Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Linalool; (*S,R*)-3,7-dimethyl-1,6-octadien-3-ol; *dl*-linalool [1]
Coriandrol; (*S*)-3,7-dimethyl-1,6-octadien-3-ol; *d*-linalool [2]
Licareol; (*R*)-3,7-dimethyl-1,6-octadien-3-ol; *l*-linalool [3]

EC numbers: 201-134-4 [1], 204-810-7 [2], 204-811-2 [3]
CAS numbers: 78-70-6 [1], 126-90-9 [2], 126-91-0 [3]

CLH-O-0000001412-86-53/F

Adopted

12 March 2015

12 March 2015

CLH-O-0000001486-86-53/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37(4) of Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemicals names:	**linalool; (*S,R*)-3,7-dimethyl-1,6-octadien-3-ol; *dl*-linalool [1]** **coriandrol; (*S*)-3,7-dimethyl-1,6-octadien-3-ol; *d*-linalool [2]** **licareol; (*R*)-3,7-dimethyl-1,6-octadien-3-ol; *l*-linalool [3]**
EC numbers:	**201-134-4, 204-810-7, 204-811-2**
CAS numbers:	**78-70-6, 126-90-9, 126-91-0**

The proposal was submitted by **Sweden** and received by RAC on **28 May 2014**. All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS).

PROCESS FOR ADOPTION OF THE OPINION

Sweden submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **24 June 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **8 August 2014**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Christina Tsitsimpikou**

Co-rapporteur, appointed by RAC: **Nikolaos Spetseris**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonized classification and labelling was reached on **12 March 2015.** The opinion was adopted by consensus.

OPINION OF RAC

RAC adopted the opinion on Linalool that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	**No current Annex VI entry**										
Dossier submitters proposal	TBD	linalool; (*S,R*)-3,7-dimethyl-1,6-octadien-3-ol; *dl*-linalool [1] coriandrol; (*S*)-3,7-dimethyl-1,6-octadien-3-ol; *d*-linalool [2] licareol; (*R*)-3,7-dimethyl-1,6-octadien-3-ol; *l*-linalool [3]	201-134-4 [1] 204-810-7 [2] 204-811-2 [3]	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]	Skin Sens. 1A	H317	GHS07 Wng	H317			
RAC opinion			201-134-4 [1] 204-810-7 [2] 204-811-2 [3]	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM			201-134-4 [1] 204-810-7 [2] 204-811-2 [3]	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]	Skin Sens. 1B	H317	GHS07 Wng	H317			

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comments

Substance Identification

According to the Dossier Submitter (DS), the substance linalool consists of the individual *d*- and *l*- isomers together with the racemate (Table 1 of Part A of the CLH report) and may be stabilised with an antioxidant identified as *d,l*-alpha-tocopherol (see Annex 2). The degree of purity is ≥ 96.7 and ≤ 98.2% (w/w) and the antioxidant stabiliser may or may not be present in concentrations of 200 to 300 ppm. This is the substance evaluated by RAC for harmonised classification and labelling purposes.

According to the DS "*impurities and additives are not considered crucial for the purpose of classification*" (Tables 7, 8 of Part B of the CLH report). Nevertheless, it is the view of RAC that the presence of an antioxidant stabiliser (i.e. *d,l*-alpha-tocopherol) needs to be considered, since the auto-oxidation properties of linalool are one of the concerns leading the DS to propose classification of linalool.

The test materials used for testing this substance in human volunteers, animal studies and *in vitro* tests referred to in the CLH report are a critical issue to this opinion. The test material used is not always the same as the substance being evaluated for classification and labelling and in some studies the exact composition of the test material is not well defined. Thus, other forms, often research materials created for a specific purpose, or indeed other linalool containing materials are also discussed throughout the CLH dossier by the DS. More specifically, the following test materials are mentioned in the report and used in the various studies:

- **pure (or non-oxidised) linalool** (commercially available, purified or re-distilled)
- **oxidised linalool** (prepared in the laboratory, of partially known composition)
- **linalool hydroperoxides** (commercially available)
- **lavender oil** (a plant extract containing linalool)
- **oxidised lavender oil**

It is the view of RAC that some of these are not directly relevant to the classification of linalool.

