

An 8-year experience with routine SL mix patch testing supplemented with Compositae mix in Denmark

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Routine patch testing with sesquiterpene lactone (SL) mix, supplemented with Compositae mix (CM) and other Compositae extracts and allergens where appropriate, was evaluated over an 8-year period. 190 of 4386 patients tested (4.3%) were Compositae-sensitive, 143 females (mean age 51.5 years) and 47 males (mean age 55 years), and 83% of reactions considered clinically relevant. 22% were suspected of occupational sensitization/dermatitis. 62% had a contact allergy to 2 or more compounds, most often to nickel, fragrance and colophonium. SL mix detected 65%, CM 87% of Compositae-allergic patients, and the overall detection rate with both mixes was 93%. Few irritant reactions and no cases of clear-cut active sensitization were recorded with the mixes, but our results emphasize the importance of differentiating late-appearing reactivation reactions from patch test sensitization. The weakly positive CM reactions could reflect some irritancy, but as they were associated with fragrance and/or colophonium allergy to a higher degree than weakly positive SL mix reactions, they probably represented cross-reactions. In conclusion, the detection rate with SL mix was high enough to support its continued use as a screening mix and it was very well and rather safely supplemented by aimed testing with CM.

Key words: allergic contact dermatitis; sesquiterpene lactones; Compositae; Asteraceae; patch testing technique; fragrance; colophonium; occupational; horticulture; plants. © Munksgaard, 2001.

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The commercial availability of first the sesquiterpene lactone (SL) mix and in recent years also the Compositae mix (CM) has made routine screening for Compositae allergy possible on a larger scale. Results from different clinics in Europe have substantiated the leading rôle of Compositae in plant dermatitis today, but also pointed out the inadequacy of the SL mix in detecting all the Compositae-sensitive, and the potential irritant and sensitizing properties of the Compositae mix (1–6). We therefore find it of interest to report our approach to diagnosing Compositae allergy in an 8-year period: routine testing with the SL mix supplemented with aimed patch testing with the Compositae mix and other composite extracts and allergens.

Materials and Methods

The SL mix 0.1% pet. and the Compositae mix 6.0% pet. were manufactured by Trolab® (Hermal, Ham-

burg, Germany) for members of the European Environmental Contact Dermatitis Research Group in the late 1980s (3, 4). The SL mix was included in our standard series in February 1990. In case of positive reactions to the mix or suspected Compositae allergy, the patients were tested with the Compositae mix and other Compositae extracts and allergens where appropriate. Since May 1990, the standard series consisted of TRUE Test® panels 1 and 2 and varying additional allergens.

Supplementary supplies of the Compositae mix were prepared by BMH from fresh plant material (yarrow, tansy and feverfew) and predried commercial plant material (arnica and wild (German) chamomile).

Extracts and allergens were applied in Finn Chambers® (Epitest Ltd., Helsinki, Finland) on Scanpor® (Norgesplaster A/S, Oslo, Norway) for 2 days (D). Readings were made on D2–D4 and, whenever possible, on D5–D8, according to the ICDRG criteria.

Table 1. Prevalence of positive Compositae reactions when screening with SL mix and supplementing with Compositae mix and other Compositae extracts/allergens

Year	Patients positive/tested	(%)
1990–1991	32/686	4.66
1991–1992	24/571	4.20
1992–1993	29/585	4.96
1993–1994	16/591	2.71
1994–1995	35/507	6.90
1995–1996	19/475	4.00
1996–1997	20/480	4.17
1997–1998	15/491	3.05
1990–1998	190/4386	4.33

The number of positive reactions to contact allergens other than Compositae was based on the results of the latest standard patch tests and possible supplementary patch tests in the 8-year period.

Atopy was defined as past or present atopic dermatitis and/or hay fever and/or asthma and/or positive prick test to 1 of the 10 common inhalant allergens.

Patients were referred both from the county of Funen, where a large greenhouse industry is located, and from neighbouring counties.

Results

From February 1990 to February 1998, a total of 4386 patients were tested with the SL mix and 549 with the Compositae mix. 190 persons tested positive to 1 or more Compositae patch test substances, making the overall prevalence of Compositae sensitivity 4.3% (Table 1). The allergy was considered relevant, current or old, in 156 cases (83%), of unknown relevance in 32 cases and not registered in 2 cases. The relevance was further categorized as definite, likely, possible or doubtful, inspired by the scoring system suggested by Lachapelle (7). 140 of the 156 reactions were considered to be of definite or likely current/old relevance.

