Advisory Committee on Plant Preparations

Oral use of Essential Oils in dietary supplements

Lavandula officinalis Chaix

Conclusion available in EN, NL and FR

1. Botanical Identification

Lavandula officinalis Chaix*,* Family : *Lamiaceae*
NL: lavendel
FR: lavande

The Royal Decree of 31 august 2021 considers as synonyms for *Lavandula angustifolia* Mill:

- *Lavandula angustifolia* subsp. *angustifolia*
- *Lavandula officinalis* Chaix
- *Lavandula spica* L.

The synonyms of this plant vary according to the website visited. World Flora Online mentions the following synonyms:

***Lavandula angustifolia* Mill.**	**Other names**	**Confidence level**
Accepted name	*Lavandula angustifolia subsp. angustifolia*	synonym
	Lavandula angustifolia var. delphinensis (Jord. ex Billot) O.Bolòs & Vigo	Synonym
	Lavandula angustifolia f. albiflora (Rehder) Geerinck	synonym
	Lavandula vera var. angustifolia Ging.	synonym
	Lavandula spica var. angustifolia (Ging.) Briq.	synonym

The species is also regularly confused with other lavender species like *L. x intermedia* Emeric. (Lavandin) and *L. latifolia* Medik. (Spike lavender), for which the composition may vary considerably. (see § 6)
If no detailed quality specifications are mentioned, the herbal substance consists of flowers from different flower species (Hänsel et al. 1993). (EMA/HMPC Assessment report 2012).

2. Used plant parts

Lavandula officinalis Chaix is on list 3 of the Royal Decree of 31 August 2021, with the additional mention: Only the use of the following plant parts is permitted: 'flowering tops'

3. Production method

Only the flowering tops can be used for the preparation of essential oil (E.O.). **This advice is valid for E.O. prepared by steam distillation.**

4. Official monograph references

- European pharmacopoeia 11.1 (04/2023)
- EMA/HMPC Herbal Monograph and Assessment Report (2012).
- AFNOR - NF ISO 3515 - Oil of lavender (*Lavandula angustifolia* Mill.) (2004)

5. Status in other regulations

The E.O. has GRAS status. (FDA 2019)

6. Quantitative and qualitative composition

The monograph in the Ph Eur, 11th Ed. gives the following specifications for the composition of the E.O. of *Lavandula officinalis*:

- Limonene: max. 1.0 %
- 1,8-cineole: max. 2.5 %
- 3-octanone: 0.1 - 5.0 %
- Camphor: max. 1.2%
- Linalool: 20.0 – 45.0 % with (S)-linalool: max. 12 %
- Linalyl acetate: 25.0 – 47.0 % with (S)-linalyl acetate: max. 1 %
- Terpinene-4-ol: 0.1 – 8.0 %
- Lavandulyl acetate: min. 0.2 %
- Lavandulol: min. 0.1 %
- α-Terpineol: max 2.0 %

3R-(-)- linalool is the predominant enantiomer present in Lavandula E.O. (94.1 % of total linalool content (Özek et al, 2010) and 96-98,2% according to Casabianca et al. 1998), while 3S-(+)- linalool (coriandrol) is the main enantiomer found in e.g. *Coriandrum sativum* E.O. (83.9 % of total linalool content (Özek et al, 2010) and 85,5-90% according to Casabianca et al. 1998). Both enantiomers have a different fragrance profile (Aprotosoaie et al 2014). The enantiomeric distribution of linalool may be useful in the quality assessment of essential oils; depending on the extraction conditions partial racemization may occur (Casabianca et al. 1998).

The limits for (S)-linalool have to be calculated relative to the total amount of linalool.
The limits for (S)-linalyl acetate have to be calculated relative to the total amount of linalyl acetate.

In order to claim conformity with the Ph Eur, the levels of the above mentioned substances, including the enantiomeric composition for linalool and linalyl acetate, must be demonstrated by a certificate of analysis.

Tisserand & Young list the composition according to the origin of the lavender (Tisserand & Young, 2014):

%	Absolute	Australian	Bulgarian	French	Moldovan	Ukranian
Linalyl acetate	44.7	36.2	46.6	41.6	38.6	43.3
Linalool	28.0	39.1	27.1	44.4	34.0	27.5
Coumarin	4.3					
β-Caryophyllene	3.2	2.6	4.1	1.8	3.9	5.9
Geranyl acetate	2.7					
Terpinen-4-ol	2.7	3.0	4.6	1.5	2.0	2.1
Herniarin (7-methoxycoumarin)	2.3					
(E)-β-Farnesene	1.2		2.4		1.6	2.0
Camphor	1.2					
1-Octen-3-yl acetate	1.1					
(Z)-β-Ocimene		4.3	5.5	0.3	5.5	4.2
3-Octanone		2.9		0.2		
Lavandulyl acetate		2.5	4.7	3.7	2.5	2.1
3-Octanyl acetate		1.8	1.1		1.1	1.1
(E)-β-Ocimene			2.2	0.1	1.3	2.4
Borneol				1.0		1.0
α-Terpineol	_			0.7	1.1	0.6
1,8-Cineole					1.6	1.5

The main components of the essential oil of *Lavandula officinalis* are monoterpene alcohols (60-65%) such as **linalool (20-50% of the fraction), linalyl acetate (25-46% of the fraction)**. Others include cis-ocimen (3-7%), terpinene-4-ol (3-5%), limonene, cineole, camphor, lavandulyl acetate, lavandulol and α-terpineol, β-caryophyllene, geraniol, α-pinene. Non-terpenoid aliphatic components: 3-octanon, 1-octen-3-ol, 1-octen-3-ylacetate, 3-octanol (ESCOP 2009; Hänsel et al. 1993; Bruneton 1999).