Auto-oxidation

Linalool is a naturally occurring alcohol that belongs to the terpene family. Terpenes are known to auto-oxidize in the presence of air at ambient temperature. Nevertheless, as shown in detail in the Background Document, auto-oxidation in the presence of tocopherol, which is the antioxidant commonly present as an additive and referred to in the CLH dossier, takes place slowly and cannot be regarded as an intrinsic property of the substance to be classified. RACs conclusions on the oxidation of linalool are therefore as follows:

- The presence of the additive tocopherol (antioxidant) needs to be considered for classification purposes, as it has been shown by industry, all be it using a semi-quantitative colorimetric method, that in the presence of 200-300 ppm alpha-tocopherol, the concentration of linalool hydroperoxides is > 30 times less than that observed in the absence of tocopherol at ambient temperature after 23 days.
- RAC is of the opinion that the experimental conditions (ambient temperature, 10-80

weeks, periodically stirred, air-exposed) for the preparation of oxidised linalool used as research test material both in human and animal studies referred to in the CLH report, do not represent the expected conditions of use and storage of products containing linalool in the market and are not realistic case scenarios for expected use and storage of commercial products containing linalool. This opinion is also based on the fact that according to Kern *et al.* (2014), the average concentration of linalool oxides on aged (at least two years) commercial products did not exceed 1.8%, while in an average test material used in oxidised linalool studies the relevant concentration reaches even 19%. The average value for linalool hydroperoxide content in aged commercial products was found to be about 0.6%, which is more than 30 times less than the respective values in the oxidised linalool used human and animal studies.

- Neither stabilised nor non-stabilised linalool will eventually become the oxidised linalool described above, which is an artificial research material rather than a commercially available substance.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

The DS proposed to classify linalool as a skin sensitiser in category 1A (Skin Sens. 1A). The proposal is based on the following arguments:

- Linalool is labile to auto-oxidation while being exposed to air. Thus auto-oxidation is an intrinsic and inherent property of linalool. Oxidation of linalool has been extensively studied and it has been shown that in the absence of antioxidant stabilisers after 45 weeks of air exposure the content of linalool drops to 30%, while that of the hydroperoxides rises to about 15% (Sköld *et al*., 2004; Christensson *et al*., 2006; Christensson *et al*., 2010). In its oxidised form, linalool becomes a strong skin sensitiser, the hydroperoxides being the main agents initiating the allergic reaction in skin through free radical generation mechanisms. The free radical formation in turn depletes the antioxidant reserve of the skin resulting in further oxidative stress and further enhancement of the sensitisation progress. The result of this scenario has been well described in animal and human patch test studies. In addition, the presence of antioxidants does not appear to protect against autoxidation as demonstrated by the high prevalence of contact allergy to oxidised linalool in Europe. The preventive effect of antioxidants on terpenes was found to be difficult to control as many factors seem to operate simultaneously (Karlberg *et al.*, 1994). An added antioxidant may work initially, but will soon be subject to degradation or other processes. Therefore, auto-oxidation according to the DS is the first argument for the skin sensitising properties of linalool.

- Linalool in its non-oxidised form is a very weak sensitiser, if at all. On the other hand, oxidised mixtures of linalool as well as pure hydroperoxides of linalool are very potent sensitisers. There is human diagnostic patch test data, animal LLNA data, Freund's complete adjuvant test (FCAT) data and *in vitro* studies to support the conclusion that oxidised linalool is a potent sensitiser. Additionally, other oxidised linalool containing products such as lavender oil, showed similar sensitising

properties. Therefore, the established sensitising properties of oxidised linalool constitute the second argument for the justification of linalool as a skin sensitiser Cat 1A.

- Linalool is widely used in products on the European market, as revealed by the more than 1500 notifications in the C&L Inventory. The substance is known to be a common ingredient in various types of consumer products with different functions. It is one of the most commonly used fragrances in Europe (SCCS, 2012). Linalool, together with limonene, has been identified as the most ubiquitous fragrance in cosmetics among the 26 fragrance substances to be labelled in the EU (SCCS, 2012). Therefore, there is a high probability that many people would come into contact with the substance, primarily via the skin. Thus, due to its widespread use, it is hard for consumers to avoid exposure and even the low concentration of linalool used in products may not adequately protect the general population from sensitisation. In conclusion, widespread use and exposure of consumers is the third argument that triggers the DS opinion towards classifying linalool as a skin sensitiser in category 1A. According to Table 3.4.2-c and Table 3.4.2-d of the Guidance of the Application of the CLP Criteria, November 2013 ("CLP Guidance"), the level of exposure combined with the frequency of skin sensitisation occurrence can differentiate between Skin Sens. 1, Skin Sens. 1A and Skin Sens. 1B.

