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INVESTIGATIVE REPORT

Multicentre Patch Testing with Compositae Mix by the Swedish Contact Dermatitis Research Group

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Sesquiterpene lactone mix detects contact allergy to these compounds present in the plant family Asteraceae. This marker is present in many baseline series. An additional marker is Compositae mix, which is not present in many baseline series. To investigate whether this allergen should be inserted into the Swedish baseline series, six dermatology centres representing the Swedish Contact Dermatitis Research Group included Compositae mix into their baseline series for 1.5 years. Of 2,818 patients tested, 31 (1.1%) reacted to Compositae mix and 26 (0.9%) to Sesquiterpene lactone mix. Active sensitization to Compositae mix was noted in two cases. Only 0.4% of Asteraceae contact allergy cases would have been missed if Compositae mix had not been tested, a frequency too low to merit its inclusion in the baseline series. Due to obvious geographical differences in frequency of simultaneous allergic reactions to Compositae mix and Sesquiterpene lactone mix, the question as to whether specific baseline series (including Compositae mix or not as a "tail" substance) should be used in the different centres must be addressed. Another option could be to remove Sesquiterpene lactone mix from the baseline series and substitute it with Compositae mix. ***Key words: sesquiterpene lactone mix; Asteraceae; Compositae mix; baseline series; contact allergy; colophony; fragrance; Myroxylon*****.**

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Sesquiterpene lactone mix (SL mix) is thought to detect patients with contact allergy to sesquiterpene lactones (SLs) present in the plant family Asteraceae (Compositae). However, some authors have proposed that patients sometimes require additional markers for the detection of this contact allergy (1). One such marker is Compositae mix (C mix). A question was put forward in the Swedish Contact Dermatitis Research Group as to whether more patients suspected of having contact allergy to Asteraceae plants would be detected with C mix than with SL mix. In a multicentre study of more than 10,000 dermatitis patients, over one third of SL mix-positive patients reacted to perfume and/or colophony (2). Thus, a further aim was to investigate whether there also was a relationship between C mix and colophony, fragrance (F) mix I and the related sensitizer Myroxylon Pereirae.

MATERIALS AND METHODS

Six dermatology departments (A–F) participated in the study, and a total of 2818 dermatitis patients were tested during the time period 1 July 2006 to 31 December 2007. Centre A and B are in Malmö and Lund, respectively, centre C is in Gothenburg, centres D and E in Stockholm and centre F in Umeå. There were 1,825 women and 993 men, with a mean age of 42.8 years for women (age range 5–88 years) and 43.0 years for men (age range 12–84 years). The baseline series encompassing the SL mix was purchased from Chemotechnique Diagnostics (Vellinge, Sweden) in centres A, C, D, E and F. In centre B Mekostest (Vitaflo Scandinavia AB, Gothenburg, Sweden) was used, and the additional test substances that make up the Swedish baseline series (including the SL mix) were purchased from Chemotechnique Diagnostics. C mix 5.0% w/w petrolatum (pet) was also purchased from Chemotechnique Diagnostics.

The test technique for the baseline series was Finn Chambers (diameter 8 mm) (Epitest Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) in centres A, C, D, and F, IQ Ultra chambers on a high-quality hypoallergenic surgical tape (Chemotechnique Diagnostics) in centre E, and Mekostest with the additional tests as described above in centre B. The Finn Chamber technique was used for the additional testing in the latter centre. The centres which used Finn Chambers for the petrolatum test preparations applied 20 mg of each test preparation into each chamber (3). Patch tests were removed after 2 days and read after an additional day or 2 according to International Contact Dermatitis Research Group criteria (4). A second reading was made 7 days after application of the patches. A dermatologist read all patch tests in centres A–E on both days, while centre F utilized a specialized nurse for the first reading and a dermatologist for the second one.

Statistical analysis

Confidence intervals (95%) were calculated for the estimated prevalences of contact allergy using the exact Clopper-Pearson method. Fisher's exact test for two proportions (two-sided) was

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used for investigating simultaneous reactions between other allergens and C mix and a $p < 0.05$ was regarded as statistically significant.