Quality/adulteration:

Lavandula latifolia Medik. (*Lavandula spica* - Spike lavender) contains a significant amount of linalool (27,2 – 43,1%), but far less linalyl acetate. 1,8-Cineol (28-34,9%) and camphor (10-23,2%) are important constituents. (Tisserand, Young, 2014)
Lavandula x intermedia (Lavandin) is a hybrid of *Lavandula angustifolia* and *Lavandula latifolia* with therefore intermediate composition. (The Herbal Academy 2020)

Different composition changes biological properties and use, toxicity and safety precautions. (e.g. Mekonnen 2019).

7. Use

Traditional herbal medicinal product for relief of mild symptoms of mental stress and exhaustion and to aid sleep (EMA/HMPC Monograph 2012).

Calming, sleeping aid, stress relief and hypotensive, spasmolytic, carminative, anti-inflammatory, wound healing, antifungal, antiparasitic. (Millet 2015)

The anxiolytic and anti-depressant-like effects of lavender E.O. may be due to modulation of the NMDA (N-methyl-D-aspartate) receptor and to inhibition of SERT (serotonin transporter), without affinity for the $GABA_A$ benzodiazepine receptor (López 2017).

Lavender essential oil may be used orally, dermatologically, or via inhalation:

- Recommendations for oral use in literature:
  - exceptionally oral use after dilution (only for adults, upon medical advice, max 3-5 drops/day (1 drop = 40 mg)[1]; use between 2-10 days) (Millet 2015)
  - 1-4 drops (approximately 20-80 mg)[1] e.g. on a sugar cube (ESCOP 2009)
  - Lavender essential oil: used for treatment of migraine, constipation, colic: 1 to 3 drops[1] with vegetable oil, honey or sugar (Verhelst 2010).
  - Oleum Lavandulae: dose 0,05 to 0,2 ml (= 1-4 drops)[1] (Todd 1967).
- Recommendations for dermal use in literature:
  - Maximum dermal use level for the absolute: 0.1%, no maximum level for the essential oil (Tisserand, Young, 2014)
- Daily intake linalool
  - Oral exposure to linalool from formulated food products was estimated at up to 72 µg/kg bw/d for Europe and the USA; adding linalool from natural sources may possibly double this, resulting in an estimated maximal daily intake of 140 µg/kg bw/d. This maximum corresponds to approximately one-quarter of the upper limit of the ADI. (OECD-SIDS 2002)
  - Average daily intake of linalool is estimated to be 0.0438 mg/kg/day (JECFA – OECD: SIDS 2002)

The authorized claims are discussed in § 11.

8. Stability / degradation products

8.1 Linalool:

The CLH (Classification and Labeling Harmonization) report shows that linalool (CAS no. 78-70-6) is auto-oxidized in air and that mainly the subsequently formed oxidation products (hydroperoxides) are responsible for the sensitizing properties of linalool. Although pure linalool is not sensitizing, and due to the autoxidation in air, which is an intrinsic property of linalool, it is practical and reasonable to classify linalool itself for sensitization. (ECHA: CLH REPORT 2014; Sköld 2004)

[1] drop size may vary considerably depending on the dropper device used. It is advisable to measure and report mass/drop for liquid preparations for an adequate and safe dosage.

Oxidized linalool is among the most common causes of contact allergy and among the most common contact allergens (Kern et al. 2014) (Christensson et al. 2012)

Oxidation products of linalool may be skin sensitizing.(Tisserand, Young. 2014)

According to IFRA, essential oils rich in linalool should only be used when the level of peroxides is kept to the lowest practical value. The addition of antioxidants such as 0.1% BHT or α-tocopherol at the time of production is recommended. (IFRA 2009)

However, although linalool hydroperoxide was detected in natural linalool, the amount was not elevated by storage in a perfume formulation exposed to air in a stability study on fragrances. Authors conclude that very low levels of linalool hydroperoxide in fragranced products may originate from raw materials, but no evidence for oxidation during storage of products has been found. The levels detected are orders of magnitude below the levels inducing sensitization in experimental animals, and these results therefore do not substantiate a causal link between potential hydroperoxide formation in cosmetics and positive results of patch tests. (Kern et al 2014)

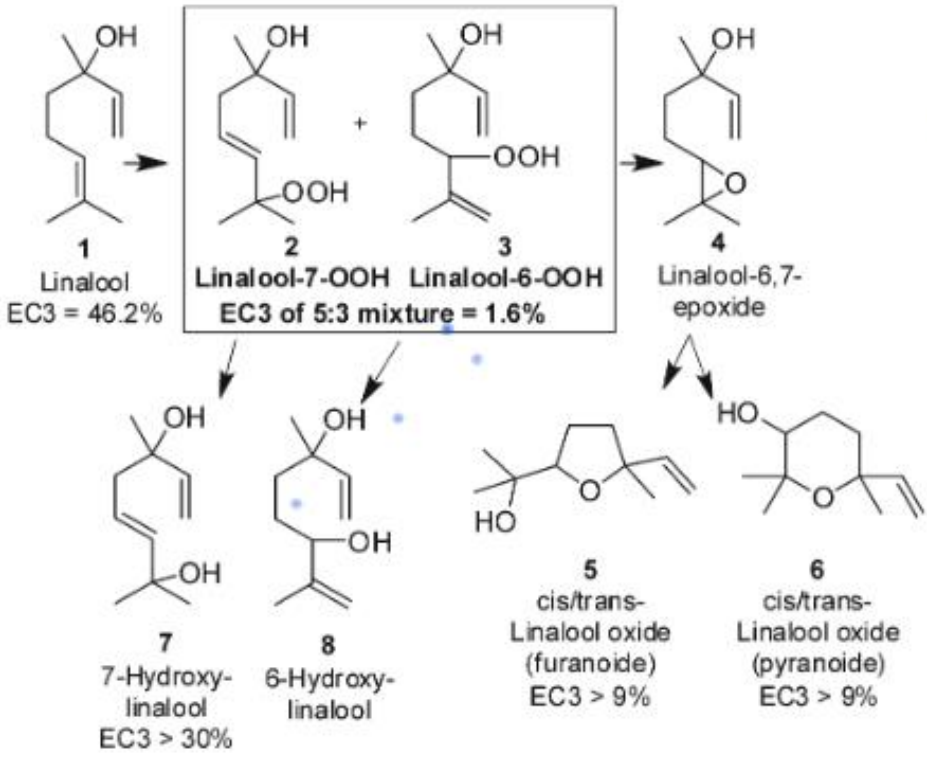

Fig 1: Autoxidation of linalool (S. Kern et al. *Analytical and Bioanalytical Chemistry* 2014)

