

Linalool Hydroperoxides

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Linalool is a fragrance widely used in cosmetics and household products. Until recently, contact allergy to linalool was considered rare because positive patch tests to it were infrequently observed. In recent years, however, it has been demonstrated that exposure of linalool to oxygen (air) results in formation of a number of oxidation products, of which the hydroperoxides have a far stronger sensitizing potency than the pure compound. By routine testing of patients suspected of having contact dermatitis with hydroperoxides of linalool, high frequencies of positive reactions were found, indicating these chemicals are important fragrance allergens. It should be realized, however, that a number of “positive” reactions may well be false-positive, irritant responses.

Fragrance allergy occurs frequently, both in the general population and in patients routinely patch tested for suspected contact dermatitis. It is estimated that 3.5% to 4.5% of the adult general population^{1,2} and up to 20% of the patch test population^{1,3} may be allergic to 1 or more fragrances. During the past decade, many articles have been published on contact allergy to linalool, a fragrance material that is widely used in fragrances, other cosmetics, household products, and many other products. Until recently, it was assumed that allergy to this chemical is rare, however, since patch testing started to be performed with its hydroperoxides, it has become clear that linalool belongs to the most frequent fragrance allergens.

In this first part of “Important New Fragrance Allergens,” linalool is discussed; limonene will be presented in part II.

WHAT IS LINALOOL?

Linalool is a naturally occurring terpene, present in large amounts in various plants, for example, in lavender, rosewood, ylang-ylang, bergamot, geranium, and jasmine.¹ There are 2 forms of linalool: (R)-linalool (synonyms: licareol, (–)-linalool, L-linalool) and (S)-linalool (synonyms: coriandrol, (+)-linalool, D-linalool); the racemate of these 2 forms is referred to as linalool. Linalool is a colorless clear liquid; its odor type is floral, and its odor is

described as “citrus, orange, floral, terpy, waxy, and rose.”⁴ It is added to processed foods and beverages, perfumes, and other cosmetics. Linalool is also used in household detergents and waxes and added to animal drugs, feeds, and other products. Other applications include or have included its use as a pesticide in pet sprays, dips, or shampoos and in carpet and surface treatments and as a pesticide fogger for indoor use.⁵ Some key data of linalool are shown in Figure 1.

PRESENCE IN ESSENTIAL OILS, COSMETICS, AND HOUSEHOLD PRODUCTS

Linalool has been identified by chemical analysis in 82 of 91 essential oils, which have caused contact allergy/allergic contact dermatitis.⁶ In 30 oils, linalool belonged to the “Top 10” of ingredients with the highest concentrations. Fifteen of these may contain linalool in a concentration of more than 10%; these are shown in Table 1 with the concentration range, which may be expected in commercial essential oils of this type.⁶ Six essential oils may even contain more than 50% linalool: rosewood oil, coriander fruit oil, thyme oil, neroli oil, lavandin oil, and basil oil (Table 1).

Linalool is among the most commonly found fragrance ingredients in consumer products presently available.¹ Various studies performed in European Union countries have investigated the presence of linalool in such commodities based on ingredient labeling data. In a 2015–2016 investigation from Denmark, for example, 50% of 5588 fragranced cosmetic products contained linalool, according to their label.⁷ In 7 similar studies, linalool was labeled to be present in 14% to 70% of cosmetic products investigated, and in most studies, it was labeled to be present in more than 50%.¹ It should be realized that linalool is only labeled (or at least needs to be labeled) when it is present at greater than 10 ppm (0.001%) in leave-on products and greater than 100 ppm (0.01%) in rinse-off products, which means that linalool may be present in lower concentrations in a number of products not labeled with linalool,

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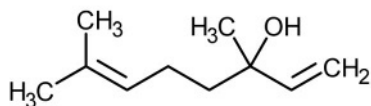
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Description/definition : Linalool is the terpene that conforms to the following structural formula:



Chemical class	: Alcohols
IUPAC name ^a	: 3,7-Dimethylocta-1,6-dien-3-ol
Other names	: Linalyl alcohol
CAS registry number ^b	: 78-70-6
EC number ^c	: 201-134-4
Merck Index monograph ^d	: 6820
Functions in cosmetics	: EU: deodorant; perfuming. USA: fragrance ingredients
EU cosmetic restrictions	: Must be labeled on cosmetics and detergent products, if present at >10 p.p.m. ^e (0.001%) in leave-on products and >100 p.p.m. (0.01%) in rinse-off products
Molecular formula	: C ₁₀ H ₁₈ O

^a IUPAC: International Union of Pure and Applied Chemistry (www.iupac.org)

^b CAS: Chemical Abstract Service (www.cas.org)

^c EC: The EC number (EINECS, ELINCS or NLP) is the official number of the chemical in the European Union (<https://echa.europa.eu/nl/information-on-chemicals/ec-inventory>)

^d Merck Index online (www.rsc.org/merck-index)

^e p.p.m.: Parts per million

Figure 1. Some key data of linalool.¹

thereby increasing the percentage of products actually containing this fragrance.

