Committee for Risk Assessment

RAC

Annex 1

Background document

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

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name: Linalool

EC Number: **201-134-4, 204-810-7, 204-811-2**

CAS Number: **78-70-6, 126-90-9, 126-91-0**

Index Number: **Not available**

Contact details for dossier submitter: **Swedish Chemicals Agency,**
Esplanaden 3a, P.O Box 2,
SE-172 13 Sundbyberg, Sweden
kemi@kemi.se
+46 8 519 41 100

Version number: 3 **Date: 28 May 2014**

CONTENTS

Part A.

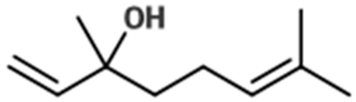
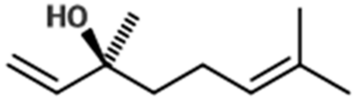
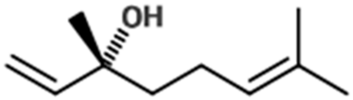
Part A.

1. PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Linalool
International chemical identifier:	Linalool; 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 number:	201-134-4 [1] 204-810-7 [2] 204-811-2 [3]
CAS number:	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]
EC name:	Linalool [1] (*S*)-3,7-dimethyl-1,6-octadien-3-ol [2] (*R*)-3,7-dimethyl-1,6-octadien-3-ol [3]
CAS name:	1,6-octadien-3-ol, 3,7-dimethyl- [1] 1,6-Octadien-3-ol, 3,7-dimethyl-, (*S*)- [2] 1,6-Octadien-3-ol, 3,7-dimethyl-, (*R*)- [3]
IUPAC name:	3,7-dimethylocta-1,6-dien-3-ol [1] (3*S*)-3,7-dimethylocta-1,6-dien-3-ol [2] (3*R*)-3,7-dimethylocta-1,6-dien-3-ol [3]
Molecular formula:	$C_{10}H_{18}O$
Molecular weight range:	154.2 g/mol

Structural formula:	[1]  [2]  [3] 
Annex VI Index number:	Not listed in Annex VI
Degree of purity:	≥ 96.7 – ≤ 98.2% (w/w)
Impurities:	≤ 3.3% (w/w)

CAS no.78–70–6, *dl*-linalool [1] refers to a substance which contains between 10 and 80 % of each isomer, [2] and [3].

"Linalool" will be used throughout this report when no specification of isomers is given or needed, denoting all possible mixtures of [2] and [3] and the pure isomer, [2] or [3]. In clinical studies and animal studies the composition of the individual isomers of linalool is not reported. It is also not expected that the two possible steric positions of the OH-group in the 3-position of linalool would chemically influence the formation of hydroperoxides in 6- and 7-position and the subsequent process of sensitization. Therefore this CLH proposal includes both the individual isomers as well as all mixtures of them. See also Part B, 2.1 for different isomeric compositions after biosynthesis and chemical synthesis of linalool.

The CLH report shows that linalool is autoxidised in air and that mainly the subsequently formed oxidation products are responsible for the sensitizing properties of linalool. Due to the autoxidation in air, which is an intrinsic property of linalool, it is practical and reasonable to classify linalool itself for sensitisation. See also Part B, 4.4.1.3 for analogy with harmonized classification of limonene and rosin.

Linalool, CAS no. 78-70-6, has been registered in a joint submission to ECHA in 2010.

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Not included in Annex VI, Table 3.1 (CLP)
Current proposal for consideration by RAC	Skin Sensitizer 1A; H317
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Sensitizer 1A; H317

1.3 Proposed harmonised classification and labelling based on CLP Regulation criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	n.e.
2.2.	Flammable gases	-	-		n.e.
2.3.	Flammable aerosols	-	-	-	n.e.
2.4.	Oxidizing gases	-	-	-	n.e.
2.5.	Gases under pressure	-	-	-	n.e.
2.6.	Flammable liquids	-		-	n.e.
2.7.	Flammable solids	-	-	-	n.e.
2.8.	Self-reactive substances and mixtures	-	-	-	n.e.
2.9.	Pyrophoric liquids	-	-	-	n.e.
2.10.	Pyrophoric solids	-	-	-	n.e.
2.11.	Self-heating substances and mixtures	-	-	-	n.e.
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	n.e.
2.13.	Oxidizing liquids		-	-	n.e.
2.14.	Oxidizing solids	-	-	-	n.e.
2.15.	Organic peroxides	-	-	-	n.e.
2.16.	Substance and mixtures corrosive to metals	-	-	-	n.e.
3.1.	Acute toxicity – oral	-	-	-	n.e.
	Acute toxicity - dermal	-	-	-	n.e.
	Acute toxicity - inhalation	-	-	-	n.e.
3.2.	Skin corrosion / irritation	-	-	-	n.e.
3.3.	Serious eye damage / eye irritation	-	-	-	n.e.
3.4.	Respiratory sensitization/irritation	-	-		n.e.
3.4.	Skin sensitization	Skin sensitizer 1A, H317	-	-	-
3.5.	Germ cell mutagenicity	-	-	-	n.e.
3.6.	Carcinogenicity	-	-	-	n.e.
3.7.	Reproductive toxicity	-	-	-	n.e.

3.8.	Specific target organ toxicity –single exposure	-	-	-	n.e.
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	n.e.
3.10.	Aspiration hazard	-	-	-	n.e.
4.1.	Hazardous to the aquatic environment	-	-	-	n.e.
5.1.	Hazardous to the ozone layer	-	-	-	n.e.

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
n.e. = not evaluated

Labelling: Signal word: Warning
Hazard statements: H317
Precautionary statements: P261, P272, P280

2. BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Linalool has not been previously discussed for harmonized classification and labelling. OECD SIDS (2004) initiated an evaluation on linalool and concluded that it was not considered to be a sensitizer. Evidence showing that the oxidation products of linalool are sensitizing in humans was scarce at that time.

Nevertheless, Scientific Committee on Consumer Safety (SCCS) has concluded linalool to be an established contact allergen in humans. It belongs to fragrances of special concern due to the high number of published cases of allergy in scientific literature, 100-1000 cases (Opinion of the SCCS, 2012).