Human Data

1. General population studies

There are no experimental data for the frequency of occurrence (prevalence) of sensitisation in the general population. In the study published by Christensson *et al.* (2009) the prevalence is estimated by the authors to be 2%. This estimation is derived from the reported frequency of 5-7% of allergy to oxidised linalool in dermatitis patients in Sweden. The figure is calculated based on the fact that the frequency of contact allergy in dermatitis patients is approximately 5 (range 2-10) times higher than in the general population (CLP Guidance; Mirshahpanah *et al.* 2007).

2. Dermatitis patients (unselected, consecutive)

a) Linalool

The frequency for sensitisation to linalool is reported to be 0.2-0.3%. The guidance value for Skin Sens. sub-category 1A is > 1.0%.

b) Oxidised linalool

The frequency for sensitisation to oxidised linalool is reported to be 0.83-7.2%. The guidance value for Skin Sens. sub-category 1A is >1.0%.

c) Linalool hydroperoxides

The frequency for sensitisation to linalool hydroperoxides is reported to be **1.1%**, when the guidance value for Skin Sens. sub-category 1A is **>1.0%**.

3. Selected dermatitis patients (aimed testing)

The frequency for sensitisation to linalool in targeted patch testing is reported to range

between **0 and 4%**. The guidance value for Skin Sens. sub-category 1A is **>2.0%**. In one study (Van Oosten *et al.,* 2009), the frequency of sensitisation to non-oxidised linalool was 0.6% (moderate sensitiser) and the authors of the publication stated that there may have been a certain degree of oxidation during the storage of their patch test preparations. In another study (De Groot *et al.*, 1987), according to the dossier submitter the frequency of sensitisation was found to be 4% (3/75 patients with contact allergy to cosmetics). This was a meta-analysis study, where three linalool-containing products (hair colour, hair lotion and after shave) gave positive responses in patch testing. Further review of the original published data revealed that the three incidences referred to cosmetic products and not to patients. Thus, RAC notes that the 4% value for aimed testing is not correct.

4. Workplace studies

a) Selected workers with known exposure or dermatitis

The frequency for sensitisation to linalool is reported to be **15%**. The guidance value for sub-category 1A is **>1.0%**. However, the authors of the specific study stated that the high percentage of occurrence could be due to cross reactivity (Schubert, 2006).

b) Number of published cases

The DS stated (in the CLH report) that the Scientific Committee on Consumer Safety (SCCS) has concluded in its opinion on fragrances (SCCS, 2012) that linalool is an established contact allergen in humans and (in the RCOM) that the number of published cases of allergy in scientific literature was in the range of 11-100 cases (SCCS, 2012). Furthermore, the DS stated that the SCCS concluded that linalool in its oxidised form is also an established human contact allergen and that it is an "allergen of special concern" since the number of reported cases in scientific literature is as many as 100-1000 (SCCS 2012). It was emphasised by the SCCS that the number of cases in the population is probably much higher than the number of published cases.

c) Other linalool containing products

Sensitisation resulting from exposure to oxidised lavender oil, one of the major components of which is linalool, could also be regarded as supporting evidence for the sensitisation properties of linalool (Hagvall *et al.*, 2008). In this regard, the dramatic increase of sensitisation to lavender oil observed in suspected contact dermatitis patients in Japan (from 0% to 14%) during a 9-year period from 1990 to 1998, could also be related to a concomitantly increased use of specific products containing lavender oil (Sugiura *et al.*, 2000).

Exposure Data

Studies on products from different markets across EU have identified the concentration of linalool in consumer products to vary between approximately 10 and 3500 ppm (0.001% and 0.35%), giving a score of 0 according to the CLP Guidance, Table 3.4.2-c, (see table below). It could be anticipated that sensitised individuals have been exposed to linalool at least daily and more than one hundred times, giving a score of 4 according to the CLP Guidance (page 357). Taken together the exposure score for linalool is 4, which indicates low exposure.