The Compositae-allergic patients comprised 143 females (75%), with a mean age of 51.5 years (median 49.4, range 17–86 years), and 47 males (25%) with a mean age of 55 years (median 60, range 20–82 years). Even though the % of males over 60 years was higher than in females (49% versus 34%), the absolute number of males was only about 1/2 that of females. The MOAHL index for 4091 patients tested in approximately the same period in our clinic showed 35% males (8).

42 persons (22%) were suspected of occupational sensitization and/or dermatitis: 31 females with a mean age of 41 years (median 41) and 11 males with a mean age of 39 years (median 32). 189 of the 190 Compositae-allergic patients were tested

with SL and 181 with Compositae mix, and Tables 2–4 show the distribution and strength of the reactions and their relationship to the relevance. Only 1 irritant reaction to the SL mix and 4 to the Compositae mix were recorded in the 8-year period.

Results of testing with the constituents of the mixes and other Compositae extracts and allergens will be presented elsewhere.

17% of the Compositae-sensitive patients had no other contact allergy, and 62% were sensitive to 2 or more compounds. This distribution was even more marked in the nonoccupationally sensitized (Table 5). Nickel was the most frequent other contact allergy, followed closely by fragrance mix (Table 6).

38 persons (20%) had only 1 positive Compositae reaction (including 2 testing positive to differ-

Table 2. Patch test reactions in those of the 190 Compositae-sensitive patients that were tested with SL mix and Compositae mix

	No. patients	
	tested	positive
SL mix	189	122 (65%)
Compositae mix	181	157 (87%)
SL and Compositae mixes tested with both mixes and positive to SL and/or Compositae	181	104 (57%)
	181	169 (93%)

Table 3. Distribution and strength of reactions to the SL and Compositae mixes in 190 Compositae-allergic patients

	–	?+	+	++	+++
SL mix	53	14	26	58	37=188 ^{a)}
Compositae mix	11	13	38	78	41=181 ^{b)}

^{a)} 1 was not tested, 1 had positive reaction with unknown strength.

^{b)} 9 were not tested.

Table 4. Reactions to the SL and Compositae mixes among 190 Compositae-sensitive patients compared to relevance of the allergy

	Relevance		total
	current/old	don't know	
Positive SL mix	109	12	121 ^{a)}
+? SL mix	12	2	14
negative SL mix	34	18	52 ^{a)}
total	155	32	187
Positive Comp. mix	137	20	157
+? Comp. mix	7	6	13
negative Comp. mix	7	4	11
total	151	30	181

^{a)} Information on the relevance was missing in 1 case from each group.

Table 5. Distribution of number of contact allergies other than Compositae in 190 Compositae-sensitive patients

No. contact allergies	No. patients	Occup. sensitized	Non-occup. sensitized
0	32 (17%)	12 (29%)	20 (14%)
1	39 (21%)	10 (24%)	29 (20%)
2	41 (22%)	8 (20%)	33 (22%)
>2	76 (40%)	11 (27%)	65 (44%)
Total	188	41 ^{a)}	147 ^{a)}

^{a)} 1 patient was left out in each group because of late reactions and no re-testing.

Table 6. Top 10 list of contact allergens in 190 Compositae-sensitive patients – results of latest patch tests

Allergen	No. positive reactions
nickel sulfate	49
fragrance mix	46
colophonium	35
thiuram mix	25
cobalt chloride	24
methylchloroisothiazolinone + methylisothiazolinone	22
potassium dichromate	21
carba mix	20
Myroxylon Pereirae Resin, chlorhexidine, 2-bromo-2-nitropropane-1,3-diol, l-carvone	12 of each
thimerosal	11

ent cultivars of 1 species): 19 tested positive to the Compositae mix, 10 to the SL mix and 9 to other reagents. The majority of the reactions were weak (+), and 25 of the total number of 32 cases of unknown relevance were found in this group. 14 of the 19 CM-positive were tested with the constituents: 8 were negative, 5 doubtful positive and 1 could not be evaluated. Likewise, 6 of the 10 SL mix-positive were tested with the allergens: 3 were negative, 2 doubtful positive and 1 could not be evaluated.

Altogether, $\frac{1}{2}$ of the patients had doubtful positive reactions to at least 1 other Compositae patch test and 4 persons had a limited, occupationally induced, relevant sensitization.