RESULTS

The number and percentage of contact allergic patch test reactions to C mix, SL mix, colophony, *Myroxylon pereirae*, and F mix I in each centre and in the whole patch tested population of 2,818 patients is shown in Table I. Of 2,818 dermatitis patients, 31 reacted to C mix (1.1 %) and 26 to SL mix (0.9 %). Of the SL mix-allergic patients, 73.1% (19/26) also reacted to C mix (Table I), and of 30 C mix-allergic patients, 19 reacted simultaneously to SL mix (63.3%, 19/30) (Table II). One C mix-allergic patient was negative to SL mix on D3 and was not read on D7, so he was deleted from this comparison (patient B5, Table II). Seven patients had a unique contact allergy to SL mix (and no reactions to C mix), one of which also reacted to *Myroxylon pereirae* and F mix I and another only to colophony. Twelve patients had a unique contact allergy to C mix. This means that 0.4% (12/2818) of all patients in the whole tested population with a contact allergy to C mix would have been missed by not testing with C mix in parallel with SL mix.

The pattern of simultaneous allergic reactions to SL mix, colophony, *Myroxylon pereirae*, and F mix I in 31 C mix-allergic individuals can be seen in Table II. Of those 31 allergic to C mix, an over-representation of allergic reactions were seen to colophony and *Myroxylon pereirae* ($p < 0.001$), but not to F mix I (Table II).

In Table III the relationship between the patch test reactivity to C mix and the likelihood of having a simultaneous reaction to SL mix is shown. There were two late (beyond D14) patch test reactions noted. In one patient C mix 5.0% pet was retested, and the allergic test reaction appeared already on D3. When comparing the allergic reactions to C mix in terms of reading days, 6% of the allergic reactions would have been missed had a D7 reading not taken place.

DISCUSSION

SL mix, containing alantolactone 0.033%, dehydrocostus lactone 0.033% and costunolide 0.033%, has been present in most baseline series for at least 15 years and is considered a good marker for contact allergy to SLs. However, it has been proposed that there are patients who are allergic to SLs that SL mix does not detect, and therefore some authors have suggested the inclusion of C mix into the baseline series (1).

In the 30 C mix-allergic patients read at both D3/4 and D7, the stronger the contact allergic reaction to C mix, the more likely it was that there would be an allergic reaction to SL mix (Table III). The strength of the allergy follows the simultaneous reactivity (5).

Furthermore, we found a statistically significant difference between simultaneous allergic reactions to C mix and SL mix when comparing centres A and B with centres D and E. In centres A and B, which are at a distance of 20 km from each other, only 12.5% of those allergic to C mix did not react to SL mix, whereas in centres D and E (which are within the same city and 300 m apart) 60% of those allergic to C mix did not react to SL mix ($p = 0.011$). This difference in frequency may reflect a difference in exposure to various Asteraceae plants. This may be true as the distance from centres A and B to centres D and E is approximately 600 km, and the distribution of plants containing sesquiterpene lactones may be different with different allergenicity and cross-reactivity. This then raises the question as to whether one centre with such a big difference between the detection rates of C mix and SL mix should include C mix in their baseline series as a "tail" substance rather than testing it only in cases suspected of having Asteraceae plant contact allergy. To include C mix into the baseline series in Sweden as a whole in parallel with SL mix is not an option considering the low frequency of missed Asteraceae-allergic patients (0.4%) if not testing with C mix. According to the literature, a frequency of 0.5–1.0% in detection rates can merit a substance to be included in a baseline series provided that clinical rele-

Table I. *Number and percentage of allergic patch test reactions to Compositae mix (C mix), sesquiterpene lactone mix (SL mix), colophony,* Myroxylon pereirae*, and fragrance mix I in each centre and in the whole patch tested population of 2,818 patients*