2.2 Short summary of the scientific justification for the CLH proposal

Linalool is a ubiquitous fragrance found in various types of consumer products available on European markets. It has been identified as one of the most used fragrances with concentration levels varying between 10 and 3500 ppm. Its wide distribution in consumer products demonstrates multiple possible exposure scenarios for the public (Buckley, 2007; Wijnhoven *et al.*, 2008; Magnano *et al.*, 2009; Yazar *et al.*, 2010).

Pure linalool is a weak sensitizer; however, it is vulnerable to autoxidation in air which makes it a potent sensitizer. It forms stable hydroperoxides as primary oxidation products which have been shown to be the main allergenic agents (Sköld *et al.*, 2002; Sköld *et al.*, 2004; Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2012). The autoxidation in air is an intrinsic property of linalool.

Both human and animal data are available that demonstrate the skin sensitizing properties of oxidized linalool. Among dermatitis patients in Europe the frequency of allergy to oxidized linalool is high and varies between 1% and 7% (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckely, 2011; Christensson *et al.*, 2012). In LLNA (Local Lymph Node Assay) as well as in FCAT (Freund's Complete Adjuvant Test) oxidised linalool was sensitising. The hydroperoxide fraction of oxidised linalool was a strong sensitiser in LLNA (Sköld *et al.*, 2002; Sköld *et al.*, 2004).

Taken together, on the basis of high frequencies of positive patch test reactions among dermatitis patients in different European clinics, positive results in animal studies and exposure to low concentrations of linalool in consumer products a harmonized classification for skin sensitization in sub-category 1A is proposed for linalool.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Not included in Annex VI, Table 3.1.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Not included in Annex VI, Table 3.2.

2.4 Current self-classification and labelling

Linalool, CAS no 78-70-6, and its two isomers, *d*-linalool, CAS no 126-90-9, and *l*-linalool, CAS no 126-91-0, have been notified to the C&L Inventory under the three different CAS numbers.

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

In the registration dossier linalool has been self-classified for Skin Irritation 2 and Eye Irritation 2. There was no self-classification for skin sensitisation as data were considered conclusive but not sufficient for classification.

A total number of 1654 companies have notified linalool, 80 companies have notified *d*-linalool and 128 companies have notified *l*-linalool in the C&L Inventory (November 2013). There were 23, 2 and 3 aggregated notifications, respectively. Only 9 notifiers classified linalool as a Skin sensitiser 1.

Summary of self-classifications as presented in the C&L Inventory:

Self-classification	**Number of notifiers**		
	CAS no 78-70-6	**CAS no 126-90-9**	**CAS no 126-91-0**
Skin sensitisation 1	9	-	-
Skin irritation 2	1588	80	128
Skin corrosion 1B	1	-	-
Eye irritation 2	1220	42	65
STOT SE 3 (respiratory irritation)	78	-	23
Flammable liquid 3	1	-	-
Aquatic chronic 3	1	-	-
Aquatic chronic 2	1	-	-

Labelling for Skin sensitisation 1 has been notified as follows.

Hazard statement: H317

Pictogram, signal word: GHS07 (exclamation mark), Warning

3. JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Broad use at low concentration

Linalool is widely used in products on the European market as revealed by the over 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 used fragrances in Europe (SCCS, 2012). Therefore, there is a high risk of being in contact with it, primarily via skin contact. It is also well-established that linalool is prone to autoxidation when it is exposed to air, which is very likely to occure in consumer products during storage or handling.

Linalool is one of the most common substances found in a wide variety of every-day-use products (including detergents, household products, cosmetics, etc.) because of its flowery and attractive odour. Linalool commonly occurs in concentrations between 10-3500 ppm in consumer products (Rastogi *et al.*, 1998; Rastogi *et al.*, 2001; Rastogi, 2002; Poulsen and Schmidt, 2008; Poulsen and Strandsen, 2011). It has also been found in 15 of 19 (78.9%) air fresheners analyzed at a range of 970-39000 ppm (Ports and Fuhlendorff, 2003; Poulsen and Schmidt, 2008). Eggert and Hansen (1999) and Tran and Mariott (2007) have detected linalool as a major component in both powder and burning incenses. Airborn linalool maycontribute to skin exposure. 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). In different surveys of household products and cosmetics on the market including children's products, linalool was found to be present in 25%-93% of the products (Fenn, 1989; de Groot, 1994; Rastogi *et al.*, 1998; Rastogi *et al.*, 2001; Rastogi, 2002; Buckley, 2007; Wijnhoven *et al.*, 2008; Magnano *et al.*, 2009; Yazar *et al.*, 2010). Thus, due to its widespread use it is hard for consumers to avoid exposure and apparently the low concentration of linalool used in products does not protect from sensitization.

The International Fragrance Association (IFRA, 2009) has set a standard to limit the peroxide level to 20mmol/l. The Scientific Committee on Consumer Safety (SCCS, 2012) has given recommendations on a general limit for the safe use of fragrances in cosmetics, 100 ppm. In the case of linalool the hydroperoxide fraction is recommended not to exceed 10 ppm. However, these recommendations are not frequently followed as shown by the studies of consumer products on different European markets.

High frequency of sensitization in humans

Although linalool is not routinely included in patch testing of dermatitis patients, available clinical studies in many member states have demonstrated that oxidized linalool is a common skin sensitizer. The frequency of allergy to oxidized linalool reported by different dermatological clinics in Europe has been found to be between 1% and 7% (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckley, 2011; Christensson *et al.*, 2012).

Animal data

In the last decade the sensitizing properties of oxidized linalool and the hydroperoxide fraction have been demonstrated in animal studies and published in scientific literature. Accordingly, oxidised linalool was sensitising in LLNA and FCAT. The hydroperoxide fraction of oxidised linalool was a strong sensitiser in LLNA (Sköld *et al.*, 2002; Sköld *et al.*, 2004).

Many countries are affected

Studies in dermatitis patients in clinics in Belgium, Denmark, Germany, Spain, Sweden and the UK as well as Australia and Singapore have demonstrated that oxidized linalool is a common contact allergen (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckley, 2011; SCCS, 2012; Christensson *et al.*, 2012).

Costs of allergy

The consequences of allergic contact dermatitis are serious health and economic burdens to the individual and the Community. The direct and indirect costs due to allergens in EU are high. According to Mugford (2004), cited in Wijnhoven *et al.*, (2008), the direct cost incurred due to contact dermatitis in 2003 in Europe was 2.3 billion Euros. Merk *et al.*, (2007) have reported the annual expense in Germany for the treatment and prevention of allergic contact dermatitis to be ca. 3 billion Euros whereas in the Netherlands it was estimated to be ca. 2 billion Euros in 2003. Further, it was stated that the share owed by contact dermatitis in Western Europe was about 20% of the total cost of all allergies (Wijnhoven *et al.*, 2008). The indirect costs are higher.

