Allergic Contact Dermatitis to Linalool*

An examination of experimental data disqualifies linalool's fragrance allergen status

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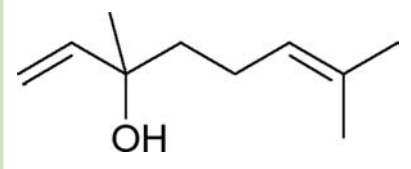
Linalool has been identified as an important fragrance allergen that must be package-labeled in European cosmetics and personal care, and is in fact one of the 26 fragrance ingredients with mandated labeling in the European Community. Does evidence-based methodology support this contention? Linalool has otherwise been cited as a moderately frequent cause of allergic contact dermatitis.

This article reviews the published data on the allergenicity of linalool (3,7-dimethyl-1,6-octadien-3-ol; CAS# 78-70-6; EINECS 201-134-4) (**F-1**) relating to its relative potency as a skin sensitizer. A semiquantitative evaluation of the different reports cited below has been made in accordance with the system outlined in Maibach et al.,[1] which is based on the procedures proposed by Benezra et al.[2] and describes the scoring system used for assigning the degree of confidence in data reported.

Linalool **F-1**



Methods

The medical literature was searched using the electronic databases Biosis[a], Caplu, Embase, RTECS[b], Toxlit, Medline/HealthStar, Toxnet[c] and Science Citation Index[d] (1960–September 2003). Search terms included linalool, allergic contact dermatitis, sensitization and patch tests. Copies of all cited publications were obtained. The Research Institute for Fragrance Materials Inc. (RIFM) kindly made available copies of unpublished studies performed by its members or carried out under its commission.

EC3 Value

The EC3 value is the estimated concentration of chemical necessary to cause a three-fold increase in proliferative activity. It correlates well with the human classification, the strongest sensitizers having low EC3 values (< 0.1%), weaker sensitizers having EC3 values generally in the 1–10% range, and nonsensitizing chemicals having EC3 values in excess of 100%.

Results

Predictive tests using animals: Several predictive tests were performed using animals.

In the Local Lymph Node Assay, stimulation indices of 2.5 at 25% and 4.8 at 50% were obtained, indicating an EC3 value (see **EC3 Value**) somewhere between 30% and 40% applied dose.[3] If this is due to allergenicity and not irritation, it can be compared with an EC3 for the standard positive control weak allergen, hexylcinnamic aldehyde, which was between 7.0% and 12.2%.[4] Under these circumstances, it appears to be significantly less potent than the boundary R 43 allergen, hexylcinnamic aldehyde. As a state-of-the-art study, this report is attributed with a degree of confidence of 4. It appears that impurities may also play a role: the EC3 of commercial linalool (97% pure) increased from 30% to 55% when it was partially purified to 98.6% pure.[5]

A Guinea Pig Maximization Test performed at topical induction and challenge concentrations of 10% was negative[6] but this study was carried out under submaximized conditions and has been given a rating of 2.

An Open Epicutaneous Test performed at a level of 20% was also negative[7] but was given a rating of only of 3 due to the extremely summarized manner in which this report was published.

A Draize Guinea Pig Test involving intradermal injections in the induction phase and dermal applications for challenge, was negative,[8,9] but the induction dose (intradermal injection of a 0.1 mL aliquot containing 0.125% linalool) may not be

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considered fully maximized, therefore a confidence level of 3 was ascribed.

A Freund's Complete Adjuvant Test involving injection of 0.1 mL of 5.1% linalool in an emulsion with the adjuvant, was also negative[10] and given a degree of confidence of 4.

Predictive tests using human volunteers: A Human Maximization Test carried out on 25 volunteers at a concentration of 8% in petrolatum gave no reactions.[11] Another Human Maximization Test carried out at 20% was also negative.[12] Both of these have been attributed a degree of confidence of 2 due to the low numbers of subjects tested.

Clinical diagnostic patch tests on patients: Linalool has been applied to patients' skin in routine patch testing. A limited number of studies relate to the investigation of special cases where patients have reacted to products containing linalool. These reports are examined in light of the criteria elaborated by Maibach et al.[1] to determine clinical relevance (i.e., if linalool had caused the allergic dermatitis from which these patients were suffering).

The following reports indicate positive elicitation reactions to linalool when this was one of the patch test substances.