Indeed, in another Danish study, 47 (53%) of 88 popular perfumed deodorants were labeled to contain linalool. However, when a subgroup of 23 deodorants selected on the basis of labeling with isoeugenol, hydroxycitronellal, hydroxyisohexyl 3-cyclohexene carboxaldehyde, and cinnamyl alcohol (ergo: not selected for linalool) was analyzed with gas chromatography–mass spectrometry, 22 (96%) proved to contain linalool in a concentration range of 8.2 to 3447.1 ppm.⁸ Although it was not specified how many of these were labeled with linalool, 10 (45%) of the 22 contained linalool in concentrations of less or greater than 100 ppm, which suggests that a significant number of products containing linalool are not identified by ingredient labels. Linalool seems to be less

prevalent in detergent products (at least in concentrations that necessitate labeling), in various studies generally ranging from 10% to 40%.¹

CONTACT ALLERGY

Sensitizing Potency

The sensitizing potency of linalool is weak.¹ However, on exposure to air, autooxidation takes place and various oxidation products are formed, especially hydroperoxides, furanoids, and pyranoids. The allergenicity of linalool then increases considerably, especially because the hydroperoxides have strong sensitizing potency as shown in animal experiments (murine local lymph node assay).^{1,9}

TABLE 1. Essential Oils That May Contain More Than 10% Linalool in Commercial Samples⁶

Common Name	INCI Name	Concentration (Min.–Max.)
Rosewood oil	<i>Aniba rosaeodora</i> wood oil	73.0%–88.4%
Coriander fruit oil	<i>Coriandrum sativum</i> fruit oil	55.0%–81.2%
Thyme oil	<i>Thymus vulgaris</i> flower/leaf oil	0.03%–68.5%
Neroli oil	<i>Citrus aurantium amara</i> flower oil	31.9%–57.7%
Lavandin oil	<i>Lavandula hybrida</i> (herb) oil	26.0%–56.2%
Basil oil	<i>Ocimum basilicum</i> herb oil	0.6%–55.8%
Lavender oil	<i>Lavandula angustifolia</i> oil	26.0%–44.8%
Spike lavender oil	<i>Lavandula latifolia</i> herb oil	0.6%–42.3%
Petitgrain bigarade oil	<i>C. aurantium amara</i> leaf/twig oil	19.8%–34.0%
Clary sage oil	<i>Salvia sclarea</i> flower oil	18.6%–31.0%
Ylang-ylang oil	<i>Cananga odorata</i> flower oil	0.1%–24.0%
Marjoram oil	<i>Origanum majorana</i> flower oil	0.2%–23.5%
Bergamot oil	<i>Citrus aurantium bergamia</i> fruit/peel oil	4.7%–16.7%
Ravensara oil	<i>Ravensara aromatica</i> leaf oil	0.05%–12.4%
Geranium oil	<i>Pelargonium graveolens</i> oil	1.4%–11.1%

INCI indicates International Nomenclature Cosmetic Ingredients.

Patch Testing With Linalool

The author has found 5 studies in which in various European countries (United Kingdom, Denmark, Sweden, Germany, Austria, Switzerland) in 1968–2001, patch tests have been performed with unoxidized linalool 10% petrolatum (pet.) in consecutive patients suspected of having contact dermatitis (routine testing).¹ The number of patients investigated ranged from 792 to 4741. The frequency of positive reactions invariably was very low (range, 0.1%–0.5%; median, 0.3%; and average [unadjusted for sample size], 0.3%). In 3 studies, no relevance data were provided, and in the other 2 studies, no data specific for linalool were shown.¹

Patch Testing With Oxidized Linalool and Linalool Hydroperoxides

Already in 2002, investigators started using oxidized linalool (LinOx) materials for patch testing.¹⁰ Up to December 2018, the author found 16 published studies with results of patch testing with LinOx, linalool hydroperoxides, or both. Concentrations used (all in petrolatum) were 2%, 3%, 4%, 6%, and 11% for LinOx and 0.25%, 0.5%, and 1% for linalool hydroperoxides.¹

Between 2002 and 2011, mostly LinOx was used. In a dose-finding study, it was shown that the frequency of positive reactions rose with increasing test concentrations of LinOx from 0.8% (2% LinOx) through 3.2% (4% LinOx) and 5.3% (6% LinOx) to 7.2% with the use of the 11% linalool oxide test material.¹¹