Self-classification not satisfactory

In the registration dossier for linalool no classification for skin sensitization was reported. In the C & L Inventory only nine of the more than 1600 notifiers have notified linalool as a Skin sensitizer 1. No notifications of the individual isomers as skin sensitisers have been reported. Therefore, due to the high frequency of contact allergy caused by linalool in Europe and the unsatisfactory self-classification of linalool by European industry there is a strong need for a harmonized classification.

A harmonized classification of linalool as a skin sensitizer in sub-category 1A means that consumer products, as well as products not intended for consumers, will be classified and labelled when the concentration of linalool is ≥ 0.1%. The specific labelling for sensitizers on non-classified products will apply from ≥ 0.01%.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1. IDENTITY OF THE SUBSTANCE

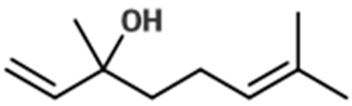
1.1 Name and other identifiers of the substance

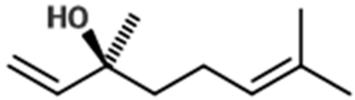
Table 5: Substance identity

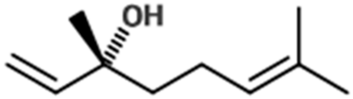
EC number:	201-134-4 [1] 204-810-7 [2] 204-811-2 [3]	
EC name:	Linalool [1] (*S*)-3,7-dimethyl-1,6-octadien-3-ol [2] (*R*)-3,7-dimethyl-1,6-octadien-3-ol [3]	
CAS number:	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]	
CAS name:	1,6-octadien-3-ol, 3,7-dimethyl- [1] 1,6-Octadien-3-ol, 3,7-dimethyl-, (*S*)- [2] 1,6-Octadien-3-ol, 3,7-dimethyl-, (*R*)- [3]	
IUPAC name:	3,7-dimethylocta-1,6-dien-3-ol [1] (3*S*)-3,7-dimethylocta-1,6-dien-3-ol [2] (3*R*)-3,7-dimethylocta-1,6-dien-3-ol [3]	
Annex VI Index number:	Not listed in Annex VI	
Molecular formula:	$C_{10}H_{18}O$	
Molecular weight range:	154.2 g/mol	

Structural formula:

[1]



[2] 

[3] 

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Linalool	97.5% (w/w)	≥96.7 - ≤98.2% (w/w)	Ref. lead reg.

Current Annex VI entry: Not listed in Annex VI of the CLP.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential	≤2.5% (w/w)		The impurities are not considered crucial for classification.

Current Annex VI entry: None of the impurities is listed in Annex VI of the CLP.

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
Confidential	Stabilizer			The additive is not considered crucial for classification. See 4.4.1.3 of CLH report.

Current Annex VI entry: Not listed in Annex VI of the CLP.

1.2.1 Composition of test material

In Table 10 available information on the composition of the test material is given for each study. Commercial grade linalool is usually 97%. In some studies it has been used as such or after redistillation without any information on possible subsequent degree of autoxidation. In other studies linalool has been stabilised to protect from autoxidation. However, the addition of antioxidants has a questionable effect, see 4.4.1.3. In some studies linalool has autoxidised under

controlled conditions and oxidation products have been identified as well as the concentrations of the oxidation products and the remaining linalool.

Regarding the isomeric composition of linalool this information is seldom given. It is not expected to influence the sensitising properties of linalool, see Part A, section 1.1.

Linalool is also a major component of lavender oil. In studies on lavender oil where the linalool concentration was reported it varied from 20% to 40%.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Clear liquid, colourless with floral odour	Registrant	Measured
Melting/freezing point	< -74°C at 993 mbar < -20^0C < 20^0C	Registrant www.wikipedia.org OECD SIDS	Key study. Measured. GLP study according to OECD Guideline 102
Boiling point	198 – 199 °C (760 mmHg); 98 – 98.3 °C (25 mmHg) 86 °C (13 mmHg)	OECD SIDS NTP	Measured Measured
Relative density	0.858 -0.868 g/ml (25°C)	OECD SIDS	Measured
Vapour pressure	~0.2 hPa (23.5°C)	OECD SIDS	Measured
Surface tension	20.969 mN/m (20 °C)	OECD SIDS	Measured
Water solubility	854 mg/l (23.5 °C) – 1589 mg/l (25 °C)	OECD SIDS	Measured
Partition coefficient n-octanol/water (log value)	log P_{OW} = 2.97 (23.5 °C)	OECD SIDS	Calculated
Flash point	77.2°C at 101.3kPa 55^0C	Registrant OECD SIDS	Measured. GLP study according to ISO standard 2719:2002, Pensky-Martens closed cup method.
Flammability	n.e.	n.e.	n.e.
Explosive properties	n.e.	n.e.	n.e.
Self-ignition temperature	260 °C (994 mbar)	Registrant	Referred
Oxidising properties	n.e.	n.e.	n.e.
Granulometry	n.e.	n.e.	n.e.
Stability in organic solvents and identity of relevant degradation products	n.e.	n.e.	n.e.
Dissociation constant	n.e.	n.e.	n.e.
Viscosity	4.465 mPa.s (298.15K)	Registrant	Referred

NTP, National Toxicology Program, USA

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.

2. MANUFACTURE AND USES

2.1 Manufacture

Linalool may be produced by plants or may be chemically synthesised. In the first case over 200 species of plants are known to produce *dl*-linalool, *d*-linalool or *l*-linalool. Chemical synthesis usually gives the racemic *dl*-linalool (OECD SIDS, 2004). The global production for the year 2000 was estimated to be 12000 t where 5400 t were extracted from synthesizing plants and the remaining 6600 t were synthetically produced by the industry. It was estimated that more than 95% of the global production of linalool was used for its fragrance and odorant properties (OECD SIDS, 2004).

Linalool, CAS no 78-70-6, has been registered in a joint submission to ECHA in the tonnage band 10000 – 100000 tons per annum.