8.2 Linalyl acetate:

The substance is not stable in the environment. It will be rapidly degraded with a calculated half-life of <4 hours when exposed to the atmosphere and it rapidly hydrolyses to linalool and acetic acid in contact with water (half-life < 1 day). (ECHA – 2014)

Linalyl acetate is also be susceptible to oxidation on air exposure, forming similar oxidation products as linalool. The content of linalyl acetate decreases over time on air exposure and other compounds were formed. Hydroperoxides, an epoxide and an alcohol were identified as oxidation products from linalyl acetate. Although linalyl acetate shows a weak sensitizing potency (EC3 25%), autoxidation increased the sensitizing potency of linalyl acetate (EC3 3.6%). As for linalool, the hydroperoxides were shown to be the oxidation products with the highest sensitizing potency. (Sköld M 2008)

9. Kinetics – Metabolism

9.1 Lavender E.O.:

- Animal research (EMA / HMPC Assessment Report 2012).

Single or multiple (14 day) administration of lavender oil (linalool and linalyl acetate represent the main constituents, i.e. 70 -80%) resulted in evident maximum levels of linalool, whereas linalyl acetate levels were not detectable or present in much lower concentrations in blood plasma or different organs/tissues (liver, kidneys, brain and fat tissue). These data indicate a quick and efficient metabolization of linalyl acetate to linalool *in vivo* without indication of accumulation after repeated application. (Nöldner , et al 2013)

Species	**Intervention**	**Outcome**
Mice	Exposure of mice to a lavender oil atmosphere	Time-dependent increase in linalool plasma levels (approximately 0.9 ng/ml after 30 minutes, 2.7 ng/ml after 60 minutes and 2.9 ng/ml after 90 minutes (Buchbauer *et al.* 1993a)
Mice	1h exposure to a medium containing the vapour of lavender oil (37.3% linalool and 41.6% linalyl acetate), linalool or linalyl acetate at 5 mg/l	Serum levels were 3 ng/ml for linalool and 11 ng/ml for linalyl acetate; after 1 h of exposure to linalool, the serum level was 8 g/ml, and after 1 h of exposure to linalyl acetate the level was 1 ng/ml and the serum linalool level 4 ng/ml (Buchbauer *et al.* 1993a; Jirovetz *et al.* 1990; Bickers *et al.* 2003)
Rats	Oral administration of labelled linalool to rats at 500 mg/kg b.w.	After oral administration of labelled linalool 55% was excreted in the urine as the glucuronic acid conjugate, while 23% was excreted in expired air and 15% in the faeces within 72 h; only 3% was detected in the tissues (Bickers *et al.* 2003)

- Human trials (EMA/HMPCHMPC AR 2012)

Patient	Intervention	Outcome
Male volunteer	Massage oil containing 2% of lavender oil (approximately 25% linalool and 30% linalyl acetate) was gently massaged onto the abdomen for 10 minutes	Trace amounts of both linalool and linalyl acetate were detected in the blood within 5 minutes of finishing the massage, and peak plasma concentrations of 121 ng/ml for linalool and 100 ng/ml for linalyl acetate were reached after 19 minutes; most of the linalool and linalyl acetate disappeared from the blood within 90 minutes, both having a biological half-life of approximately 14 minutes (Jäger et al 1992)

9.2 Linalool:

Linalool is rapidly absorbed after oral administration (at least 85%). After 72h, 97% of the administered radioactivity was excreted. 3% of the dose was detected in tissues (liver, gut, skin and skeletal muscle) 72 h after dosing. Linalool was excreted mainly via urine (60%), exhaled air (23%) and faeces (15%) and is subject to enterohepatic recirculation. Both phase I and phase II enzymes (mainly glucuronidation) are responsible for the metabolism of linalool, 8-hydroxylation seems to be the major phase I pathway.

The dermal absorption of linalool is low: 0.17% after 4 hours exposure (occluded). Experiments show that most of the dermally applied linalool evaporates from skin. (ECHA 2014)

9.3 Linalyl acetate:

Data indicate an extensive ester hydrolysis of linalyl acetate in intestinal fluids, which results in linalool and acetic acid as metabolites. In acidic artificial gastric juice, linalyl acetate is found to be rapidly hydrolyzed ($t_{1/2}$< 5 min) to yield linalool which rearranges into and the ring closed form alpha-terpineol (Bickers 2003). In contrast, linalyl acetate is slowly ($t_{1/2}$= 121 min) hydrolyzed to a mixture of linalool and the ring closed form in neutral gastric juice. Hydrolysis occurs thus more rapidly at the low pH of gastric fluids. Linalyl acetate also hydrolyzed in homogenates of rat intestinal mucosa, blood, and liver, but at rates much slower than in acidic gastric juice (rate constant for hydrolysis k=0.01 - 0.0055 min^{-1} vs. > 5 min^{-1} in gastric juice). Based on these observations, it is concluded, that linalyl acetate hydrolyzes in gastric juice to yield linalool which to some extent is ring-closed to yield alpha-terpineol. It is expected that linalool and acetic acid are the substances that will enter the systemic circulation after oral uptake of linalyl acetate. (ECHA 2014)

10. Overview toxicological data

General remark toxicological data enantiomers: There are no data available allowing to assess the difference in activity/toxicity between (R)- and (S)-linalool. Most studies have been conducted on R-(-)-linalool, linalool racemate or the compound without any specified enantiomeric identity. The mechanisms of activity have been demonstrated predominantly for linalool racemate and (R)-(-)-linalool (Aprotosoaie et al 2014). Therefore, when evaluating the toxicological data in this advice, no distinction will be made between (S)- and (R)- enantiomer.