Centre	Compositae mix 5.0% pet	SL mix 0.1% pet	Colophony 20.0% pet	*Myroxylon pereirae* 25.0% pet	Fragrance mix I 8.0% pet	Total no. of tested patients
A	10 (0.95%)	13 (1.2%)	39 (3.7%)	74 (7.0%)	81 (7.7%)	1051
B	7 (2.2%)	7 (2.2%)	17 (5.4%)	6 (1.9%)	23 (7.3%)	314
C	2 (0.3%)	0	22 (3.2%)	40 (5.8%)	55 (8.0%)	685
D	5 (2.1%)	3 (1.3%)	6 (2.5%)	15 (6.3%)	12 (5.0%)	239
E	6 (1.7%)	1 (0.3%)	12 (3.4%)	21 (5.9%)	9 (2.5%)	356
F	1 (0.6%)	2 (1.2%)	6 (3.5%)	7 (4.0%)	6 (3.5%)	173
Total number of allergic reactions , 95% CI	31 (1.1%) (0.8–1.6)	26 (0.9%) (0.6–1.4)	102 (3.6%) (3.0–4.4)	163 (5.8%) (5.0–6.7)	186 (6.6%) (5.7–7.6)	2818
Simultaneous allergy to C mix[a]	Not relevant	19/26 (73.1%)	8/102 (7.8%)	8/163 (4.9%)	4/186 (2.2%)	

[a]Contact allergy towards sesquiterpene lactone mix, colophony, Myroxylon pereirae, and fragrance mix I, respectively.
CI: confidence interval.

Table II. *Patch test results in 31 patients (out of the 2,818 tested) with a contact allergy to Compositae mix (C mix) and the pattern of simultaneous allergic patch test reactions to sesquiterpene lactone mix (SL mix), colophony, fragrance mix I, and* Myroxylon pereirae*, respectively. Significant differences between obtained and expected figures are indicated*

	C mix 5.0% pet		SL mix 0.1% pet		Colophony 20.0% pet		Fragrance mix I 8.0% pet		*Myroxylon pereirae* 25.0% pet	
Centre and pat. no.	Day 3/4	Day 7	Day 3/4	Day 7	Day 3/4	Day 7	Day 3/4	Day 7	Day 3/4	Day 7
A 1	+++	++	+++	++	–	–	–	–	++	+
A 2	+++	+++	++	++	?	–	–	–	–	–
A 3	+++	+++	?	++	?	–	–	–	–	–
A 4	++	++	+	+	–	–	–	–	–	–
A 5	+++	+++	+++	+++	–	–	–	–	–	–
A 6	+	+	+	+	–	–	+	+	+	+
A 7	+++	+++	+++	+++	+++	+++	–	–	–	–
A 8	+	+	–	–	–	–	–	–	–	–
A 9	+++	+++	+++	+++	–	–	+++	+++	++	+
A 10	–	+	–	–	–	–	–	–	?	–
B 1	++	++	+	++	–	–	–	–	–	–
B 2	+++	+++	+++	+++	–	–	–	–	–	–
B 3	+++	+++	+++	+++	?	++	?	?	–	–
B 4	+++	–	+++	–	++	–	?	–	++	++
B 5	++	nr	–	nr	–	nr	–	nr	++	nr
B 6	+++	nr	+++	nr	–	nr	–	nr	–	nr
B 7	–	++	+++	+++	–	–	–	–	–	–
C 1	++	+	–	–	–	–	–	–	–	–
C 2	+	–	–	–	–	++	+	+	+	–
D 1	+	–	+	–	+	+	+++	++	+	+
D 2	+	–	–	–	–	–	–	–	–	–
D 3	+++	–	++	++	–	+	–	–	–	–
D 4	++	++	++	++	++	++	–	–	–	–
D 5	+	+	–	–	–	–	–	–	–	–
E 1	++	++	–	?	–	–	–	–	?	?
E 2	++	+	–	–	–	–	–	–	+	–
E 3	+++	+++	+++	+++	–	–	–	–	–	–
E 4	+	++	–	–	+	+	–	–	–	–
E 5	+	–	–	–	–	–	–	–	–	–
E 6	+	–	–	–	–	–	–	–	–	–
F 1	+	IR	++	++	–	–	–	–	–	–
Total number of allergic reactions/sensitizer	31		19		8		4		8	
Simultaneous allergy to C mix and *p*-values			0.67% (19/2818) $p<0.001$		0.28% (8/2818) $p<0.001$		0.14% (4/2818) $p=0.14$		0.28% (8/2818) $p<0.001$	
Expected frequency of simultaneous allergy to C mix if there was no connection to C mix			0.01%		0.04%		0.07%		0.06%	

[a]Contact allergy towards sesquiterpene lactone mix, colophony, fragrance mix I, and *Myroxylon Pereirae*, respectively.
nr: not read; IR: irritant reaction.

vance can be found (6). On the other hand, substituting SL mix for C mix could be an option, as C mix detects more allergic individuals.