2.2 Identified uses

The following product categories (PC) were reported in the registration dossier:

PC1: Adhesives and sealants

PC3: Air care

PC5: Artists supply, hobby preparations

PC8: Biocidal products (e.g. antibacterial/antimicrobial/preservative, disinfectants, pest control)

PC9a: Coatings and paints, thinners, paint removers

PC9b: Fillers, putties, plasters, modelling clay

PC9c: Finger paints

PC18: Ink and toners

PC31: Polishes and wax blends

PC28: Perfumes, fragrances

PC35: Washing and cleaning products (including solvent based products)

PC39: Cosmetics, personal care products

Apart from these uses linalool has been in use in scented clothes, eraser, toys, paper articles and CD.

Linalool was one of the active substances to be examined under the EU review programme for biocidal products (Commission Regulation (EC) 1451/2007). However, later on it was removed from this programme (Commission Decision 2009/324/EC); thus linalool can no longer be used as an active ingredient in biocidal products.

In a recent Danish survey it was documented that linalool concentrations in some cosmetic products have exceeded the recommended limits, being common up till a range of 130-2800 ppm of product (Poulsen and Strandsen, 2011). Linalool has been found in 91% and 90% of the cosmetic and toiletry products in the Netherlands and the USA, respectively (de Groot *et al.*, 1994; Fenn, 1989) and it was in "The Top 10" list of fragrances in both studies. It was found in 135 (92.5%) of the 146 cosmetic products at a concentration range of 223-511 ppm (in sprays) and 9-1927 ppm (in deodorants) in products purchased from markets in Denmark, England, France, Germany and Sweden (Rastogi *et al.*, 1998). In successive studies it was identified in 36 (61%) of the 59 household products analysed in Denmark at concentrations up to 439 ppm (Rastogi *et al.*, 2001); later on it was found in 17 (40%) of 43 detergent products analysed (Rastogi, 2002) and in 190 (63%) of the 300 consumer products sold in the UK (Buckley, 2007). According to Poulsen and Schmidt (2008) analyses of 47 deodorants in Denmark showed that 53.4% of the products contain linalool between 8.2-3447 ppm whereas out of 45 children's cosmetics 21.6% were known to contain the substance at a range of 7-1100 ppm. A study by Glensvig and Ports (2006) of children's articles such as paper, eraser and yellow speed marker found linalool up to a concentration of 3800 ppm. Likewise, in the Netherlands it was quantified in 70% of 16 children's cosmetic products, the content ranging from 63 to 1534 ppm (Wijnhoven *et al.*, 2008). In liquid hand soaps in Denmark it has been found in concentrations over 0.01% (100ppm) and was the most frequently encountered fragrance, being common in 39.5% of the products analyzed (Larsen and Andersen, 2006). Furthermore, based on labels, it was found to be included in 74 (25.4%) of the 291 liquid household detergents in Italy (Magnano *et al.*, 2009) and in 87 (29%) of the 301 cosmetic and detergent products surveyed in Sweden (Yazar *et al.*, 2010). Moreover, apart from its fragrance function in consumer products linalool is included in cosmetics as a preservative as identified and quantified in Danish markets (Poulsen and Strandsen, 2011).

3. CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated.

4. HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, distribution, metabolism and elimination)

Monoterpene fragrances are small chemicals which are known as excellent skin penetrants (Kitahara *et al.*, 1993). They may be used as effective skin penetration enhancers for transdermal drug delivery. This has been extensively documented for linalool in both *in vitro* and *in vivo* studies on human volunteers (Cal *et al.*, 2001; Cal, 2006b; Cal and Krzyzaniak, 2006). Linalool has been found to be fastly absorbed into the stratum corneum and epidermis irrespective of the type of vehicle used (Cal, 2006a). The mechanism of skin penetration is through lipid extraction and disruption (Sapra *et al.*, 2008). Furthermore, linalool has been found to accumulate evenly in the stratum corneum without any elimination or slow rate of drainage into the dermis (Cal and Sznitowska, 2003; Cal, 2006a; Cal and Krzyzaniak, 2006).

Studies on unoxidized versus oxidized linalool have found unoxidized linalool to have a weak or no sensitizing property in different patch test studies. Inconsistent results could be attributed to the use of non-standardized test materials where the purity and identity of the substance does not conform to pure linalool (Brandáo, 1986; Ryan *et al.,* 2000; Basketter *et al.*, 2002). Nevertheless oxidized linalool has been identified as a potent sensitizer in all studies at various concentrations. However, it was difficult to trap the causative agents and separate them from the mixture of oxides (Basketter *et al.,* 2002).

Later on, however, Sköld *et al.,* (2002a,b; 2004) identified the formation of linalool hydroperoxides in the oxidation mixture, formed by autoxidation. Bäcktorp *et al.,* (2006) have further elucidated the mechanism of their formation which was found to involve biradical intermediate formation to initiate autoxidation. Redeby *et al.,* (2010) and Kao *et al.,* (2011) have found that the hydroperoxides can enter the skin intact and get activated by Fe (II)/Fe(III) to form adducts with proteins via a radical mechanism. The formation of adducts via the radical pathway was believed to promote the binding of the hydroperoxides to skin proteins to form antigen structures. These protein-hydroperoxide adducts could thus trigger immunostimulatory effects (Sköld *et al.,* 2004; Christensson *et al.*, 2006; Hagvall *et al.,* 2008; Karlberg *et al.*, 2008; Kao *et al.*, 2011). These experimental studies together with the clinical findings by Sköld *et al.,* (2002a), Matura *et al.*, (2005) and Christensson *et al.,* (2010; 2012) show that the hydroperoxides are the major immunogens in oxidized linalool (Sköld *et al.*, 2002a; 2004).

