females; FM 2, fragrance mix 2; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.
*Testing from 1 July 2006 to 31 December 2011.
†Testing from 1 January 2007 to 31 December 2011.
‡Testing from 1 October 2006 to 31 December 2011.

(10). Patch tests were removed by the patients after 2 days (D2), and read on D3 or D4 according to International Contact Dermatitis Research Group criteria (11). A second reading was performed on D7. A dermatologist read the patch tests on both days in all centres except for Umeå, where a nurse read tests on the first reading day and a dermatologist on the second reading day.

Fisher's exact two-tailed test was used to compare the contact allergy rate between males and females. The differences were considered significant at $p < 0.05$.

Positive patch test results from D3/4 and D7 are summarized into positive reactions, irrespective of reading day. Of 10 010 dermatitis patients tested at six departments, 337 (3.4%; range 2.1–6.3%) reacted to FM 2 containing 2.5% HICC, and 171 (1.7%; range 1.1–3.5%) to HICC 5.0% pet. tested separately. There were statistically significant differences between men and women in contact allergy to FM 2 (2.4% versus 3.9%, $p < 0.001$) and in contact allergy to HICC (1.2% versus 2.0%, $p = 0.006$). Twenty-three patients (0.2%; range 0.1–0.4%) were positive to HICC only. Simultaneous positive reactions were seen in 148 patients (1.5%) (Table 1).

Discussion

In this study comprising six departments, only 23 dermatitis patients (0.2% of all tested patients or 13.5% of the HICC-allergic patients) were patch test-positive to HICC without concomitant reactivity to FM 2. We do not question the inclusion of FM 2 at 14.0% pet., in which HICC is an ingredient at 2.5%, in the baseline series as a helpful additional marker for fragrance allergy (9). In a large German study comprising 35 490 patients, both fragrance mix 1 (FM 1) and FM 2 were tested, and 2.8% of the patients tested negative to FM 1 but positive to FM 2 (3). In the present study, ~1.6% of the patients tested negative to FM 2 but positive to FM 1 (unpublished observations).

HICC and farnesol are the most common sensitizers in FM 2 (2, 5). The other components are citral, coumarin, citronellol, and α-hexyl cinnamal. Contact allergy rates from various European centres of between 1.5% and 3% were reported when HICC was tested at 5.0% pet. in consecutive dermatitis patients (4–8). Our figures are very similar. Recent publications reported prevalence rates of sensitization in 2010 of < 1.6% in Denmark (12) and 2.1% in Germany (13). Moreover, a time trend analysis from the Information Network of Departments of Dermatology was recently published, in which patch test results from 2002 to 2010 and 84 733 patients indicated a slight decrease in sensitization, particularly during the last few years (14). The Scientific Committee on Consumer Safety concluded, in its opinion on fragrance allergens in cosmetic products, based on all available data, that the risk of sensitization by exposure to HICC is high, and that the use of HICC in consumer products is not considered to be safe (15).

However, is the inclusion of HICC 5.0% pet. as a separate patch test substance in a baseline series justified

when FM 2 is present? In the article from 2008, it was stated that 'HICC in pet. at 5.0% w/w fulfils the requirement of a contact sensitizer to be included in a baseline series' (9). The generally accepted requirements are that the substance is common in the environment, has a contact allergy rate above 0.5–1.0% in routinely tested dermatitis patients, and produces reliable patch test results with a high degree of clinical relevance, and minimal adverse effects (16). At that stage, there were no published reports on simultaneous and parallel patch testing with FM 2 and HICC, so it was not known to what extent there was simultaneous reactivity or not. However, some publications have recently addressed this topic. In the aforementioned German study, patch testing with HICC in addition to FM 2 was performed as part of the baseline series, and 108 patients sensitized to HICC were diagnosed who would have been missed if only FM 2 had been tested. These 108 patients represented 12.9% of those sensitized to HICC and 0.3% of the total test population (3). Furthermore, in a Belgian study in which HICC and FM 2 were tested simultaneously in 3401 patients, only 6 were positive to HICC alone, that is, 0.2% of the tested population or 10.3% of those allergic to HICC (17). Considering these data and our data in this study of > 10 000 patients, the inclusion of HICC 5.0% in the baseline series seems to be surplus to requirements, as our detection rate is only 0.2% better in the whole tested population of > 10 000 dermatitis patients, a figure too low to merit its inclusion as a separate patch test substance in the Swedish baseline series according to the present recommendations for such series (16). Our recommendation regarding the Swedish baseline series is therefore to consider having this patch test preparation removed, and perhaps this consideration is also valid for the European baseline series. We also strongly advise that FM 2-positive patients should be patch tested with HICC 5.0% pet. and with the other individual FM 2 ingredients, which should also be tested at twice the concentration of that in the mix. Also, FM 1-positive patients should be tested with FM 1 ingredients, to facilitate avoidance of exposure to the specific allergen, instead of going 'fragrance-free'. It is, moreover, essential to continue to monitor the prevalence of contact allergy to HICC and other fragrance allergens, which requires testing with the individual ingredients.

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