Dossier Submitter's proposal: comparison with CLP criteria

Table 1: Frequencies of sensitisation to linalool, oxidised linalool or linalool hydroperoxides amongst patients and general populations according to DS

Human diagnostic patch test data	**Frequency, Guidance values for sub-cat. 1A**	**Frequencies according to CLH proposal**		
		Linalool	**Oxidised linalool**	**Hydroperoxide fraction**
General population studies	**≥ 0.2%**	*2% (anticipated by Christensson, 2009)*		
Dermatitis patients (unselected, consecutive)	**≥ 1.0%**	*0.2-0.3%*	*0.83-7.2%*	*1.1%*
Selected dermatitis patients (aimed testing, usually special test series)	**≥ 2.0%**	*0-4%*		*3.5%*
Workplace studies: 1) all or randomly selected workers 2) selected workers with known exposure or dermatitis	**≥ 0.4%** **≥ 1.0%**	*15%*		
Number of published cases	**≥ 100 cases**	**11-100 (SCCS, 2012)*	**101-1000 (SCCS, 2012)*	

** Values corrected by the DS after PC*

Table 2: Scores for exposure to linalool and comparison with the criteria according to DS

Exposure data	**Low exposure. Guidance values and scores for sub-cat. 1A**	**High exposure. Guidance values and scores for sub-cat. 1B**	**Exposure to linalool according to CLH proposal**
Concentration/ dose	< 1.0% < 500 µg/cm^2 (score 0)	≥1.0% ≥500 µg/cm^2 (score 2)	*7 ppm - 3800 ppm / 0.38%* *(score 0)*
Repeated exposure	< once daily (score 1)	≥ once daily (score 2)	*anticipated score 2*
Number of exposures (irrespective of concentration of sensitiser)	< 100 exposures (score 0)	≥100 exposures (score 2)	*anticipated score 2*

Animal Data

Local Lymph Node Assay (LLNA)

The criteria relating to EC3 values in the CLP Regulation are ≤ 2% for Skin Sens. 1A and > 2% (with no upper limit defined) for Skin Sens. 1B. As explained in the CLP Guidance, page 360, sensitisation potency is measured as a function of derived EC3-values, with an inverse relationship existing. As described in the OECD Test Guideline (TG) for Skin Sensitisation (Local Lymph Node Assay, OECD 429, 2010), the results of the LLNA are expressed as the Stimulation Index (SI). According to the CLP Regulation, a significant skin sensitising effect in LLNA is defined when the SI is ≥ 3.

a) Linalool (purified)

The EC3 value for pure linalool is **30%**. The study authors consider pure linalool as a weak skin-sensitiser (Basketter *et al.*, 2002).

Redistilled pure linalool (EC3 = **46.2**% (Skold *et al.,* 2004), EC3 = **55**% (Basketter *et al,* 2002)) is considered either as a non-sensitiser (Sköld *et al.*, 2004) or as a weak skin-sensitiser, with the re-distillation considerably reducing its sensitising potency (Basketter *et al.*, 2002).

b) Oxidised linalool

The EC3 value for oxidised linalool is 4.8% (Sköld *et al.*, 2004) and both the study authors and the DS considered oxidised linalool to be sensitising. The RAC notes that such an EC3 value meets the criteria for Sens. 1B.

c) Lavender oil (non-oxidised and oxidised)

The EC3 value was reported as 36% for non-oxidised lavender oil and as 4.4% for the oxidised lavender oil. The authors stated that the sensitising potency of lavender oil increased accordingly on air exposure and that oxidised lavender oil only can elicit allergic contact dermatitis (ACD) (Hagvall *et al.*, 2008).

d) Linalool hydroperoxides

The EC3 value for linalool hydroperoxides is 1.6%. It supports classification as Skin Sens. 1A, according to both the study authors' and the DS's opinion (Sköld *et al.*, 2004).

Freund's Complete Adjuvant Test (FCAT)

RAC notes that FCAT in the study reported in the CLH report is performed according to Boman *et al*., 1988[5] and it is not an OECD Guideline assay. In Boman *et al*. (1988), FCAT is compared with the guinea pig maximization test – GPMT, which is an OECD Guideline assay and mentioned in the CLP Regulation. According to the study authors, the FCAT method was found to be advantageous over the GPMT method in that it is technically simpler to use and a smaller amount of test substance is needed.