4.1.1 Non-human information

Linalool is a lipophilic alicyclic monoterpene fragrance with a partition coefficient of P_{ow}=2.97 at 23.5^{0}C as shown in Table 10. As a terpene, it is known to have a very high skin penetrating capacity (Gerberick *et al.,* 2005). Linalool is autoxidized upon contact with oxygen and two stable linalool hydroperoxides have been identified as primary oxidation products, i.e the linalool-7-hydroperoxide (7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol) and linalool-6-hydroperoxide (6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol) (Sköld *et al.,* 2004). The hydroperoxides are small, highly lipophilic prehaptenes. As they penetrate the skin they readily form adducts to skin proteins, such as histidine, through a radical mechanism (Kao *et al.*, 2011). Thus, once the hydroperoxides penetrate the epidermis they form potentially reactive oxygen- and carbon-centred radicals that upon the presence of Fe(II) or Fe(III) interact with proteins. This radical initiation using iron redox cycles is a common biological phenomenon which has been confirmed by *in vitro* studies. They suggest that the same processes could take place *in vivo* as long as the hydroperoxides have the ability to penetrate into the epidermis. This has been demonstrated in patch test studies (Sköld *et al.*, 2002a; Matura *et al.*, 2005; Christensson *et al.*, 2012). The formation of different reactive radical intermediates indicates that different protein modifications with sensitising properties may arise (Kao *et al.*, 2011). The major activation mechanism for linalool so far documented is autoxidation (SCCS, 2011). No epoxides were detected in the oxidized mixtures of linalool (Karlberg *et al.*, 2008). However, it has also been found that enzymatic (metabolic) activation of epoxides, involving CYP2B6 and CYP1A2, 3A4, 2C19, 2E1 and 1A1, to electrophilic oxidation products such as 6,7-epoxy-linalool could be another pathway apart from autoxidation. CYP2B6 has been found to be predominant in epoxy metabolism in human skin among the CYP families which have been identified (Bergström *et al.*, 2007; Merk *et al.*, 2007). The epoxides could be formed in the skin from the hydroperoxides or serve as prohaptens being activated in the skin upon entry, leading to further interaction with proteins to form complexes readily engulfed by the dendritic cells (Meesters *et al.*, 2007; Hagvall *et al.*, 2008).

4.1.2 Human information

The hydroperoxides generated from linalool upon autoxidation are known to form specific antigens which give rise to allergic contact dermatitis (Christensson *et al.*, 2006). Upon exposure to the skin, the hydroperoxides penetrate the cutaneous layer and interact with epidermal proteins to form immunogenic complexes, specific to the allergen, which will induce sensitization. The hydroperoxides could also be further oxidized into epoxides in the skin. The epoxides are suggested to be enzymatically activated to form reactive compounds that interact with proteins. There is no direct absorption of the reactive oxides into the circulation since they bind to cutaneous proteins. Thus, both the hydroperoxides and the epoxides are likely not to be subject to metabolic processing allowing their elimination from the body. The immunogenic complexes will be processed by the dendritic (Langerhan's) cells and presented to the nearest lymph nodes for further presentation to Th1 (T helper) cells to develop memory. Studies have revealed that there is no cross reaction to the sensitization from hydroperoxides as they have specificity to the allergic reaction they cause (Christensson *et al.*, 2006; Meesters *et al.*, 2007; Hagvall *et al.*, 2008).

An *in vitro* study on human endothelial cells and fibroblasts revealed the strong cytotoxic effects of linalool. The mechanism of cytotoxicity was suggested to involve membrane damage (Prashar *et al.*, 2004). This event *in vivo* is known to deplete body antioxidant level and aggravate allergic contact dermatitis by increasing oxidative stress (Redeby *et al.*, 2010). In addition, linalool has been found to increase reactive oxygen species (ROS) formation and decrease glutathione (GSH) enzymes in HepG cells (Usta *et al.*, 2009).

4.1.3 Summary and discussion on toxicokinetics

Linalool is subject to autoxidation in air and the resulting hydroperoxides, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol, have been identified as the main agents responsible for the immunotoxic properties expressed as skin sensitization in humans. Linalool is a lipophilic monoterpene which readily penetrates the human skin and its hydroperoxides have strong affinity towards proteins. The hydroperoxides are small compounds which are ready prehaptanes which upon skin contact can penetrate and travel into the epidermis. They form oxygen radicals while binding to skin proteins and thereby create immunogenic complexes of various forms. They are processed as specific immunogens provoking the immune memory instead of being metabolized directly and eliminated out of the body. The hydroperoxides are thus known to serve as specific antigens causing induction of sensitisation and, upon re-exposure, elicitation. This reaction may eventually be expressed as allergic contact dermatitis (ACD). Epoxides may also contribute to the allergenic properties, though absorbed into the epidermis as intact prohaptens and then activated via Cytochrome P450 to become protein reactive. Later on they are likely to follow a similar immunogenic pathway to induce sensitization.

4.2 Acute toxicity

Not evaluated.

4.3 Irritation

Not evaluated.

4.4 Sensitisation

4.4.1 Skin sensitisation

Table 10 Summary tables of relevant skin sensitization studies

Table 10a. Human Studies

(i) Unoxidized (pure) linalool

Method	Results	Remarks	Reference
Patch test: 985 unselected dermatitis patients tested with 10% stabilized linalool in petrolatum.	2/985 patients (0.2%) had positive reactions.	Interdepartmental multicenter project (IVDK[a]), Germany (2005-2008).	Uter *et al.*, 2010.
Patch test: 320 eczema patients suspected of allergy to fragrances were tested with 10 % linalool in petrolatum (no further specification given).	2/320 patients (0.6%) had positive reactions.	Groningen, The Netherlands (2005-2007).	van Oosten *et al.*, 2009.
Patch test: 2401 consecutive, unselected dermatitis patients were tested with 10% linalool (stabilized) in petrolatum.	7/2401 patients (0.3%) had positive reactions. Pure linalool was believed to become a potent allergen upon oxidation.	The IVDK project, Germany (2003-2004).	Schnuch *et al.*, 2007.
Patch test: 26 perfume fillers suffering from dermatitis were tested with 10% linalool in petrolatum (no further specification given).	4/26 patients (15.4%) were positive to linalool; 2 of these four patients and other two reacted to neroli oil which also contains linalool as a component fragrance.	Site inspection at a perfume factory, Germany (2005). Job change to other rooms without further exposure to the fragrance resolved dermatitis completely.	Shubert, 2006
Patch test: 1825 unselected dermatitis patients tested with 20% linalool in petrolatum (no further specification given).	3/1825 patients (0.2%) were positive.	Multicenter study, The Netherlands (1998-1999).	de Groot *et al.*, 2000.
Patch test: 75 cosmetic allergy patients tested with linalool (concentrations unknown).	3/75 patients (4%) reacted positive to linalool and linalool-containing skin care products. Linalool was a frequent fragrance allergen.	The Netherlands (1981-1986).	de Groot, 1987.
Patch test: 179 cosmetic allergy patients tested with 30% linalool in petrolatum (its stability was checked; after 6 months at least 90% remained).	None of the patients were positive.	The Netherlands, year not stated. The quality of linalool was checked indicating that the test material was really unoxidised.	de Groot *et al.*, 1985.
Patch test: A 52-year old man with facial psoriasis patch tested with 30 % dl-linalool in petrolatum.	Patient was positive.	Case report, The Netherlands (1982).	de Groot and Liem, 1983.