10.1 Acute toxicity

10.1.1. Acute toxicity *Lavandula officinalis* E.O.

Overview LD50-data for the essential oil:

Animals and administration route	**LD50-values (mg/kg)**	**Reference**
Rat, oral	>5 g/kg b.w	Buchbauer et al. 1991; Delaveau et al. 1989; von Skramlik 1959).
Rat, oral	♂ 6.2 ml/kg ♀ 5.0 ml/kg	
Rat, oral	♂ 5 ml/kg ♀ 3 ml/kg	
♀ rat, oral, E.O.: linalool 32.5%, linalyl acetate 21,5%	3.55 g/kg b.w.	Da Silva . et al. 2015
Mice, i.p.	6,5 g/kg b.w.	Altaei 2012

- Investigations on rats showed that the acute toxicity of essential oil of lavender (OL), given p.o. in olive oil, was relatively low, while when given to mice pharmacological tests demonstrated that it had anxiolytic effects and prolonged sleep induced by i.p. pentobarbital Na, though the latter effect was reduced after repeated p.o. administration. Impaired balance, piloerection and hypersalivation sometimes occurred. The authors concluded that, if its chronic toxicity is also low, OL might be used instead of more active anxiolytics or tranquilizers for minor conditions (Delaveau et al. 1989).
- Undiluted lavender oil was not irritant when applied to the backs of hairless mice or pigs, but was slightly irritant on intact or abraded rabbit skin under occlusion for 24 h (Opdyke 1976).

10.1.2. Acute toxicity Linalool

Animals and administration route	**LD50-values (mg/kg)**	**Reference** Tisserand, Young, 2014
Rats, oral	2.79 g/kg	Jenner et al 1964
Mice, oral	2.2, 3.5 and 3.92 g/kg	Letizia et al 2003a
Rats, i.p.	307 and 687 mg/kg	Letizia et al 2003a
Mice, i.p.	200, 340 and 495 mg/kg	Letizia et al 2003a
Rabbits, dermal	5.61 g/kg	Opdyke 1975

- An MTD (Maximum tolerated dose) of 125 mg/kg has also been reported (Letizia et al 2003a).
- Acute toxicity from high doses is derived from the depressant effect and presents as ataxia and narcosis (Powers & Beasley 1985; Letizia et al 2003a). Linalool induced marked sedation in mice with 500 mg/kg i.p. (Letizia et al 2003a).

10.1.3. Acute toxicity Linalyl acetate

Animals and administration route	**LD50-values (mg/kg)**	**Reference**
Rodents, oral	5.0-48.8 g/kg for linalyl esters	Bickers et al. 2003
Rabbits, dermal	➢ 5 g/kg	Bickers et al. 2003
Rat, oral	14.5 g/kg and > 10 mL/kg	Letizia et al 2003b
Mice, oral	13.36 g/kg and 13.5 g/kg	Letizia et al 2003b
Rats, i.p.	♂ 2,778 mg/kg, ♀ 2,984 mg/kg	Letizia et al 2003b
Rats, dermal	➢ 5 g/kg	Letizia et al 2003b

10.2 (Sub)Chronical toxicity

10.2.1. (Sub)chronical toxicity *Lavandula officinalis* E.O.

Animals and administration route	**NOAEL-value (mg/kg/day)**	**LOAEL-value (mg/kg/day)**
Rat, oral, 28 days	160 mg/kg bw/day linalool	Read-across from Coriander EO (ECHA 2014)

10.2.2. (Sub)chronic toxicity linalool

Animals and administration route	**NOAEL-value (mg/kg/day)**	**Reference**
Rat, oral, 28 days	117 mg/kg bw/day linalool	Read-across from Coriander EO (ECHA 2014)
Rat, dermal, 90 days	250 mg/kg/day Derived oral NOAEL, for 14,4% dermal absorption: 36 mg/kg/day	RIFM 1980

- Linalool was administered once daily for 13 weeks to the shaved backs of rats in doses of 0.25, 1.0 or 4.0 g/kg. There were no changes at the lowest dose, except for transient erythema and depressed activity. At 1.0 g/kg it produced decreased weight gain, decreased activity and erythema. At the high dose, decreased body weight and increased liver weight was observed, and nine females and two males died from a total of 120 animals (Letizia et al 2003a, Bickers et al. 2003).
- In a 90-day study, a 1:1 mixture of linalool and citronellol was added to the diet of rats to provide an intake of about 50 mg/kg/day of each substance. A slight retardation of body weight gain was observed in the males, but no effects were evident from histopathology, haematology, clinical chemistry or urine analysis at weeks 6 and 12 (Bickers et al. 2003).

10.2.3. (Sub)chronic toxicity linalyl acetate

Is generally derived from the toxicity of linalool.

10.3 Genotoxicity

10.3.1. Genotoxicity for *Lavandula officinalis* E.O.

Lavandula E.O. was primarily reported to be non-mutagenic, with also indications of antimutagenic properties.

