

Contact allergy to farnesol in 2021 consecutively patch tested patients. Results of the IVDK*

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Farnesol is one of the fragrances considered to be a significant contact allergen. Therefore, it was decided by the European Union to label products containing farnesol. Farnesol was tested [5% petrolatum (pet.)] together with the standard series between 1 January 2003 and 30 June 2003 in 2021 consecutive patients, 1243 females and 778 males. Of these, 22 [1.1%, 95% confidence interval (CI): 0.7–1.6%] had a positive reaction to farnesol. 147 (8.1%) of those 1825 tested to *Myroxylon pereirae* resin (balsam of Peru, 25% pet.) at the same time reacted positively, 143 (7.8%) of those 1823 tested to the fragrance mix (FM) (8% pet.) and 34 (1.9%) of 1831 tested to propolis (10% pet.). With regard to concomitant reactions in farnesol-positive patients, 5 of 22 reacted additionally to the FM [odds ratio (OR): 4.3; CI: 1.53–12.15] and 2 (of these 5) additionally to *M. pereirae* resin (OR: 1.27; CI: 0.29–5.54). The strongest association was seen to propolis (OR: 6.2; 95% CI: 1.4–27.7). Compared to those with negative reactions to farnesol, the group of patients allergic to farnesol was characterized by a higher proportion of young females and office workers, and the hand and the face were more often affected. In conclusion, farnesol is an important allergen. We recommend that farnesol should be included in a fragrance patch-test preparation and that its use should be regulated for consumer safety reasons. Furthermore, the extent of exposure to farnesol should be further studied.

Key words: CAS 4602-84-0; contact allergy; farnesol; fragrance mix; *Myroxylon pereirae*; propolis.
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Accepted for publication 1 March 2004

Contact allergy to the fragrance mix (FM), the most important patch-test preparation for diagnosis of allergies to fragrances, is still frequent (1). 2–4% of the general population (2) and more

than 10% of patients having undergone contact dermatitis investigation have been shown to be sensitized to the FM (3). However, fragrance allergy is only partially diagnosed through the FM in patients with a history of fragrance intolerance, indicating that further fragrance compounds beyond those contained in the FM are involved in contact allergy to fragrances (4, 5). On the other hand, there are fragrance compounds rarely causing allergies (6). Hence, fragrances cannot be regarded as a homogeneous group concerning contact allergy risk.

The impact of sensitization to a specific allergen on the general population level is often estimated based on studies in patch-test patients (2). Results of such studies are thus the basis for preventive and regulatory decisions. Labelling can be one of these regulatory decisions: the European Union has decided that, if consumer products contain one or several fragrances out of a list of 26 fragrances, these fragrances should

*The following centres of the IVDK, all members of the German Contact Dermatitis Research Group (DKG), contributed data to this analysis (in alphabetical order): Augsburg (A. Ludwig), Basel (A. Bircher), Berlin Charité (T. Zuberbier and M. Worm), Dortmund (P.J. Frosch, R. Herbst and C. Pirker), Dresden (R. Aschoff), Erlangen (M. Fartasch and V. Mahler), Essen (U. Hillen), Göttingen (Th. Fuchs and J. Geier), Graz (W. Aberer and B. Kränke), Halle (G. Gaber and D. Lübke), Hamburg (R. Weißbecher), Heidelberg (U. Jappe), Homburg/Saar (P. Koch), Jena (A. Bauer and M. Kaatz), Krefeld (M. Lilie and S. Wassilew), Lübeck (J. Grabbe), Marburg (H. Löffler), München Schwabing (M. Agathos), Münster (R. Brehler), Rostock (H. Heise) and Ulm BWK (H. Pillekamp).

be labelled (7). One of these fragrance compounds is farnesol, which is not only used as a fragrance but also used as a natural microbicide (8). In this publication, we present the results of patch testing 2021 consecutive patients with this compound.

Patients and Methods

The multicentre project IVDK (Information Network of Departments of Dermatology, <http://www.ivdk.org>) is an instrument of epidemiological surveillance of contact allergy and has been described in detail elsewhere (3, 9). Briefly, patients suspected of allergic contact eczema and attending the contact allergy clinics participating in the multicentre project were usually patch tested with the standard series of the DKG, and partially with additional series, depending on the history. The patch tests were performed in accordance with the guidelines of the German Contact Dermatitis Research Group (DKG) (10) and current international recommendations (11). Patch-test material was obtained from Hermal (Reinbek, Germany) and applied for 24 h or 48 h. Readings were taken until at least 72 h using the following gradings: neg, ?, +, ++, +++, irrit, follicular. The patch-test results of every reading, a standardized history [comprising age, sex, atopic diseases, current and former occupation(s) and presumptive causal exposures], as well as final diagnosis, and site of dermatitis were assessed and documented. All data were regularly (every 6 months) transferred to the data centre in Göttingen in an anonymous format.