[a]*IVDK, Information Network of Departments of Dermatology in Germany, Austria and Switzerland.*

Table 10a (i) presents human diagnostic patch test data where unoxidised linalool has been tested. In three studies on unselected dermatitis patients the positive patch test frequency was 0.2-0.3%. In three studies on selected groups of patients the positive frequency varied between 0 and 4%. In one work place study the positive frequency was 15%. One positive case report was also available.

(ii) Oxidized linalool/hydroperoxides

Method	Results	Remarks	Reference
Patch test: 2900 consecutive dermatitis patients tested with 6% oxidized linalool (containing 1% linalool hydroperoxides) in petrolatum. At week 25 of air exposure of linalool, which was chosen to calculate the adequate patch test concentration in this study, the concentration of linalool was reduced to 61% and the major hydroperoxide concentration was 14.6% (the major hydroperoxide, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol, was approx. 80% and the minor 20% of the hydroperoxide fraction). The original linalool was commercial grade, 97%, which was further purified by distillation.	200/2900 patients (6.9%; range of 3-13%) had positive reactions. The prevalence for oxidised linalool, 6.9%, places linalool as the most common cause of contact allergy to fragrances.	The study was conducted in nine clinics in Spain, Denmark, Sweden, UK, Australia and Singapore (2010-2011). 6% oxidized linalool in petrolatum (containing 1% linalool hydroperoxides) was proposed as patch test concentration for use in routine screening for contact allergy in dermatitis patients.	Christensson *et al.*, 2012 (key study).
Patch test: 483 consecutive dermatitis patients tested with 3% oxidized linalool in petrolatum (Chemotechnique Diagnostica, Sweden).	11/483 patients (2.3%) showed positive reactions.	Swindon, UK (2007-2010). 3% oxidized linalool was recommended for future testing.	Buckley, 2011 (key study).
Patch test: 3418 consecutive dermatitis patients tested with 2%, 4%, 6% and 11% oxidized linalool in petrolatum. At week 45 of air exposure of linalool, which was chosen to calculate the patch test concentration, the linalool content was reduced to 30% and the major hydroperoxide content was 15%. The original linalool was commercial grade, 97%, which was further purified by distillation.	Positive responses: 14/1693 patients (0.83%) to 2.0%; 67/2075 patients (3.2%) to 4.0%; 91/1725 patients (5.3%) to 6.0%; and 72/1004 patients (7.2%) to 11% oxidized linalool. Clear dose-response relationship was observed. Thus 5-7% of the patients showed positive patch test reactions to oxidized linalool.	Gothenburg and Malmö, Sweden (2006-2007). Linalool was concluded to be one of the most frequent allergens among patch tested patients. The optimal patch test concentration was proposed to be 6% oxidized linalool in petrolatum.	Christensson, 2009; Christensson *et al.*, 2010 (key study).
Patch test: 29 colophonium positive patients tested with 0.5 % linalool hydroperoxides in petrolatum (a 5:3 mixture of 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol).	1/29 patients (3.5%) was positive. Evidence was found for the formation of specific antigens by hydroperoxides.	Gothenburg and Malmö, Sweden (2004).	Christensson *et al.*, 2006 (key study).
Patch test: 1511 consecutive dermatitis patients tested with 2.0% oxidized linalool (w/w)	20/1511 patients (1.3%) were positive to 2.0% oxidized linalool, 16 (1.1%) were	Multicenter study in Copenhagen, Dortmund, Leuven, London, Malmö and	Matura *et al.*, 2005 (key study).

and 0.5% of the hydroperoxide fraction in petrolatum. At week 45 of air exposure of linalool the linalool content was reduced to 30% and the major hydroperoxide content was 16% (the major hydroperoxide, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol, was approx. 83% of the whole hydroperoxide fraction). The oxidation mixture at week 45 was used for patch testing. The original linalool was commercial grade 97%.	positive to 0.5% hydroperoxide fraction.	Odense (2002-03). Oxidized linalool was found a frequent allergen in Europe.	

Table 10a (ii) presents human diagnostic patch test data, where patch testing has been performed with oxidized linalool or the hydroperoxide fraction of oxidized linalool. In four studies on unselected dermatitis patients the positive patch test frequency for oxidized linalool was 0.83 - 7.2%. For the hydroperoxide fraction the positive patch test frequency was 1.1% in one study with unselected patients and raised to 3.5% in a selected group. The studies are key studies that have demonstrated the increased positive patch test frequency of oxidized linalool as compared to the unoxidised form. The allergenicity of the major oxidation product of linalool, the hydroperoxide fraction, was also demonstrated.