Rahimifard et al. (2010) investigated the mutagenic and antimutagenic activities of lavender (and cardamom) oil by reverse mutation assay in the same strains of *Salmonella typhimurium* with and without S9 (microsomal mutagenesis assay) for 7 dilutions. No mutagenicity was seen for concentrations between 0.13 and 0.80 mg/plate. On the contrary, there was an antimutagenic effect when 0.4 mg lavender essential oil per plate was applied.

Lavender oil was not mutagenic in *S. typhimurium* strains TA98 and TA100, or on E. coli WP2 uvrA strain, either with or without metabolic activation. The oil was dose-dependently antimutagenic, reducing mutant colonies in the TA98 strain exposed to 2-nitrofluorene, and was moderately antimutagenic when the same strain was exposed to 1-nitropyrene (Evandri et al 2005).

De Martino et al (2009) also found lavender oil non-mutagenic in T98 and T100 with or without S9. (Tisserand, Young, 2014)

10.3.2. Genotoxicity for linalool

In several different assays, linalool was primarily found to be non-mutagenic, with and without metabolic transformation, and non-genotoxic. Isolated reports mention possible anti-mutagenic and anti-genotoxic effects, linked to the antioxidant properties of linalool.

Linalool was not mutagenic in Ames tests with and without S9 (Rockwell & Raw 1979; Eder et al 1980,; Ishidate et al 1984; Heck et al 1989; Di Sotto et al 2008), nor was it mutagenic in CA tests (Ishidate et al 1984; Letizia et al 2003a), or in a mouse micronucleus assay (Letizia et al 2003a).

Rat urinary metabolites of linalool were also non-mutagenic (Rockwell & Raw 1979).

In the mouse lymphoma assay, no effects were seen with linalool without metabolic activation at concentrations up to 300 µg/ml; weak positive effects were observed in the presence of metabolic activation at doses of 200 µg/ml and above (Bickers et al. 2003).

Linalool did not induce chromosomal aberrations when incubated with Chinese hamster fibroblast cells at concentrations up to 0.25 mg/ml (Ishidate et al. 1984) nor with Chinese hamster ovary cells at concentrations up to approximately 300 µg/ml (Bickers et al. 2003).

No induction of unscheduled DNA synthesis in rat hepatocytes was seen at concentrations of linalool up to 50 µg/ml or linalyl acetate up to 300 µg/ml (Bickers et al. 2003).
Linalool was mutagenic in one *Bacillus subtilis* rec assay (Yoo 1986), produced questionable results in a second (Kuroda et al 1984b) and was not mutagenic in a third (Oda et al 1978).

Several studies have failed to detect any antimutagenic effect for linalool (Ohta et al 1986; Yoo 1986; Ohta 1995; Di Sotto et al 2008), but a strong antimutagenic action was reported by Berić et al (2007), who noted that this was linked to antioxidant activity.

Linalool was not genotoxic in a mouse bone marrow micronucleus test (RIFM 2001b, cited in Belsito et al 2008). Linalool did not induce sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells (Sasaki et al 1989) nor did it induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes (Heck et al 1989; RIFM 1986c, cited in Belsito et al 2008).

At nanomolar concentrations, linalool suppressed t-butyl hydroperoxide induced genotoxicity, both in bacteria and cultured human cells. This was predominantly mediated by radical scavenging activity (Mitić-Culafić et al 2009). (Tisserand, Young, 2014)

10.3.3. Genotoxicity for linalyl acetate

Reports on linalyl acetate show primarily non-mutagenic results.

Linalyl acetate was not mutagenic in Ames tests with or without S9 activation (Heck et al 1989; Di Sotto et al 2008). Linalyl acetate was however mutagenic in one of four assays, both with and without S9. Linalyl acetate did not induce UDS in primary rat hepatocytes, and it was not clastogenic in cultured human lymphocytes (Heck et al 1989; Letizia et al 2003b). (Tisserand, Young, 2014)

In the micronucleus test on peripheral human lymphocytes, linalyl acetate increased the frequency of micronuclei significantly and in concentration-dependent manner in concentrations 0.5–100 µg/ml, whereas linalool was devoid of genotoxicity. (Di Sotto 2011)

10.4 Carcinogenicity

10.4.1 Carcinogenicity for *Lavandula officinalis* E.O.

Lavender oil contains no known carcinogens. (Tisserand, Young, 2014)

Lavender oil showed moderate chemopreventive activity against human mouth epidermal carcinoma (KB) and mouse leukemia (P388) cell lines, with respective IC50 values of 0.445 and 0.206 mg/mL (Manosroi et al 2005). Lavender oil was cytotoxic to human prostate, lung and breast cancer cells with IC50 values of 0.05%, 0.13% and 0.14%, respectively (Zu et al 2010). Lavender oil was not significantly cytotoxic to cultured human umbilical vein endothelial cells (Takarada et al 2004, Tisserand, Young, 2014)

10.4.2 Carcinogenicity for linalool

Species / cell line	Dose(s)	Exposure Time	Results	Refs
Mice	DMBA + 20% linalool in acetone	1x/week, 33 weeks	Weakly tumor promoting	Roe & Field 1965
Mice	DMBA + 10 % linalool in acetone	3 days before until 3 days after DMBA	10,4 papilloma's per mouse compared to 15 for acetone control	Gould et al 1987