Linalool was found to be a non-sensitiser in the FCAT experiment (Sköld *et al.*, 2002). Oxidised linalool on the other hand sensitised 33-87% of the animals, depending on the challenge concentration (Sköld *et al.*, 2002). It is noted that the challenge concentrations used in this experiment exceeded the value for intra-dermal induction for Skin Sens. 1A. In addition, when the challenge concentration used was 1% the percentage of sensitised animals was not significant (1/14 ≈ 7%). In conclusion the DS stated that based on the

FCAT experimental data it cannot be excluded that linalool is a strong skin sensitiser.

Dossier Submitter's assessment

Diagnostic patch test data, obtained from several dermatology clinics in Europe, showed positive patch test reactions to oxidised linalool in 0.83-7.2% of consecutively tested dermatitis patients (Matura *et al.*, 2005; Christensson *et al.*, 2010; Christensson et.al, 2012; Buckley 2011). These frequencies exceed the guidance values (≥ 1.0%) for subcategory 1A given in the CLP guidance[1].

Some 1.1% of 1511 consecutively tested dermatitis patients and 3.5% of 29 selected patients were patch test positive to the hydroperoxide fraction of oxidised linalool (Christensson *et al.*, 2006; Matura *et al.*, 2005). These frequencies exceed the guidance values (≥ 1.0%) for subcategory 1A given in the CLP guidance[1].

Up to 1000 case reports are published in scientific literature for sensitisation to oxidised linalool, though being subject to a severe underestimation of the real number of cases in the population. The number of cases exceeds the guidance value (> 100 cases) (≥ 1.0%) for subcategory 1A given in the CLP guidance[1].

The low exposure score of 4 together with the high number of published cases (101-1000) supports the sub-categorization as sensitiser 1A for oxidised linalool.

Sub-category 1A is also supported by the following evidence from animal studies: the EC3 value for a 5:3 mixture of the hydroperoxide fraction of oxidised linalool is 1.6% in the LLNA (Sköld *et al.*, 2004). Moreover, 33%-87% of the animals were sensitised to oxidised linalool in the FCAT (Sköld *et al.*, 2002), but the data, according to both the study authors and the DS, are not sufficient to definitely support Skin Sens. 1A or to distinguish between Skin Sens. 1A and 1B (questionable concentrations).

Dossier Submitter's conclusion

Linalool has the intrinsic property to autoxidise in air, making it a potent sensitiser. Therefore, it should be classified as a skin sensitiser based on human and animal data. It should be classified as Skin Sens. 1A due to a high frequency of positive diagnostic patch test reactions in European dermatological clinics and low concentrations in products which consumers are exposed to. According to the DS, Skin Sens. 1A is also supported by animal studies on the oxidation products of linalool.

Comments received during public consultation

During public consultation (PC) (24/06/2014-08/08/2014) 17 comments were received; most of them were from Industry and also from four Member State Competent Authorities (MSCAs). A summary of the comments provided during PC is provided below.

Three MSCAs were in favour of classification for Skin Sens. 1A, based on the evidence for sensitisation potential (with non-oxidised and oxidised linalool) shown in data from humans. One MSCA proposed classification as Skin Sens. 1B, as the results for oxidised linalool are not clear enough for classification as Skin Sens. 1A and animal studies (LLNA and FCAT) fulfil the criteria as Skin Sens. 1B for pure linalool. One MSCA stated that animal studies alone would not be sufficient for sub-categorisation. One MS suggested that the need for a SCL should be explored.

Industry was not in favour of classification for sensitisation. The main issues raised by Industry can be summarised as follows:

- The relationship of the test materials used in the various studies referred to in the CLH report compared to the substance being evaluated for classification and labelling is questioned;
- Auto-oxidation of linalool as an intrinsic property is questioned (due to the presence of stabiliser, kinetics of auto-oxidation, structural alert);
- Validity of patch test for classification purposes is questioned;
- The frequency of sensitisation incidences of linalool in the population differs (Industry interprets the same literature data differently from the DS);
- No data on exposure to oxidised linalool or presence of linalool oxidation derivatives in commercial products exists;
- Relevance of literature data on oxidation products of linalool is questioned and the positive LLNA linalool test results (SI > 3) is also questioned due to possible irritation effects;
- Reasonably expected use conditions of linalool containing products placed on the market are not relevant to the auto-oxidation procedure applied in the experimental studies with oxidised linalool;
- The relevance of the skin penetration kinetics presented in the CLH report for classification are questioned;
- Current specifications (IFRA peroxide limit, labelling) for linalool and its oxidised form in consumer products ensure consumers safety.