(iii) Lavender oil and other linalool-containing products

Method	Results	Remarks	Reference
Patch test: 3 patients with known positive patch test reactions to oxidized linalool were tested with oxidized linalool (4%, 2%, 1%, 0.5%); mixture of linalool hydroperoxides (1%, 0.75%, 0.5%, 0.25%, 0.12%, 0.06%); oxidized lavender oil 4%; and oxidized linalyl acetate 4%, all in petrolatum. (Original linalool was commercial grade, 97%.)	All 3 patients had positive reactions to oxidized linalool and oxidized lavender oil. 1/3 patients had positive reaction to oxidised linalyl acetate. 2/3 patients had positive responses to the linalool hydroperoxide mixture. Unoxidised lavender oil contained 36-39% linalool. After 10 weeks the linalool content was 28-30% and after 45 weeks 5%. There was evidence, together with animal data, that the lavender oil is just as prone to autoxidation with formation of allergens as is the pure linalool.	Gothenburg, Sweden (2006-2007). Connections shown between allergenicity to oxidized linalool and oxidized lavender oil.	Hagvall *et al.*, 2008
Patch test: 1483 dermatitis patients suspected of having cosmetics contact dermatitis were tested with 20% lavender oil in petrolatum between 1990 and 1998 together with 9 other cosmetic fragrances. (No information on linalool content was given.)	The rates of positive patch test reactions to lavender oil increased from 1.1% in 1990 to 13.9% in 1998 (mean 3.7%) in 9 years. None of the other 9 fragrances had corresponding increase over time. Extended use of lavender oil in aromatherapy as a fashion in 1997 caused a sudden increase.	A 9-years Japanese patch test study (1990-1998). During the 1990s aromatherapy using lavender oil became a new trend in Japan.	Sugiura *et al.*, 2000
Patch test: A 71-year old woman with a facial eczema patch tested with lavender absolute (2% pet., Chemotechnique).	Patient reacted positive on days 2 and 4. Dermatitis resolved permanently when use of the oil was abandoned and the pillow replaced.	Case report, UK (1999). The patient was using lavender oil drops on her pillow.	Coulson and Kahn, 1999.
Patch test: A 76-year-old retired male physician with a unilateral right-sided facial dermatitis patch tested with lavender absolute (2% pet., Chemotechnique).	Patient was positive on days 2 and 4. Avoidance of the oil resolved the dermatitis.	Case report, UK (1999). The patient had been using lavender oil to his pillow for ease of relieving problems of insomnia.	Coulson and Kahn, 1999.
Patch test: A 32-year-old female aromatherapist with hand eczema tested with lavender absolute (2% in pet.; >20% linalool) and several other oils, perfumes and cosmetic products.	Patient was positive to lavender oil, Bulgarian rose oil, cananga oil, ylang ylang, clary sage and facial lotion. These products had linalool as a common component: Bulgarian rose oil contained 1.5-2.7% linalool whereas the others contained >20% linalool. Dermatitis improved when	Case report, UK (1997). The patient did aromatherapy massages and facial treatments with essential oils.	Cockayne and Gawkrodger, 1997.

	patient was off work.		
Patch test: A 53-year old patient with relapsing eczema patch tested with lavender oil 1%, rosewood oil 1%, jasmine oil 1% and linalool 2%, all in petrolatum. 10 controls were also patch tested. (No information on linalool content of lavender oil was given.)	Patient reacted positive to all of the essential oils and linalool; linalool was the common component in the three oils. The 10 controls were negative to all four test materials.	Case report, Germany (1994). Patient practised aromatherapy with lavender oil baths and used lamps for evaporation of oils. The ACD appeared to be airborn. Complete renewal of the interior of patient's flat was the last solution to resolve the dermatitis.	Schaller and Korting, 1995.
Patch test: An 18-year old female hairdresser with severe allergic contact dermatitis from daily use of lavender oil shampoo (exact composition unknown) was tested with 5% of the shampoo in water and lavender oil 1% in ethanol.	In both cases she had strong positive responses. The patient was negative to geraniol.	Case report, Portugal (1985).	Brandáo, 1986.

Table 10a (iii) shows the sensitizing properties of lavender oil, where linalool is a major component. Autoxidation was shown by Hagvall *et al.*, (2008) to be a common feature of linalool and lavender oil. Sensitising properties increased along with time of air exposure, as demonstrated in animal experiments (see Table 12b). The study by Sugiura *et al.*, (2000) demonstrated the increase in prevalence of ACD as a result of the sudden expanded use of aromatherapy with lavender oil in Japan. Five case studies are reported with positive patch test reactions to lavender oil. With complete avoidance of lavender oil in three cases the skin problems resolved.

Table 10b. Animal Studies

Method	Result	Remarks	Reference
LLNA[d] using pure linalool (commercial grade 97%); LLNA conducted according to Kimber *et al.*(1995). *Toxicology* 103, 63-73.	Pure linalool was not sensitizing; the EC3[e] was 46.2%. After 10 weeks' air exposure of linalool the EC3 was reduced to 9.4% and after 45 weeks' air exposure the EC3 was further reduced to 4.8% indicating that oxidation products are responsible for the allergenic properties. The two hydroperoxides 7-hydroperoxy-3, 7-dimethylocta-1, 5-diene-3-ol and 6-hydroperoxy-3, 7-dimethylocta-1, 7-diene-3-ol were identified as the main allergens of the oxidation products. A 5:3 mixture of them gave an EC3 of 1.6%. It was demonstrated that after 10 weeks of air exposure linalool was reduced to 75% and the two main hydroperoxides were increased to 5%. After 45 weeks the linalool content had gone down to 30% and the hydroperoxides increased to 19%.	The sensitizing potential of oxidized linalool increased with air exposure; the hydroperoxides being the main allergens.	Sköld *et al.*, 2004 (key study).
Freund's complete adjuvant test (FCAT) using linalool (commercial grade 97%, which was purified) and oxidized linalool (air exposed for 10 weeks). FCAT conducted according to Boman *et al*. (1988). *Contact Dermatitis* 18, 25-29.	In the experiment with purified linalool no sensitization occurred. For oxidized linalool a significant response was obtained at the following challenge concentrations: 2.6% (5/15 animals, 33.3%), 5.1% (8/15 animals, 53.3%) and 10.3% (13/15 animals, 86.7%); no significant response was recorded for 1%. The intradermal induction concentration was 5.1%. At re-challenge, 5 of the control animals gave positive results to 10.3% oxidized linalool suggesting that they became sensitized at first challenge. The 10 weeks' oxidized linalool contained approx. 80% linalool.	15 animals each were used for test and control. Minimum criterion for a positive reaction was confluent erythema.	Sköld *et al.*, 2002a (key study).
LLNA using lavender oil; LLNA conducted according to Kimber *et al.*(1995). *Toxicology* 103, 63-73.	Linalyl acetate, linalool and β-caryophyllene were major constituents in lavender oil (50%, 36%, and 2%, respectively in one of the batches). Lavender oil is prone to autoxidation (linalool content 28% and 5% after 10 and 45 weeks, respectively) and build-up of oxidized products with time (0.48% linalool hydroperoxides after 10 weeks, no quantification performed at 45 weeks). In LLNA EC3-values decreased with time; from 36 for pure lavender oil to 11 after 10 weeks' air exposure and further to 4.4 after 45 weeks. A synthetic mixture of the three major components of lavender oil with the same concentration ratio as in lavender oil, autoxidized as lavender oil and had an EC3 of 14% after 10 weeks'	Lavender oil autoxidizes in air and becomes a more potent allergen.	Hagvall *et al.*, 2008

	air exposure, thus comparable to lavender oil.		
LLNA using commercial grade 97% linalool and redistilled linalool; LLNA conducted according to Kimber and Basketter (1995) *Food Chem Toxicol* 30, 165-169.	Commercial grade linalool was a weak skin sensitizer with an EC3 of 30%. Purification by re-distillation reduced the potency, giving an EC3of 55%. Linalool and dihydrolinalool[f] which are present in distilled linalool were not protein-reactive. Formation of reactive species by autoxidation or metabolic activation or both were believed to be the cause of the allergenicity of linalool.	Autoxidation or metabolic activation or both were suggested as factors responsible for converting linalool to a sensitizer.	Basketter *et al.*, 2002.
LLNA using commercial grade (97%) linalool; LLNA conducted according to a standard protocol as described in the study.	Commercial grade linalool induced sensitization when diluted to 50% and at 100% concentrations with an SI of 4.8 and 8.3, respectively.	The causative agents suspected were oxidation products (impurities). EC3 value not given.	Ryan *et al.*, 2000.