Data obtained from all patients tested with a monitor series between 1 January 2003 and 30 June 2003 were analysed retrospectively. The monitor series of the IVDK is conceived as an ad hoc screening series tested together with the standard series in consecutive patients, with allergens of presumed or doubtful importance introduced for testing only for a limited time, normally for 6 months (12). The monitor series of the first half of 2003 was tested in 21 contact allergy clinics and comprised one preservative in different concentrations and several fragrance compounds not part of the current FM. Results were analysed separately, after completion of the yet ongoing study on fragrance compounds.

In a routine interim analysis, a remarkably high frequency of sensitization to farnesol, one of the compounds of the monitor series of the first half of 2003, which was tested [5% petrolatum (pet.)] in 2021 patients, was found. The farnesol patch-test preparation contains, according to the manufacturer, 4 stereoisomers, mainly in the *trans/trans* (59%) and *cis/trans* (30%) configuration

(Fig. 1). In the present paper, the cases of sensitization to farnesol are analysed, including concomitant reactions to the FM, *Myroxylon pereirae* resin (balsam of Peru) and propolis.

Frequencies of sensitization (as percentage of patients tested) were calculated as crude proportions and as proportions standardized for sex and age (3). The reaction index (RI), relating the number of allergic reactions to the number of doubtful or irritant reactions (13), and the positivity ratio (PR), relating the frequency of + reactions to the total number of allergic reactions (14), were calculated as further parameters to assess a patch-test preparation.

For comparison of the demographic characteristics of farnesol-allergic and farnesol-non-allergic patients, the MOAHLFA index was used. MOAHLFA is the acronym for male, occupational, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis and age >40 (3). The association between the factors of the MOAHLFA index and farnesol sensitivity was quantified with odds ratios (ORs) mutually adjusted for these factors in a logistic regression analysis, accompanied by the corresponding 95% confidence interval (CI). Further information from the patient history, particularly the occupation of farnesol-allergic and farnesol-non-allergic patch-test patients, was considered.

For data management and analysis, the statistical software package SAS 8.2 (SAS Institute, Cary, NC, USA) was used.

Results

In total, 2021 patients were patch tested with farnesol (5% pet.), 1243 females and 778 males. Of these, 22 (1.1%, 95% CI: 0.7–1.6%) had a positive reaction to farnesol. 147 (8.1%) of those 1825 tested to *M. pereirae* resin (balsam of Peru, 25% pet.) at the same time reacted positively, 143 (7.8%) of those 1823 tested to the FM (8% pet.) and 34 (1.9%) of 1831 tested to propolis (10% pet.). With regard to concomitant reactions of patients reacting positively to farnesol, 5 of 22 reacted additionally to the FM (OR: 4.3; CI: 1.53–12.15) and 2 (of these 5) additionally to *M. pereirae* resin (OR: 1.27; CI: 0.29–5.54) (Fig. 2). The strongest, albeit still relatively limited, association was seen to propolis (OR: 6.2; 95% CI: 1.4–27.7). In the 143 FM-allergic cases, 55 reacted concomitantly to *M. pereirae* resin (OR: 10.9; CI: 7.32–16.21). The pattern of patch-test reactions to farnesol is shown in Table 1. The RI is 0.19 and the PR 77%.

The group of patients reacting allergically to farnesol differed from the non-allergic group with

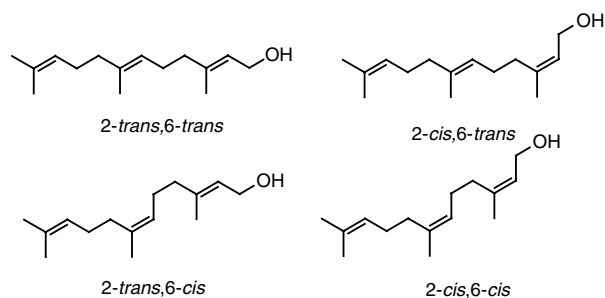


Fig. 1. Structure of the stereoisomers of the sesquiterpene farnesol ($C_{15}H_{26}O$; CAS 4602-84-0), which are contained in commercially available mixtures and the patch-test preparation in following quantities: *trans/trans* (CAS 106-28-5), ~60%; *cis/trans* (CAS 3790-71-4), ~30%; *trans/cis* (CAS 3879-60-5), ~8%; and *cis/cis* (CAS 16106-95-9), <1%.

regard to the following characteristics of the MOAHLFA index (Table 2): There were less men, patients were younger and the face and the hands were more often affected, whereas leg dermatitis was rare. However, none of these differences was statistically significant. Farnesol-allergic patients also differed with regard to the frequencies of occupations, with more office workers (22.7% versus 4.4%; OR: 6.4; 95% CI: 2.3–17.7). The frequencies of cases per department was as follows: 10 of 21 with no case, 6 with 1 case, 2 with 2 cases, 2 with 3 cases and 1 with 4 cases. The number of patients tested per department ranged from 24 to 176 (contributing 1.2–8.7% of the total patch-test population).