Assessment and comparison with classification criteria

For the decision logic for classification of sensitising substances, please see Section 3.4.2.2.6. of the CLP Guidance.

Animal Studies

Evaluation of animal data and comparison with classification criteria is based on Annex I: 3.4.2.2.3.2. Annex I: 3.4.2.2.3.3., Table 3.4.3, Table 3.4.4 and Table 3.4.2.e of the CLP Regulation[7] and according to the CLP Guidance.

RAC notes that in the CLH report the DS does not refer to stimulation indices (SIs), but these are included below. A number of different preparations were used as the study material for testing.

RAC considered the Local Lymph Node Assay (LLNA) from Sköld *et al*. (2004). The table below provides the SI and EC3 values obtained at different concentrations of pure linalool.

Table 3: SI and EC3 values obtained at different concentrations of pure linalool

Concentration of the test material (pure linalool)	SI	EC3
25%	1.9	46.2
50%	3.2	
100%	3.0	

The EC3 value for pure linalool (97% not redistilled) was found to be 46.2%, which is a non-sensitising value according to the study authors on the basis of the relative skin sensitisation potency reported by Kimber *et al*., 2003:

Table 4: EC3 values

Category	EC3 (%)
Extreme	<0.1
Strong	$\geqslant 0.1$ to <1
Moderate	$\geqslant 1$ to <10
Weak	$\geqslant 10$ to $\leqslant 100$

Recommended scheme using EC3 values derived from the local lymph node assay.

According to the authors, concentrations of 50-100% of pure linalool are known to cause irritation. Furthermore, linalool is self-classified in the REACH registration dossier and notified in the C&L inventory (1572 notifiers in February 2015) as Skin Irrit. 2.

The OECD 429 Guideline states that "*Existing acute toxicity and dermal irritation data should be considered, where available, in selecting the three consecutive concentrations so that the highest concentration maximizes exposure whilst avoiding systemic toxicity and excessive local skin irritation*".

Furthermore, in the OECD 429 Guideline it is stated that the results of the LLNA are expressed as the Stimulation Index (SI). According to the CLP Regulation, a significant skin sensitising effect in LLNA is defined when SI ≥ 3. As explained in the CLP Guidance, page 360, EC3 values represent the sensitisation potency. It is further clarified in the OECD 429 Guideline that "*if it is necessary to clarify the results obtained, consideration should be given to various properties of the test substance, including whether it has a structural relationship to known skin sensitizers, whether it causes excessive skin irritation, and the nature of the dose response seen*". These and other considerations, as mentioned in the OECD 429 Guideline, are discussed in Basketter *et al*.(1998). The criteria for false positive reactions in skin sensitisation tests reported in Basketter et al. (1998) are presented in the table below:

Table 5: False positive reactions in skin sensitisation tests reported in Basketter et al. (1998)

GPMT	LLNA
Test substance does not have a structural alert	Test substance does not have a structural alert
Test substance is known to be a significant skin irritant	Test substance is known to be a significant skin irritant
Primary challenge reactions are weak and scattered	Dose response is odd and/or weakly positive, only at high test concentration
Reactions are more intense at the early scoring time(s)	Inter-animal and/or inter-experiment variation is high
Reactions are poorly reproducible in suspect animals at rechallenge	Draining lymph node cells do not have surface markers characteristic of skin sensitization

It is well known that linalool has no structural alert for sensitisation, which is also acknowledged by Sköld et al. (2004). In this study, SI values marginally greater than or equal to 3 are obtained only for concentrations that could be irritating and there is not a

clear dose response relationship. The EC3 value is more than 20 times larger than the 2%, notifying classification for Skin Sens 1B.

Therefore, RAC is of the opinion that the findings from Sköld *et al*. (2004) are marginal, constitute a borderline case and will not be used for classification.

In a study considered adequate for classification, Basketter *et al.* (2002) investigated the sensitising activity of non-oxidised linalool. Commercially available linalool was analysed and found to contain a number of impurities.

Upon redistillation, all impurities were removed below their respective detection limits except for dihydrolinalool which was only reduced to 1.4%. Both analytical grades of pure linalool were tested in LLNA studies.