C mix 5.0% pet was used in this study. It is a mixture of plant extracts composed of *Arnica montana*, *Tanacetum vulgare*, *Chamomilla romana*, *Achillea millefolium* and *parthenolide*, substances that are contact allergens present in Asteraceae plants and that make up one of the largest plant families in the world. C mix was originally developed by Hausen as an ether extract of Asteraceae plants at a concentration of 6.0% in contrast to SL mix, which was developed by Ducombs et al. (7). The test preparation C mix is nowadays sold by, for example, Chemotechnique Diagnostics at 5.0% pet and by Trolab Hermal (Reinbeck, Germany) at 6.0% pet. It has been proposed that a locally prepared Compositae mix should be superior to the commercial C mix obtainable at present because the variety of allergenic Asteraceae plants varies from region to region. Our differing results between test centres may well support this observation. However, it would probably be very difficult, if not impossible, for small dermatology units to make up their own test preparation. There would also be a difficulty with standardization of the test preparation, as the concentration of the various components may vary from season to season and in different parts of the plant. Therefore, in the present study this was not an issue, even if, for example, the Malmö department could have prepared such a mix.

Table III. *The stronger the contact allergic reaction to Compositae mix (C mix), the more likely an allergic reaction to the sesquiterpene lactone mix*

If +++ to C mix	100% concordance (12 patients)
If ++ to C mix	50% concordance (8 patients)
If + to C mix	30% concordance (10 patients)

Furthermore, it has been stated that C mix is irritating (8) and may cause patch test sensitization (9) in contrast to SL mix, which is claimed to be non-sensitizing and non-irritating (8).

The risk of patch test sensitization would probably be higher with a "home-made" extract than with the commercial test preparations, even if in our study two cases of presumed patch test sensitization were seen from testing with the commercial test preparation C mix (the two patients are not shown in Table II).

No cases of patch test sensitization were, however, seen with SL mix. To minimize the risk of patch test sensitization the concentration may have to be lowered to 50% of its present concentration, but the lower the dose the higher the risk of not detecting any contact allergies.

As stated previously, SL mix does not detect all patients with contact allergy to Asteraceae plants (1). According to some authors, only 30% of cases of sensitization are detected (10), while others claim that approximately 60–70% of all cases of Asteraceae contact allergy is revealed by the SL mix (8), figures much like ours looking at the 6 centres together. The poor sensitivity could partly be explained by phytogeographic variations (11). When patch testing gardeners in Denmark the C mix detected twice as many of the sensitized individuals as did SL mix, but the overall detection rate when testing simultaneously with both mixes was still not higher than 76% (12). However, according to the same authors, in consecutively patch tested dermatitis patients, testing with both mixes raised the detection rate to 93% (13). In a European multicentre study more than 10,000 consecutively patch tested dermatitis patients were tested with SL mix and 1% (range 0.1–2.7%) reacted to the mix, with 75% of these reactions having past or current relevance. The prevalence was highest in areas with pot flower and cut plant industries. Of the ones reacting, more than one-third also reacted to perfume and/or colophony, suggesting "cross-reactivity" (2). In our study similar figures were seen, as 10 of the 26 SL mix-allergic patients also had simultaneous allergic reactions to fragrance mix I and/or colophony. Eight of these 10 patients belonged to the SL-mix positive patients with a concomitant contact allergy to C mix. In the two patients with a unique contact allergy to SL-mix very few simultaneous allergic reactions were seen to fragrance mix I, colophony, and/or *Myroxylon pereirae*. In conclusion, the results from our study do not merit the inclusion of C mix into the baseline series. Substituting SL mix with C mix is another option.

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