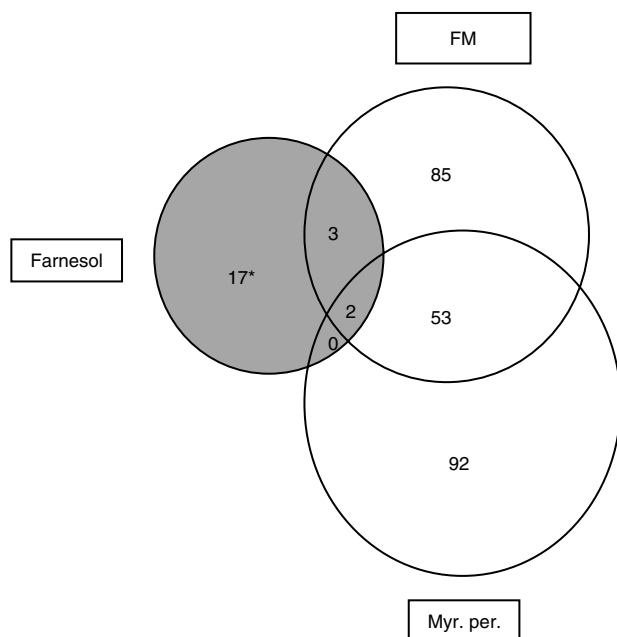


Fig. 2. Patients with allergic reactions to farnesol, the fragrance mix (FM) and *Myroxylon pereirae* resin (Myr. per.)

Table 1. Patch-test reactions to farnesol (5% pet.) in 2021 patients tested

n	2021
neg	1984
?	13
irrit	0
follicular	2
+	17
++	5
+++	0
pos%	1.1
RI	0.19
PR	77%

RI, reaction index; PR: positivity ratio.

The proportion of positive reactions ranged from 4.2% (1/24) to 0.6% (1/156) among those 11 centres observing farnesol contact allergy at all and down to none of 176 patients tested in the remaining 10 centres. This seemingly large variation of farnesol allergy prevalence, however, is not significant (Monte Carlo estimate of the exact likelihood ratio chi-square test: $p=0.12$; 99% CI: 0.11–0.13). To illustrate this descriptively, the 95% CI for 0 of 176 positive cases is 0–1.7% and for 1 of 24 cases 0.1–21.1%, i.e. broadly overlapping.

Discussion

In a multicentre study conducted for 6 months with 21 participating patch-test clinics, we found 1.1% (22/2021) of patients reacting allergic to farnesol (5% pet.). The number of allergic reactions exceeded the number of doubtful and irritant reactions, resulting in a positive RI (13), and with 5 ++ reactions, the PR (14) was less than 80%. Hence, the patch-test preparation appears suitable for diagnosing sensitization to farnesol from this point of view. Using a higher concentration (10%), Sugai (15) did not detect any more allergic reactions than with 5% when patch testing 457 and 456 patients (yielding 7 positive reactions). Conversely, only 2 of 454 reacted positively when tested with 2%. With 5 confirmed allergic reactions (as 2 of 7 reacted to the vehicle also), the proportion of positive reactions was 1.1% (15). While the results of Sugai's study confirm our patch-test concentration as suitable, the identical frequency of sensitization (1.1%) must be interpreted with caution, as no information was given on the selection and the characteristics of the patch-test population (patients with contact dermatitis). Furthermore, the study was conducted in Japan in 1985, so the results cannot be transferred to the exposure situation of central Europe in 2003.

Table 2. Parameters of the MOAHLFA (male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis and age >40) index in farnesol-positive and farnesol-negative patients and results of a logistic regression analysis with the outcome 'farnesol positive' (versus 'farnesol negative') and the MOAHLFA factors as explanatory variables

Variable	Index	Farnesol positive		Farnesol negative		OR	95% CI	
		n	%	n	%			
Men	M	6	27.3	772	38.6	0.53	0.20	1.41
Occupational dermatitis	O	4	18.2	275	13.8	0.94	0.25	2.91
Atopic dermatitis	A	4	18.2	358	17.9	0.73	0.20	2.07
Hand dermatitis	H	9	40.9	541	27.1	2.59	0.85	8.32
Leg dermatitis	L	2	9.1	227	11.4	1.52	0.22	6.83
Face dermatitis	F	5	22.7	299	15.0	2.52	0.72	8.51
=40 years	A	11	50.0	1287	64.4	0.59	0.24	1.47