Among 38 persons with + reactions to the Compositae mix (Table 3), 45% had positive reactions to fragrance mix (FM) and/or Myroxylon Pereirae Resin (balsam of Peru) and/or colophonium, while this was the case in 32% of 119 persons with ++++ reactions to the Compositae mix ($p=0.21$). In the SL mix-positive patients, the distribution of perfume/colophonium allergy was independent of the strength of the SL mix reactions ($p=0.76$).

Table 7 shows a comparison of the strength of reactions to Compositae mix and perfume/colo-

Table 7. Strength of CM reactions compared to fragrance mix (FM) and colophonium reactions

No. of patients (42 ^{a)})	No. of patients (32 ^{a)})
CM=FM 15 (36%)	CM=colophonium 7 (22%)
CM>FM 14 (33%)	CM>colophonium 19 (59%)
CM<FM 13 (31%)	CM<colophonium 6 (19%)

^{a)} 4 and 3 patients, respectively, were not tested in our clinic and thus could not be included.

phonium. Altogether 66 persons (35%) tested positive to FM and/or Myroxylon Pereirae Resin and/or colophonium.

On the other hand, in the 156 persons with current/old relevance of the Compositae allergy, 24% had positive reactions to FM and/or Myroxylon Pereirae Resin and in the remaining 32 persons with unknown relevance 31% tested positive to FM and/or Myroxylon Pereirae Resin. If reactions to other fragrance materials were included, the %s rose to 27.5% and 37.5%, respectively. Adding positive colophonium reactions to these figures almost equalized them (38.5% versus 41%), since the majority of colophonium-positive patients had relevant Compositae reactions.

Active sensitization was not recorded with any of the mixes. In a few patients, however, the pattern of patch test reactions made distinction between active sensitization and late-appearing reactivation reactions difficult (Table 8). Late-appearing (D7) positive SL mix reactions were seen in another 13 patients.

Atopy was found in 53 patients (28%), 44 females with a mean age of 47 years (median 44) and 9 males with a mean age of 54 years (median 60). 6% of the patients had no other contact allergy, 26% were sensitive to 1, 23% to 2 and 45% to more than 2 other contact allergens. The prevalence of persons with no other contact allergies was significantly lower in atopics compared to nonatopics ($p=0.01$). In 9 patients the diagnosis was based on a positive prick test without concomitant skin or mucosal symptoms.

The MOAHL index for 4091 patients tested in approximately the same period showed an atopy prevalence of 19%.

Discussion

The prevalence of Compositae allergy, though variable from year to year, is high and not diminishing as might be expected some years after the introduction of a new allergen (9), and this seems to be an exact reflection of the way the mixes have been used.

Routine screening with the SL mix in Europe has shown prevalences between 0.9 and 1.8% (1, 2,

Table 8. Patch test reactions in Compositae-sensitive patients with possible active sensitization or slow reactivation

Pt. no.	Allergen	1st test	2nd test	Other Comp. reactions	Relevance
1	SL mix	?+ D7	++ D3 and D7	?+ CM and camomile	D
2	SL mix	?+ D5-7, + D10	++ D6	several positive	D
3	SL mix	?+ D5, ++ D14	NT	several positive	O
4	CM	?+ D5	++ D3	0	D

CM: Compositae mix.

D: don't know.

O: old.

9, 10). On the other hand, in Hausen's 6-year study of the CM as an optional addition to the standard series, 3851 of 6337 patients were tested and 3.1% were positive (at least ++) (4, 11), while screening with both SL mix and CM in a recent English study caused the prevalence to rise to 5.9% (modified to 4.7% after application of criteria to detect genuine Compositae allergies) (5). The most recent report comparing the 2 mixes is a German multi-centre study: they found 3.2% CM-positive and 1.7% SL mix-positive among 3037 patients tested with both (12). The overall prevalence of 4.3% in our study thus represents a basal SL mix detection rate of 2.8% reinforced by aimed testing with the CM. The high rate of definite and likely relevance supports that the positive reactions represent genuine Compositae allergy.

Previous studies of European Compositae-sensitive patients have shown either an equal sex distribution or a majority of women of about 60% (2, 4, 10), making the % of females in our study the highest ever reported. A more equal female:male ratio has also been reported in newer studies from the USA and India, and the results support the rôle of changes in exposure as an important factor in the sex distribution (13, 14). This notion is also supported by a study of occupational Compositae dermatitis where sex was found not to be an independent risk factor (15).