Species / cell line	Dose(s)	Exposure Time	Results	Refs
Mice	ip injection linalool in tricapryllin 0,6 – 3,0 g/kg	24x over 24 weeks	Incidence primary lung tumors not higher than controls	Stoner et al 1973
Mice	Ip injection linalool 0,6 – 3,0 g/kg	3x/week; 8 weeks	no increase in primary lung tumor induction	Powers & Beasley 1985
Rat	DMBA-induced		did not significantly reduce the average number of tumors per rat or the median tumor latency period – mammary carcinogenesis	Russin et al 1989
human melanoma and adenocarcinoma cell line	linalool		human amelanotic melanoma: IC_{50} = 23.16 µg/mL renal cell adenocarcinoma cell lines IC_{50} = 23.77 µg/mL	Loizzo et al 2007
Carcinoma cell lines	linalool		cervix (HeLa, IC50 0.37 µg/mL), stomach (AGS, IC50 14.1 µg/mL), skin (BCC-1/KMC, IC50 14.9 µg/mL) lung (H520, IC50 21.5 µg/mL) bone (U2OS, IC50 21.7 µg/mL) also active against mouth, kidney, lung (H661), and bladder cell lines	Cherng et al 2007
Hep G2 cells	linalool		0.4 µM (61.6 µg/L): reduction of 50% viability 2.0 µM (308 µg/L): reduction of 100% in viability	Usta et al 2009
Human lymphoma and leukemia cell lines	linalool		histiocytic lymphoma U937 cells IC_{50}= 3.51 µg/mL Burkitt lymphoma P3HR1 cells IC_{50}= 4.21 µg/mL Active against leukemia K562 cells	Chiang et al 2003
Human leukemia cell lines	linalool		Growth inhibition, apoptosis induction	Gu et al 2010

None of the studies showed a carcinogenic or significant tumor promoting activity for linalool. On the contrary, inhibitory concentrations on diverse tumor cell cultures could be demonstrated.

10.4.3 Carcinogenicity for linalyl acetate

Species / cell line	Dose(s)	Exposure Time	Results	Refs
mice	ip injection linalyl acetate in tricapryllin 4,8 - 24 g/kg	24x over 24 weeks	incidence of primary lung tumors was no higher than in the control group	Stoner et al 1973
mice	Linalyl acetate dermal	3x/week; 460 days	No carcinogenic activity for linalyl acetate alone or with 1 µg B[a]P A weak cocarcinogenic activity for linalyl acetate with 5 µg B[a]P	Van Duuren et al 1971

No carcinogenic activity could be demonstrated for linalyl acetate.

10.5 Reprotoxicity

10.5.1. Reprotoxicity for *Lavandula officinalis* E.O.

Lavender oil is estrogenic *in vitro* (Henley et al 2007) but is not estrogenic *in vivo* (Politano et al 2013).

Nevertheless, three cases of gynecomastia in prepubertal boys were seen after topical application of products that contained lavender and tea tree oils. The boys were between 4 and 10 years old. Exposure was as a 'healing balm' with lavender on the skin, styling gel containing lavender on hair and scalp and the use of lavender-scented soap. Gynecomastia resolved after discontinuing of the therapy. No re-application is mentioned. Nevertheless, causality was accepted between the topical use of the plant species mentioned and the gynecomastia (Henley et al. 2007).

Inhaled lavender oil (1 mL/hour) attenuated the damage caused by inhaled formaldehyde (10 ppm/hour) to male rat sperm count and motility (Köse et al 2011).

10.5.2. Reprotoxicity for linalool

Linalool was administered by gavage to pregnant rats without fetal toxicity or teratogenicity up to 1,000 mg/kg/day, on gestational days 7–17. Since there was some maternal increase in relative body weight and feed consumption in the high dose group, the NOAEL for maternal toxicity was 500 mg/kg/day (Politano et al 2008). (Tisserand, Young, 2014).

The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d in an assay on coriander essential oil (equivalent to 365 mg/kg bw linalool), based on the decreased litter size at birth and pup morbidity/mortality thereafter (OECD-SIDS linalool 2002)

10.5.3. Reprotoxicity for linalyl acetate

The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d in an assay on coriander essential oil (equivalent to 464 mg/kg bw linalyl acetate), based on the decreased litter size at birth and pup morbidity/mortality thereafter (OECD-SIDS linalyl acetate 2002)

10.6 Miscellaneous toxicity

10.6.1 Dermal irritation / allergy

Considering the high usage of **lavender oil** on the skin in aromatherapy, the reported incidence of skin reactions is low (Tisserand, Young, 2014). Lavender oil does not seem to be a major sensitizing substance (Hausen & Vieluf 1997).

A retrospective database review was performed of patients attending patch testing clinics at the Skin and Cancer Foundation, Victoria, Australia, from January 1, 1993 to December 31, 2017. Among the 2178 patients patch tested with lavender over this period, a total of 58 positive reactions were recorded in 49 individuals, giving a positive patch test prevalence for patients tested with lavender of 2.2%. Twenty-seven patients were diagnosed with acute contact dermatitis. The most common sources of exposure to lavender were personal care products and essential oils. Of the patients with ACD, 74% were tested with lavender absolute, with positive results in 90% of cases (Bingham et al. 2019).

However, there have been reports of contact dermatitis associated with lavender essential oil in shampoo, and facial dermatitis after application of the oil to pillows for its sedative properties (Sweetman 2009). (EMA/HMPC Assessment Report 2012)