In contrast, a multicentre study recently conducted in 6 European departments reflected more appropriately the actual sensitization (and exposure) situation (4). From October 1997 to October 1998, farnesol (5% pet.) was patch tested in 1855 consecutive patients. There were 10 + reactions (0.5%) and no stronger (++ and +++) reactions but a higher proportion of doubtful reactions (21 = 1.1%). In a subsequent study, the same group evaluated a new FM with 6 constituents. Farnesol 5% pet. had elicited a total of 0.35% positive reactions in 1703 consecutive patients (5 + and 1 ++); the number of doubtful/irritant reactions was found to be 1.76% (P. Frosch, unpublished data).

These differences between the 3 studies (between the 2 European studies themselves and further between the European studies and ours) may partly be explained by different exposure to this allergen but partly also by different patch-test reading conventions despite the high degree of standardization already achieved. This is an important issue to be further discussed for international harmonization.

Nevertheless, with results from a 20-year-old study reporting again 1.1% positive reactions (16) together with several case reports (17–19), there is no doubt that farnesol must be considered an important sensitizer, although its potency was classified as only weak (20) to moderate (21) in animal experiments.

Farnesol was shown to be present in small amounts in *M. pereirae* resin as well as in poplar buds (20). In our data set, only 2 patients with positive reactions to farnesol also reacted positively to *M. pereirae* resin and to propolis. According to the manufacturer, the concentration of farnesol, if present in the patch-test preparation of *M. pereirae* resin, would have been too low to elicit a positive reaction. This is supported by a chemical analysis of different *M. pereirae* resin samples, where farnesol could not be detected (21). The 2 cases should therefore be interpreted as being sensitized independently to

farnesol and *M. pereirae* resin. It seems that co-exposure to both fragrances is very low (the OR of 1.3 being not statistically significant). However, the significant association between farnesol and FM and even propolis, although stronger, is also in a range commonly observed even in unrelated allergens (be it in terms of structure or co-exposure) (22).

As might be expected, the proportion of concomitant reactions to *M. pereirae* resin in FM-positives was high (53/143; OR: 10.9), in accordance with previous results (22) and the literature (23, 24). Co-sensitization between different allergens may be regarded as a hint of a common exposure [e.g. in rubber exposure the IPPD/thiuram association (OR: 7.1) or in cement exposure the Cr/Co association (OR: 12.5)] (22). In this regard, the distinct pattern of almost missing co-sensitizations of farnesol, compared to marked association between the FM and *M. pereirae* resin, may be cautiously interpreted as a hint of exposure pathways to this fragrance, which are relatively independent from the exposures to FM and *M. pereirae* resin. The population characteristics (MOAHLFA) differed essentially in terms of a high proportion of hand dermatitis and face dermatitis in patients with contact allergy to farnesol. These patients were also much younger, and more often females, although these results are not significant, due to the relatively small sample size. Face dermatitis may be caused by cosmetics (25, 26), but hand dermatitis may be caused also by household products. It seems that exposure to farnesol may occur via a more restricted panel of products (i.e. only cosmetics and household products) and be less influenced by topical medicaments, occupational exposure and leg dermatitis (as may be assumed in FM and *M. pereirae* resin-sensitive patients). On the other hand, farnesol may be used not only as a fragrance but also as an antimicrobial substance (8), e.g. in deodorants, but possibly otherwise, too, extending the exposure beyond classical cosmetics. Until now, we have

no explanation for the fact that office workers were overrepresented in the farnesol-allergics. The typical characteristics of farnesol-allergic patients, namely female, young and cosmetic dermatitis, together with the fact that female clerks are the major occupational group among young females in the general working population in Germany (Bundesanstalt für Arbeit, Referat IIIa6, Nürnberg, Germany), may explain this association. The modes of exposure to farnesol should be studied further.

In summary, farnesol should be regarded currently as one of the more important fragrance allergens. 77% of farnesol-allergic patients would not have been diagnosed by the FM. Therefore, it should be included in a fragrance patch-test series for diagnostic reasons (4). It may be even a candidate for the standard series in certain geographical areas. Applying our clinical epidemiology and drug utilization research (CE-DUR) approach (2), i.e. extrapolating from clinical data to the general population, we can assume that some 10000 of the general population in Germany may be affected. For reasons concerning consumer safety, the labelling of farnesol-containing cosmetics seems to be fully justified and some further regulation of its use may be necessary, although we would not classify it in the same group of definitely more important substances of the list of 26 (7), such as oak moss or isoeugenol, for which we would favour a more rigid regulatory procedure (27).

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