The mean age is in accordance with both that of classic Compositae dermatitis and that found in recent European reports (2, 10). In all studies males were a little older than females, and in Ross et al.'s study males >60 years outnumbered females, which was not the case in the Funen patients, even if the % of males was considerably higher. This may reflect the same trend and possibly a slightly different referral pattern, since the English patients were seen in a clinic with a special interest in photosensitivity, which is mainly a disease of elderly males.

The prevalence of occupational sensitization to Compositae ranges between 11–19% (SL mix) and 28% (CM~optional) in consecutively tested patients (2, 4, 10). The last-mentioned prevalence was seen in an area with a large greenhouse and out-

door floral industry in Germany (4), and the prevalence thus may not just reflect the higher detection rate of the CM. Despite the greenhouse industry in our county the prevalence was only 22%, but this is probably a minimum figure: previous studies of the occupationally exposed have shown a Compositae sensitization rate 2× as high as that of the consecutively tested, and not all affected gardeners are seen by dermatologists (15). In accordance with other European studies, the mean age is lower in the occupationally than in the non-occupationally sensitized (2, 4, 10), but it is surprising that it is actually lower in males. This may support the findings of a previous Danish study of occupational Compositae dermatitis, where the prevalence of Compositae-related symptoms was inversely correlated with age in males (15). The reason for this apparent risk in younger male gardeners is unknown.

When comparing SL mix screening with CM/plant extract screening, the detection rate of the former ranges between 35 and 77% in 3 British, 1 German and 1 Danish study (3, 5, 12, 16, 17). The present SL mix detection rate of 65% (Table 2), combined with almost negligible irritant and sensitizing properties, justifies continued inclusion of the mix in the standard series in our area. The higher detection rate with the CM is on a par with that reported by von der Werth et al. (5), but lower than the 92% reported by Geier and Hausen (12) (Table 2). However, among Compositae-sensitive patients tested with both mixes, only 57% were positive to both, but the 2 mixes supplemented each other very well, making the overall detection rate as high as 93% (Table 2). The majority of positive reactions to both mixes were strong and the % of ++/+++ reactions to SL mix was slightly higher than that to CM, indicating clinically relevant reactions considering the low irritant potential of SL mix (Table 3). This is partly confirmed by the figures in Table 4: among 32 patients with unknown relevance, only 37.5% in the SL mix-tested group had positive reactions, while this was the case for 66.6% in the CM-tested group.

On the other hand, 46 cases of current/old relevance were missed by the SL mix, so, while a posi-

tive SL mix reaction is likely to represent a clinically relevant Compositae allergy, a negative reaction by no means excludes it.

We recorded very few irritant reactions, perhaps because of the well-known difficulty in distinguishing between weakly allergic and weakly irritant reactions. Testing with constituents of the 2 mixes, in those with positive reactions to SL mix or CM only, elicited negative or doubtful positive reactions. This could be due to irritancy or a synergistic/additive effect of the mixes in those persons with low-grade sensitization. Even if the prevalence of doubtful positive reactions to SL mix and CM was almost the same in the Compositae-allergic patients, the prevalence of these reactions was higher with CM among non-Compositae-allergic patients (not shown). Perhaps this should be expected when performing aimed patch testing in patients suspected of Compositae allergy, but it might also reflect irritancy. Likewise, the frequent CM + reactions, most of which were of unknown relevance, could be due to irritancy; however, the high prevalence of perfume/colophonium allergy in these patients indicates cross-reactions to CM as another possible explanation. Even if the prevalence of perfume/colophonium allergy in the patients with + reactions to CM was not significantly higher than in the patients with ++ or +++ reactions, there was a trend which was not found in SL mix-positive patients. This, combined with the higher frequency of fragrance allergy in patients with unknown relevance of Compositae allergy, suggests cross-reaction from fragrance to Compositae extracts, possibly through related terpenes (18, 19). Based on our results, cross-reactions between colophonium and Compositae, previously suggested by Storrs et al. (20), could be reciprocal: colophonium reactions were seen in patients with + CM reactions, but the majority occurred in patients with strongly positive, relevant CM reactions, indicating either concomitant sensitization or cross-reactions from the more strongly reacting Compositae extracts to colophonium (Table 7).