- In clinical studies involving patients treated orally with a lavender flower tincture (Buchbauer et al. 1993b), and patients or healthy volunteers treated with lavender oil either topically (Dale & Cornwell 1994; Cornwell & Dale, 1995; Yip & Tse 2004; Dunn et al. 1995) or by inhalation (Diego et al. 1998; Louis & Kowalski 2002; Kane et al. 2004), only a few mild adverse events have been reported.
- At a concentration of 16% in petrolatum, lavender oil did not produce any irritation after 48 h in the closed-patch test and produced no sensitization reactions in the maximization test (Opdyke 1976).
- In very rare cases allergic reactions have been reported due to contact with lavender oil. Coulson & Khan (1999) described two case reports of mild facial ‘pillow’ dermatitis due to lavender oil allergy.
- A case of allergic reactions have been reported in young students (20 years). When an aromatherapy student started massaging the feet of a client with a mixture of *Lavandul*a, *Origanum* and *Juniperu*s oil, her hands started to tingle and became swollen with redness to her arms and throat area. Shortness of breath occurred within 3 minutes of exposure. The symptoms were reversible upon cleaning the skin of lavender oil (Maddocks-Jennings 2004). Another case of contact dermatitis was reported after rubbing the face with hands that were not cleaned from a massage gel, containing 5% benzylamine and lavender fragrance. Erythema, followed by acute vesicular dermatitis developed (Rademaker 1994).
- A 38-year-old non-atopic male patient presented with chronic dermatitis of his hands, especially involving the palmar, thenar eminences, and first two fingers. He had worked as masseur for years. During the previous 4 months, he had begun to practice a new kind of relaxing massage with pure lavender essential oil, diluted 3% in “pet. oil”. Topical steroids gave only transient relief, whereas spontaneous improvement of the eczema during holidays and weekends was reported. Patches were applied under occlusion on the patient’s back for 2 days; readings were performed on day (D) 2 and D4. The patient showed positive reactions to the lavender oil tested (Corazza et al. 2019).
- A 40-year-old atopic masseur with a history of psoriasis presented with chronic eczema of both wrists and the palms of his hands, and with fissured acral pulpitis. The stop-restart test with the massage

oils used gave a positive result. Positive reactions on patch tests were observed to lavender absolute 2% “pet.-oil” (Corazza et al. 2019).

For **linalool and linalyl acetate** skin and eye irritation have been reported (Bickers 2003).

- Undiluted linalool caused slight to severe irritation to guinea pigs and rabbits when applied to open or occluded skin; no irritation was observed at 10% dilution.
- Undiluted linalyl acetate caused slight to severe skin irritation in guinea pigs and rabbits; at 5% dilution it was slightly irritating to rabbits.
- From evaluation of linalool and linalyl acetate for skin irritation in male volunteers, no irritation was observed with 20% linalool or up to 32% linalyl acetate, while mild irritation was observed with 32% linalool.
- No sensitization reactions were observed in the human maximization test with linalool at concentrations of 8% or 20% in 50 volunteers, nor with 10% linalyl acetate in 131 volunteers. With linalyl acetate at 12% and 20% no reactions were observed in 25 subjects.

Linalool: According to the harmonised classification and labelling (ATP10) approved by the European Union, this substance may cause an allergic skin reaction. (ECHA -). Additionally**,** the classification provided by companies to ECHA in REACH registrations identifies that this substance causes serious eye irritation and causes skin irritation. (ECHA -)

Linalool / linalyl acetate
Cause skin irritation, eye irritation; may cause allergic skin reaction (PubChem compound summaries)

10.7 Interactions / cumulative effects with other E.O. or chemicals

No known clinically relevant interactions.
Hazards: non known (Tisserand, Young, 2014).

10.8 Contra-indications

The use of old and oxidized oil should be avoided.

11. Authorized claims for E.O. *Lavandula officinalis*

Health claims must be in accordance with the general principles of regulation 1924/2006 and the relevant regulations. You can find more information about this on the web page "Permitted claims" of the FPS Public Health.

12. Recommendations for oral use

The use of this essential oil in capsules may be considered, because

- The daily dose is more accurate and constant
- The oil is less exposed to air
- Less risks for accidents or misuse of the oil

When the essential oil is packed in bottles, following recommendations can help to avoid the use of oxidized oil:

- The packaging should be done in airtight bottles, in dark glass to protect the oil from light.
- A 'best before' date has to be mentioned, as well as a 'maximum period after opening'. The maximum period after opening cannot be more than 1 year and is only valid if the containers are stored in the dark and the cold. If these conditions are not met, oxidation can start within 10 to 20 weeks and progresses rapidly[27].
- The use of small bottles (e.g. 5 ml) is encouraged.
- The use of an approved anti-oxidant (e.g. BHT, α-tocopherol) or storage under inert gas (e.g. argon) after production may be considered.
- The bottle should make it easy to dose the oil as accurately as possible.
- The dropper should be designed in such a way that confusion with other uses/products is minimal

The consumer should be advised not to put the E.O. in a glass of water or an aqueous solution, the E.O. will not dissolve and will not be distributed in the water. To avoid a local high concentration of the E.O., the use of an edible oil (e.g. olive oil) or honey may be recommended.

- **Lavender essential oil can be considered as safe.** There is no limit reported in the EU Monograph (EMA/HMPC Monograph 2012).
- **Contact dermatitis may be possible in rare cases,** but is important to consider, given the potential for exposure through the use of personal care items and essential oils. (EMA /HMPC AR 2012; Corazza et al. 2019; Bingham et al. 2019).
- For **linalool and linalyl acetate**, the major constituents in lavender essential oils compliant with the Ph. Eur. 10th ed. Monograph, an ADI of 0,5 mg/kg/day has been established (JECFA). The same ADI has been set for citral, geranyl acetate, citronellol, linalool, and linalyl acetate, and is expressed as citral (JECFA). It should be taken into account that this ADI has been established for a long term use as food additives.
- When taking into account the NOAEL for linalool of 117 mg/kg/day (https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/14501/7/6/2) and a security factor of 10 (species difference) x 10 (transfer animal-human), an **ADI of 70 mg linalool + linalyl acetate** for an adult of 60 kg could be accepted. For these components, a possible cumulative effect with the other plant extracts of the formula will be assessed. This ADI is in line with the traditionally recommended posology of lavender essential oil with the composition according to the European Pharmacopoeia monograph, including the maximum levels set for the enantiomers (max. 12 % (S)-linalool and 1 % (S)-linalylacetate) as indicators for the quality of the E.O.)
- Use of lavender E.O. to limit stress-induced sleeping difficulties should be **limited to a maximum of 14 days**; if prolonged use would be considered, cause of the stress should be identified. Medical advice is then warranted.
- Due to lack of data indicating absence of toxicity during **pregnancy and lactation**, food supplements with lavender E.O. should be **avoided** in these conditions.