- One patient of 119 who reacted to different fragrance and cosmetic ingredients also reacted to closed patches containing linalool (at 10%).[13] In fact, only 53 patients reacted to any of the test materials but a total of 147 reactions were observed. This study received a rating of only 2 because the causative role of linalool was not established.
- Three patients of 75 who reacted to different fragrance and cosmetic ingredients (taken from 1,781 patients over a six-year period) also reacted to closed patches containing linalool at 10%.[14] Only 32 of these patients gave any reactions at all, but this group still gave 82 positive reactions. A rating of 1 was given to this publication, which reviews 11 publications by the same group.
- Of 16 patients who reacted to Peru balsam and other fragrance ingredients, one patient also reacted to a closed patch containing linalool at 10% concentration.[15] No information was given regarding the severity of the observed reaction, particularly with regard to the patient's reaction to Peru balsam. A confidence level of 2 was ascribed.
- Three patients reacted to closed patches containing linalool at 20%.[16] These patients were examined in a multicenter study involving 1,825 patients of whom 193 were positive to the fragrance mix and 78 produced 109 reactions to nine individual substances including linalool. Of the three patients reacting to linalool, two reacted to the fragrance mix as well. No information is available regarding the severity of these three reactions or their relationship to specific products. A degree of confidence of 2 was accorded.
- A patient with airborne allergic contact dermatitis to several aromatherapeutic preparations also reacted to a closed patch containing linalool at 2%.[17] This patient also reacted to closed patches containing the fragrance mix and benzaldehyde as well as to a number of essential oils, some of which contain high concentrations of linalool and some of which contain only a small proportion of this substance. A level of confidence of 3 was ascribed.

Additional examples for predictive and diagnostic tests can be found in **T-1** and **T-2**.

Evidence that Autoxidation Leads to Allergenic By-products

Autoxidized linalool can be produced by agitation of linalool in the presence of air for 10 weeks to the point where only 80% linalool remains. Data from predictive tests on oxidized linalool carried out on animals and rated with a confidence level of 4 show that autoxidized linalool is a sensitizer, whereas unoxidized linalool is not.[10,18]

Another study has shown that the allergenic potency of commercial linalool is reduced when partial purification is carried out.[5]

Linalool is not normally regarded as being predisposed to autoxidation and is considered to be acceptably stable in fragrances without the addition of antioxidants. The kinetics of linalool's autoxidation would not seem to be as rapid as those of limonene.[19] Karlberg's group[10,18] indicates that linalool can indeed undergo autoxidation under special conditions, leading to the formation of allergenic by-products such as 3,7-dimethyl-7-hydroperoxy-1-octen-3-ol. It remains to be determined how readily linalool autoxidizes under the conditions of foreseeable use of products containing fragrances and in patch test materials where the optimized mixing of air and substrate are less than optimal.

Comment

From predictive tests in animals, data on linalool indicate with a good degree of confidence that this substance does not have a particularly significant sensitization potential. The degree of confidence attributed to the different tests varies; some studies were unable to demonstrate any sensitization potential; on the other hand, the murine Local Lymph Node Assay indicated a weak potential. The degree of confidence obtained from negative predictive tests in humans is always less than in highly maximized animal tests. However, these human studies confirm the low sensitization potential of linalool.

Only two clinical studies clearly linked patients' allergy with their prior use of products containing linalool. However even in these cases, the patients reacted to other substances and hence a degree of confidence of 3 was ascribed to both studies (in each case involving only one patient).

Another review cited three other (unpublished) cases where patients reacting to specific products also reacted to linalool. Here again, however, a low degree of confidence (2) was ascribed because there was no

Questions evaluating the surveyed reports describing predictive testing of linalool **T-1**

Questions	Reference numbers of the surveyed reports 2	3	5	7	10	11	12
Was the test material identified?	no data	97%	97%	no data	97%	no data	no data
What type of test was used?[a]	CET	LLNA	LLNA	OET	FCAT	Draize	Draize
Were the test conditions provided?	no data	yes	yes	yes	yes	yes	yes
Was the test fully maximized?[b]	no, at 10%	yes, 100%	yes, 100%	20%	yes	no, at 8%	20% SLS
Were the controls adequate?	no data	yes	yes	no data	yes	no data	no data
Was the number of subjects sufficient?[c]	no data	OECD	OECD	8	14	25	25
Were results presented in adequate detail?	no	yes	yes	yes	yes	no	yes
Final rating of confidence[d] in this report?	2	4	4	3	4	2	2