The prevalence of contact allergy to compounds other than Compositae was high in both the occupationally and nonoccupationally sensitized, though more pronounced in the latter group where 66% had multiple contact allergies. This suggests that Compositae sensitization occurs in either heavily exposed individuals, such as gardeners, or in a subgroup of persons, occupationally or non-occupationally exposed, with an increased susceptibility to allergic contact dermatitis (21). Also, it is highly surprising that fragrance allergy is on a par with nickel allergy and that Myroxylon Pereirae Resin, a contact allergen of declining import-

ance in Northern Europe, is found in the "top 10" list. A similar association with FM/Myroxylon Pereirae Resin/colophonium was also found in the latest multicentre SL mix study (2) and in the German multicentre study of CM (12). This could be related to cross-reactivity, as discussed above, or concomitant sensitization to these common contact allergens.

l-carvone, a contact allergen included in the standard series from 1991 to 1994, was significantly associated with Compositae allergy, but the carvone reactions were not reproducible and the relationship between carvone and Compositae allergy remains unclear (22).

Active sensitization to SL mix is rare and yet 3 of 4 cases were suspected of this (Table 8). Patient no. 2, however, had several positive Compositae reactions in subsequent patch testing performed within a few weeks, and patient no. 3 tested positive to CM and feverfew applied 1 week after SL mix. Sensitization is thus less likely in these 2 persons. Patients nos. 1 and 4 both had gardens with herbaceous borders; patient no. 4 had widespread eczema with exacerbation in spring and autumn, while patient no. 1 had had eczema of the right hand for about 1 year. Even if active sensitization is a possibility, we view the reactions in the light of several examples of late-appearing, clear-cut relevant reactions: an elderly man with Compositae allergy was re-tested after 2.5 years and several positive reactions appeared on D11, an atopic woman with previous positive CM and arnica reactions had positive Compositae reactions at D15–D17 on 2 separate test occasions with an interval of 5 years, and a young female gardener with occupational Compositae sensitization and positive reactions to CM, feverfew and chrysanthemum on D3 developed ++ reactions to SL mix and parthenolide within the next 19 D. Likewise, in an occupationally sensitized nursery worker re-tested after 9 years, we saw positive reactions on D3 and D7 to several extracts, but the feverfew and tansy reactions, weakly and doubtful positive on D7 respectively, persisted and developed into +++ reactions by D28. It thus seems that re-testing after years may evoke late-appearing and long-lasting reactivation reactions. This type of reactivation must be differentiated from patch test sensitization. The clinical implications of these phenomena are not clear. Late-appearing positive SL mix reactions were seen in other patients, and it is possible that patient no. 1 had an even later appearing reaction due to reactivation. The clinical features in patient no. 4 support relevant Compositae allergy, but sensitization cannot be ruled out.

However, we have not recorded patients returning with positive SL or CM reactions as de-

scribed by Wilkinson & Pollock (6), which may reflect the restricted use of CM for aimed patch testing only in our clinic. Furthermore, no case of active sensitization has been seen at the Department of Dermatology of the University Hospital in Hamburg, Germany, where they have patch tested with CM for more than 20 years (12), though this could be due to the fact that the patches are applied for 24 h only (4).

The relationship between atopy and Compositae sensitization is controversial, ranging from Mitchell's statement that ragweed dermatitis often occurs in atopic persons to the more sceptical conclusions of newer reviews of no clear experimentally based association (23–26). Nevertheless, close to 1/3 of all Compositae-sensitive patients were atopics in our study, a high figure compared to the overall atopy prevalence of 19% in all consecutively tested patients. Perhaps atopic persons are more extensively patch tested than other groups of eczema patients to rule out complicating contact allergy. At any rate, the findings confirm that sensitization does occur in atopic persons, and considering the significantly lower prevalence of persons with no other contact allergy, perhaps even more so than in nonatopic individuals (27).

It could be argued that not all of the 38 persons with only 1 positive Compositae reaction had a genuine Compositae allergy. However, we think it important to include patients with unknown relevance of the allergy and/or weakly-positive reactions, because of the possibility of cross-reactivity, limited sensitization, or emerging, not fully established, Compositae allergy.

In conclusion, the detection rate with the SL mix is high enough to support its continued inclusion in the standard series, and it is very well and rather safely supplemented by the CM, making the overall detection rate of Compositae allergy by the 2 mixes >90%. Weakly positive CM reactions may represent both cross-reactions to perfume and/or colophonium or weakly irritant reactions. Since Compositae allergy seems to occur in either younger persons with heavy, often work-related, exposure or middle-aged persons with multiple contact allergies and recreational exposure, aimed patch testing with CM and other Compositae extracts should be restricted to these groups to avoid inadvertent sensitization.

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