Lavender E.O. is **not recommended to be used under 18 years** by lack of adequate data, and by the fact that the body weight could be lower than 60 kg for younger persons.

13. Conclusion (EN)

Link naar NL: Conclusie

Lien vers FR: Conclusion

In view of the above information,

Considering the opinions that the committee has previously given during the sessions of 16th October 2012, 15th October 2013, 15th December 2015, 26th March 2018, 19th February 2019, 11th April 2019, 24th October 2019, 15th January 2020 and 25th August 2020.

The Advisory Committee on Plant Preparation decides at the meeting of … the following:

The oral use of the E.O. of *Lavandula officinalis* in or as a food supplement is permitted under the following conditions:

- The use of old and oxidized E.O. has to be avoided
- The daily intake of **linalool + linalyl acetate** by *Lavandula officinalis* essential oil and other sources thereof that may be present in the preparation should not exceed **70 mg.**
- The analysis of the essential oil used in a food supplement must determine its **linalool and linalyl acetate** content, as well as the composition of the oil.
- Except for use as an aroma, the use of this E.O. is **not recommended** during **pregnancy and lactation** and **under 18 years**
- The use of this E.O. in food supplements should be limited to a **maximum of 14 days**; medical advice is warranted if prolonged use is considered
- Unless otherwise indicated on the packaging, the weight of one drop E.O. is 40 mg.

The present advice does not imply any statement on the determination of the status of products containing *Lavandula officinalis* essential oil; this status should be determined on a case-by-case basis and taking into consideration all characteristics of each product.

The Advisory Commission on Plant Preparations reserves the right to re-examine this advice in the light of new considerations.

Conclusie (NL)

Overwegende de bovenstaande gegevens,

Overwegende de adviezen die de Commissie reeds eerder heeft verleend tijdens de zittingen van 16 oktober 2012, 15 oktober 2013, 15 december 2015, 26 maart 2018, 19 februari 2019, 11 april 2019, 24 oktober 2019, 15 januari 2020 en 25 augustus 2020.

Beslist de Commissie van Advies voor Plantenbereidingen in de zitting van … het volgende:

Het oraal gebruik van de E.O. van *Lavandula officinalis* in of als een voedingssupplement is toegestaan onder de volgende voorwaarden:

- Het gebruik van oude en geoxideerde E.O. moet vermeden worden
- De dagelijkse inname van **linalool + linalylacetaat** door *Lavandula officinalis* essentiële olie en andere bronnen van deze stoffen die in de bereiding aanwezig kunnen zijn mag niet hoger zijn dan **70 mg.**
- De analyse van de essentiële olie gebruikt in een voedingssupplement moet het **linalool en linalylacetaat** gehalte bepalen evenals de samenstelling van de olie
- Behoudens het gebruik als aroma is het gebruik van deze E.O. **niet aanbevolen** tijdens de **zwangerschap**, periodes van **borstvoeding** en bij een leeftijd **lager dan 18 jaar**
- Het gebruik van deze E.O. in voedingssupplementen zou beperkt moeten blijven tot een **maximum van 14 dagen**; indien verlengd gebruik wordt overwogen is medisch advies gerechtvaardigd
- Tenzij anders vermeld op de verpakking is het gewicht van één druppel E.O. gelijk aan 40 mg

Het voorliggende advies houdt geen uitspraak in over de bepaling van de status van producten die de essentiële olie van *Lavandula officinalis* bevatten; deze status moet geval per geval worden bepaald op basis van het geheel van kenmerken van elk product.

De Commissie van Advies voor Plantenbereidingen behoudt zich het recht voor om dit advies in het licht van nieuwe overwegingen opnieuw te onderzoeken.

Conclusion (FR)

Considérant les informations qui précèdent,

Considérant les avis que la Commission a déjà rendus lors de ses séances des 16 octobre 2012, 15 octobre 2013, 15 décembre 2015, 26 mars 2018, 19 février 2019, 11 avril 2019, 24 octobre 2019, 15 janvier 2020 et 25 août 2020,

La Commission d'avis des préparations de plantes décide ce qui suit en sa séance du … :

L'utilisation de l'H.E. de *Lavandula officinalis* par voie orale dans des compléments alimentaires ou en tant que complément alimentaire est autorisée aux conditions suivantes :

- Il faut éviter d'utiliser de l'H.E. vieille et oxydée.
- La dose journalière de **linalol + acétate de linalyle** provenant de l'H.E. de *Lavandula officinalis* et d'autres sources de ces substances qui peuvent être présentes dans la préparation ne peut pas être supérieure à **70 mg.**
- L'analyse de l'huile essentielle utilisée dans un complément alimentaire doit déterminer sa teneur en **linalol et en acétate de linalyle, ainsi que la composition de l'huile.**
- À l'exception de son utilisation en tant qu'arôme, cette H.E. **n'est pas recommandée à** un usage pendant **la grossesse** et les périodes d'**allaitement**, ni à un âge **inférieur à 18 ans.**
- L'utilisation de cette H.E. dans les compléments alimentaires devrait être limitée à un **maximum de 14 jours**. Si une utilisation prolongée est envisagée, un avis médical se justifie.
- Sauf autre indication sur l'emballage, le poids d'une goutte d'H.E. est de 40 mg.

Le présent avis ne constitue pas une prise de position quant à la détermination du statut des produits contenant de l'huile essentielle de *Lavandula officinalis*; ce statut doit être déterminé au cas par cas sur base de toutes les caractéristiques de chaque produit.

La Commission d'avis des préparations de plantes se réserve le droit de réexaminer le présent avis à la lumière de nouvelles considérations.

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