Table 6: LLNA studies based on different analytical grades of pure linalool

Test material	Concentration of the test material (pure linalool)	SI	EC3
Linalool (commercial)	25%	2.5	30%
	50%	4.8	
	100%	8.3	
Linalool (purified, redistilled)	25%	2.1	55%
	50%	2.9	
	100%	4.9	

According to the study authors, pure commercial grade linalool (97%) was shown to be a weak sensitiser with an EC3 value of 30%. RAC notes that the commercially available linalool is not protected by any antioxidant and contains, as shown by the authors, oxidised material. The EC3 value for the purified/redistilled linalool (98.6 % purity) was calculated to be 55%. An SI value greater than 3 was obtained at a concentration 100% only. Following the same line of reasoning as described above, but with linear dose response correlation ($r^2_{\text{commercial linalool}}$ = 0.9949; $r^2_{\text{purified linalool}}$ = 0.9973), as calculated by RAC, RAC concludes that the (commercial) linalool meets the criteria for classification for Skin Sens 1B.

The FCAT study of Sköld *et al.* (2002) showed that pure linalool did not sensitise the animals. No reactions to linalool were found in the exposed animals or in the controls. In the same experimental setting, 3 out of the 15 (20%) animals exposed to oxidised linalool in the first challenge, in the rechallenging phase had a positive reaction to pure non-purified linalool. Sköld *et al*., (2002) stated that "Three reactions were seen to the non-oxidised, unpurified linalool but the response was not significant."

RAC notes that the FCAT study reported in the CLH report was performed according to Boman *et al.* (1985) and that it is not an OECD Guideline assay. However, RAC concludes that no sensitisation effects were observed for non-oxidised linalool in Sköld *et al*. (2002).

Studies in humans

Evaluation of human data and comparison with classification criteria is based on Annex I: 3.4.2.2.2.1. Annex I: 3.4.2.2.2.2., Table 3.4.2.b and Table 3.4.2.d of the CLP Regulation and according to the CLP Guidance.

RAC agrees with the assessment of the DS that exposure to linalool, either stabilised or

non-stabilised, is low. Concerning the number of published studies contributing to the data from humans, the RAC reports that the actual numbers of positive patch test reactions for non-oxidised linalool (stabilised or not) in the SCCS 2012 report are **18** cases out of **6602** patients (SCCS, 2012; van Oosten *et al.*, 2009; de Groot *et al.*, 1985; Uter *et al.*, 2010; de Groot *et al.*, 2000; Frosch *et al.*, 1995; Schnuch *et al.*, 2007). The actual number of positive patch test reactions for oxidised linalool in the SCCS (2012) report is **275** cases out of **8491** patients (Matura *et al.*, 2005; Christensson *et al.*, 2010; Buckley, 2011).

In relevant Human Studies, the comparison with criteria and RAC opinion varies depending on the study under consideration.

As shown in the table below, from a total of 10 705 patients discussed in the available human studies, only 32 are reported sensitised. The overall sensitisation frequency is therefore very low (average 0.3%).

Human studies using stabilised or non-oxidised linalool

Table 7: Overview of human studies using stabilised or non-oxidised linalool

Study reference **study population**	**Test material**	**Prevalence of sensitisation**	**RAC opinion**
Patients			
de Groot *et al.*, 1985 179 consecutive dermatitis patients (56 with atopic disease)	linalool 30% (no stabiliser mentioned, stable after 6 months, 90% intact)	0	The findings do not meet the criteria for classification (0% prevalence)
de Groot *et al.*, 1987 , de Groot & Liem, 1983 Meta-analysis on 76 dermatitis patients with cosmetic allergy (aimed-testing)	cosmetic products containing linalool (i.e. after-shave, hair lotion, dry shampoo)	One or two patients allergic to 3 products containing linalool (1.31-2.63%)* The authors do not establish the number of patients that were found allergic to the commercial products listed. RAC going through the relevant references in this study managed to identify only one patient being allergic to two of the three products.	Sensitisation is observed but no definite conclusion can be reached regarding the frequency. The findings cannot be considered for sub-categorisation
van Oosten *et al.*, 2009 320 patients with eczema (2005 – 2007)	10% linalool pet	0.6% (2 patients +, 0 IR) #	Low frequency of sensitisation. The findings could provide evidence for classification of non-stabilised linalool as **Skin Sens. 1**
de Groot *et al.*, 2000 1825 consecutive patients in the Netherlands (September 1998 – April 1999)	9 fragrance allergens (linalool included, 2% & 30% pet)	Prevalence: 0.2% (3 patients)#	
Audrain et, 2014 4731 consecutive patients in UK	10% stabilised linalool	0.3% (12 patients, 3 patients with IR) #	Low frequency of sensitisation. The findings could provide evidence for classification of stabilised
Schnuch *et al.*, 2007 2401 consecutive	10% stabilised linalool	0.3% (7 positive patch test reactions – PPT: 6 +, 1++, 0+++, 1 follicular	