[a] LLNA = Local Lymph Node Assay; CET = Closed Epicutaneous Test; OET= Open Epicutaneous Test; FCAT = Freund's Complete Adjuvant Test; Draize = Draize Guinea Pig Test; [b] SLS = sodium lauryl sulfate added to give irritant reactions; [c] OECD = according to OECD guidelines; [d] 4 = high, 2 = low

Selected contents of the surveyed reports describing diagnostic patch tests implicating linalool **T-2**

Content	Reference numbers of the surveyed reports 13	14	15	16	17
Primary report or other?[a]	multi cent	review	primary	primary	primary
Number/Condition of patients[b]	119 / CosmA	75 / Ecz	16 / Ecz	1825 / Ecz	1 / FM mild
		Peru balsam	193 / FM mild		
Patch testing conditions given?[c]	10% pet	D/V unknown	10% pet	20% pet	2% pet
Number of patients reacting	1	3	1	3	1
Scores of patients reacting	not reported	not reported	not reported	not reported	strong positive
Has irritancy been excluded?	no	no	no	no	not reported
Reaction to other materials?	147 in 53	82 in 30	possible	109 in 78	8 in 1
Cross-reactions likely?[d]	possible	possible	possible	possible	possible
Excited skin excluded?	no	no	no	no	no
ROAT or PUT used?	cosmetic only	cosmetic only	no	no	no
Linkage to specific product?[e]	no	coinc	no	no	AT oils

[a] Primary = primary report of cases; Multi Cent = multicenter study, may be reported separately; Review = primary reports cited; [b] CosmA = cosmetic allergic; Ecz = eczematic; FM = fragrance mix; Peru Balsam = Myroxylon pereirae Klotzsch (Peru balsam) oil, a marker for fragrance hypersensitivity; [c] pet = petrolatum; D/V = dose/vehicle; [d] possible = cross-reactions are possible but cannot be determined from the report; [e] coinc = coincidence of reaction to substance and to cosmetic product. However, no indication that substance is in the product; AT = aroma therapy

clear evidence that the products contained linalool—or any of the other substances producing reactions in these patients—in sufficient amounts to have been responsible for the allergies.

Other studies ascribe reactions to linalool in multiple-substance patch testing on prior-sensitized patients. However, none of those studies offers a degree of confidence above 2 in establishing likely clinical relevance according to currently suggested procedures.[20–22]

Conclusions

The fragrance material linalool has been cited as a moderately frequent cause of allergic contact dermatitis. This review of the literature showed that when the underlying clinical and experimental data are analyzed, a clear cause-effect relationship has infrequently or rarely been established. Data from predictive tests in animals and on humans indicates with a reasonable degree of confidence that linalool is a weak sensitizer. On the basis of the generally weak sensitizing potential of this substance, coupled with its generally low exposure conditions, the prevalence of clinical cases would not be expected to be particularly high. This is not to say that linalool is a frequent inducer of type IV allergy in members of the public. It remains to be seen, however, how often such allergy, once established, is responsible for any of the cases of clinical allergic contact dermatitis. Indeed, in some cases, patch test conditions may not be optimal for differentiating between clinically relevant and irrelevant allergy to linalool.

Linalool is susceptible to autoxidation giving rise to products that are skin sensitizers in predictive animal tests. It is most probable that autoxidation of linalool is well controlled during the normal lifetimes and under foreseeable usage conditions of cosmetics and household products. However, studies should be performed to determine the degree of autoxidation that occurs under the useful lifetimes of these products. The same should be done for linalool when used as a patch test material.

On the basis of the low frequency of positive patch tests and the underlying weakness in their association with linalool being the causative agent, it is concluded that, regardless of the possibility that autoxidation may enhance the allergenic potential of this substance, it is not yet documented as a major fragrance allergen.

Determining the clinical relevance of fragrance patch test positivity presents a challenge to physicians and dermatologists. This should be simplified when more data becomes available as to appropriate nonirritant patch test concentrations and vehicles together with clinical correlations to Provocative Use Test/Repeat Open Application Tests (PUT/ROAT).[23] Recent expedited schema for providing fragrance allergens should be of value.[24]

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