There were many dubious-positive (?+) reactions, increasing with the higher test concentrations. Oxidized linalool 6% (which contains approximately 1% hydroperoxides) was chosen as the test material for future screening.¹¹ In 6 studies routinely testing 6% LinOx, the prevalence rates of positive patch test reactions ranged from 3.3% to 7.4%, with an average (unadjusted for sample size) of 5% and a median of 4.7%.¹

In nearly all studies performed after 2010, linalool hydroperoxides have been used for patch testing. In 2 dose-finding studies performed in Spain¹² and in the United Kingdom,¹³ patients were patch tested with 1%, 0.5%, and 0.25% linalool hydroperoxides. With rising concentrations, the percentages of positive patch test reactions also increased, up to 4.9%¹² and 7.7%¹³ with the 1% test material, which was subsequently advised for routine testing by both groups of investigators. Meanwhile, 7 such studies have been published,^{12–18} in which the prevalence rates of positive reactions have ranged from 3.9% to 11.7%, with an average (unadjusted for sample size) of 6.9% and a median of 5.9%. The highest rates were observed in the Netherlands (11.7%¹⁴), followed by 2 studies from the United Kingdom: 9.8%¹⁵ and 7.7%.¹³ In fewer than half of the studies was the subject of relevance addressed.

The percentage of positive patch test reactions considered to be relevant ranged from 20% to 66%. Culprit products were mentioned by only 2 groups of investigators and were mainly perfumes, other cosmetics, detergents, essential oils, and wet wipes.^{12,17} It should be noted that although exposure to linalool as indicated by product labeling is common, clinical relevance in terms of proven skin contact

with presumably sufficient levels of these hydroperoxides in culprit products is less well documented.¹⁹

Some 60% to 70% of sensitizations to linalool were not detected by positive reactions to the indicators of fragrance allergy (fragrance mixes I and II, *Myroxylon pereirae* resin [balsam of Peru], colophonium) or the fragrance hydroxyisohexyl 3-cyclohexene carboxaldehyde present in the baseline series.^{12–14,16}

It is important to know that in various studies with linalool hydroperoxides 1% pet., in addition to the high percentages of positive reactions, many dubious-positive (?+) (up to 22%) and irritant reactions (up to 14%) have been observed.^{1,14–16} In 4% of allergic reactions, a positive patch test was observed only at the D7 reading.¹⁴

Recently, the European Society of Contact Dermatitis has proposed²⁰ and recommended²¹ to test linalool hydroperoxides in addition to the European baseline series, first suggesting 1% as test material,²⁰ but shortly thereafter 1% and 0.5%.²¹ It was “highlighted that frequent irritant and doubtful patch test reactions to these haptens have been observed, and that, to aid in interpretation, two dilutions of each (ie, linalool and limonene hydroperoxides) should be tested if these haptens are tested routinely.”²¹

All studies with routine testing have been performed in European countries. There is probably limited experience with testing linalool hydroperoxides in the United States, but in a small group of 96 patients suspected of having fragrance allergy, 19 (20%) had positive patch tests to linalool hydroperoxides 1% pet.,²² indicating that this fragrance may also be an important allergen there. Indeed, the authors suggested that “patch testing to the hydroperoxides of linalool (and limonene) should be performed in all patients with suspected fragrance allergy.”²²

CONCLUSIONS AND ADVICE FOR PRACTITIONERS

Linalool hydroperoxides seem to be a frequent cause of contact allergy and very likely also of allergic contact dermatitis in Europe and probably in the United States as well.²² Testing of linalool hydroperoxides 0.5% and 1% in petrolatum (available at www.chemotechnique.se) in all patients suspected of having contact dermatitis or, when preferred, of patients suspected of having fragrance allergy, will reveal a considerable number of sensitizations, a large percentage of which may not be picked up by the fragrance markers in the baseline series. However, the optimal test concentration is as yet unknown, and dubious-positive (?+) and irritant reactions occur frequently, especially to the 1% concentration.

Assessing whether ?+ reactions are weakly allergic or irritant patch test reactions is very difficult. In case of a ?+ reaction to 1% and a negative reaction to the 0.5% test material, contact allergy to linalool hydroperoxides may not be diagnosed with certainty, and this may also apply to weak positive (+) patch test reactions, especially in the case of absence of a history of fragrance intolerance. The chance that such reactions do represent contact allergy increases with a positive fragrance intolerance history, when positive patch test reactions are observed to other fragrances (including to limonene

hydroperoxides, which frequently coreacts) or to the indicators of fragrance allergy in the baseline series and when the patient proves to apply linalool-labeled (or nonlabeled) fragranced products at the site of dermatitis. In the latter scenario, the result of stopping the use of these products can be awaited. In case of doubt on the nature of the patch test reaction, a second test with both materials may provide new relevant information. A repeated open application test with the patch test material could give definite clues sometimes but is unfortunately outside formal investigational studies hardly practicable.

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