dermatitis patients in Germany		reaction, 12 IR or doubtful reactions)#	linalool as **Skin Sens. 1**
Uter et al., 2010 985 dermatitis patients (2005-2008)	10% stabilised linalool	0.2% (0.1% +, 0.1% ++/+++, max scoring +++, 0.81% irritant (IR) or doubtful reactions)	
Buckley, 2011 88 selected patients suspected of having fragrance allergy (aimed testing)	extended fragrance battery including 10% stabilised linalool	4 patients (4.5%)* 3 patients have already been positive patch tested to 3% oxidized linalool (doubts for cross-reactivity expressed by the study author) and 1 patient (1.13%) reacted only to 10% stabilized linalool	
Frosch *et al.*, 1995 100 consecutive patients in Andersen, Odense RAC's opinion: RAC's opinion: the findings do not meet the criteria for classification (0% prevalence)	a. 1% linalool b. 5 % linalool	a. 0% (1 IR or + doubtful) b. 0% (1 IR or + doubtful)	(a) and (b): The findings do not meet the criteria for classification (0% prevalence)
Workers			
Schubert, 2006 26 workers in a perfume factory	Fragrance series, 30 individual ingredients (linalool 10% pet), 4 perfumes produced	11.5-15.3% 3 female bottlers ppt + in linalool, 1 bottler in Neroli oil (contains linalool, ++) Authors' comment: *"vicariously for other cases" "the positive reactions to linalool, citronellol, dipentene and turpentine observed in one person may be cross-reactions to a common terpene body and the individual results in other persons indicated that simultaneously occurring positive reactions to fragrances and essential oils were based on cross-reactivity in general rather than concomitant sensitisation."*	Difficult to draw conclusions either on the occurrence of sensitisation or on the frequency thereof. The findings cannot be considered as evidence for classification.

*2% distinguishes between high or low frequency where aimed testing is used for dermatitis patients (CLP Guidance)

#1% distinguishes between high or low frequency for unselected, consecutive dermatitis patients (CLP Guidance)

Conclusion of RAC

The Dossier Submitter proposed to classify linalool as Skin Sens. 1A, based on the findings from diagnostic patch testing in humans, using "oxidised linalool". These studies have shown a high frequency of positive test reactions in European dermatological clinics, supported by animal studies conducted with the oxidation products of linalool. However, RAC is of the opinion that classification for skin sensitisation should not be based on evidence from studies conducted with the research material "oxidised linalool", as its relationship to linalool as marketed in the EU is unclear.

It is the opinion of RAC that skin sensitisation to humans to either stabilised or non-stabilised linalool is limited, as the frequency is very low.

RAC recognises that there are no animal studies available on stabilised linalool which appears to be the predominant form of the substance on the market in the EU.

While, there was no reaction in the FCAT test with non-stabilized linalool, RAC considers on balance the results from the animal study with non-stabilised, purified linalool by Basketter *et al*., 2002 (LLNA) to be appropriate for the purposes of classification.

In conclusion, based mainly on one valid animal study (LLNA) with an appropriate sample of linalool and supported by the low exposure and frequency of sensitisation (based on CLP criteria) observed in human studies, **RAC concludes that linalool [(*S,R*)-3,7-dimethyl-1,6-octadien-3-ol; *dl*-linalool] and its two isomers should be classified as Skin Sens. 1B (H317).**

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RIFM-Research Institute for Fragrance Materials I, 1986, Acute dermal irritation study, RIFM report number 5664

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report during public consultation, response to comments provided by the Dossier Submitter and by RAC (excl. confidential information)