[d]LLNA: Local Lymph Node Assay; [e]EC3, the estimated concentration of a chemical required to produce a 3-fold increase in lymph node proliferative activity in comparison with vehicle-treated controls; [f]dihydrolinalool, a major impurity in commercial linalool 1.92% by weight).

Table 10b presents available animal studies on linalool, oxidized linalool and lavender oil in LLNA and FCAT. EC3 values of 46.2% and 30% were demonstrated for pure linalool; 55% for redistilled linalool. However, sensitisation increased with time of air exposure as shown by the decline of the EC3 values; 9.4% and 4.8% after 10 weeks and 45 weeks of air exposure, respectively. The 45 weeks' air exposure had the highest potency and accumulation of oxidation products. A mixture (5:3) of the two major oxidation products, the hydroperoxides, had an EC3 value of 1.6%, indicating their strong sensitising capacity. Lavender oil had an EC3 of 36%, decreasing to 11% after 10 weeks of air exposure and to an EC3 of 4.4% after 48 weeks. Thus linalool and lavender oil are equally susceptible to autoxidation and similar oxidation products are formed. In FCAT oxidized linalool sensitized 33 to 87% of the animals, depending on the challenge concentration.

Table 10c. In vitro studies

Method	Results	Remarks/Comments	Reference
Linalool, linalyl acetate, and lavender oil were tested on survival of human skin cells (HMEC-1[g], HNDF[h], and 153 BR[i])	Linalool (>0.044%), linalyl acetate (>0.064%) and lavender oil (>0.125%) were cytotoxic to all cell types in a dose-dependent fashion. Linalool had a similar pattern of activity as lavender oil, suggesting linalool to be the active component of lavender oil.	Membrane damage was the proposed mechanism for cytotoxicity.	Prashar *et al.*, 2004
20 fragrances including linalool were tested for their effects on survival of human liver cells (HepG2).	Linalool at 0.4 µM affected viability in 50% of the cells while 2 µM caused 100% death of the cells; linalool was the most potent among the 20 fragrances tested. Linalool's effects on mitochondria were dose-dependent and affected ATP[j] and GSH[k] levels and increased ROS[l] production.		Usta *et al.*, 2009

[g]HMEC-1, endothelial cells; [h]HNDF, fibroblasts; [i]153 BR, fibroblasts; [j]ATP, Adenosine triphosphate; [k]GSH, Glutathione; [l]ROS, Reactive oxygen species.

Table 10c presents a dose-dependent pattern of cytotoxicity to human endothelial cells, fibroblasts (skin cells) and human liver cells *in vitro* for linalool, linalyl acetate and lavender oil.. The major active component in lavender oil was presumably linalool. Linalool was found to be the most toxic fragrance of 20 fragrances tested on human liver cells *in vitro.*

4.4.1.1.Non-human information

Five animal studies on pure (unoxidized) linalool, oxidized linalool, unoxidised lavender oil and oxidized lavender oil are described in Table 10b. Two of them are key studies as they are of high quality and as they clarify the association between autoxidation of linalool and increased sensitizing potential.

Pure linalool is not sensitising, or a weak sensitizer, as demonstrated by its high EC3 value, 46.2%. However, linalool is autoxidized when exposed to air. Air-exposed samples of linalool showed clear positive responses in LLNA (Local Lymph Node Assay); EC3 was reduced to 9.4% after 10 weeks' and to 4.8% after 45 weeks' air exposure of linalool.

In FCAT (Freund's Complete Adjuvant Test) 33-87% of the animals became sensitised to oxidised linalool. The primary oxidation product was the hydroperoxide, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol. FCAT is a guinea pig test using adjuvans. It is comparable to OECD Test Guideline 406, Guinea Pig Maximisation Test, in sensitivity.

A 5:3 mixture of the two major hydroperoxides, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol, in oxidised linalool had an EC3 value of 1.6%, indicating a strong sensitising capacity.

The major hydroperoxide, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol, was 80% of the total content of the hydroperoxide fraction; the rest percentage comes from the other minor hydroperoxide and furan oxides, pyranoxides, linalool alcohols and minute level of linalyl aldehyde (Matura *et al.*, 2005; Christensson *et al.*, 2012). The linalool hydroperoxides have been found to form specific antigens (Sköld *et al.*, 2002; Sköld *et al.*, 2004; Christensson *et al.*, 2006; Hagvall *et al.*, 2008; Karlberg *et al.*, 2008; Kao *et al.*, 2011). The aldehyde was found to be a moderate sensitizer whereas the alcohols, furan oxides and pyranoxides had no significant sensitizing potentials when tested in FCAT (Bezard *et al.*, 1997). Ryan *et al.*, (2000) and Basketter *et al.*, (2002) have observed reactivity with commercial linalool in the LLNA. They referred the inherent

activity to the oxidation products although they haven't detected them. Sköld *et al.*, (2004) have later on identified and demonstrated that linalool hydroperoxides are the strongest sensitizers in oxidized linalool. It was also shown that the sensitizing potential of the oxidized linalool is dependent on the time of air exposure along with the formation of hydroperoxides.

Hagvall *et al.*, (2008) have shown that lavender oil which contains linalool is not capable of self-protecting from autoxidation although there are naturally occurring antioxidants. Upon exposure to air the sensitizing potential of lavender oil was found to increase with time; an EC3 value of 36% decreased to 4.4% after 45 weeks. The major cause of the increased allergenic effect was the formation of hydroperoxides on air exposure.

In vitro studies on human skin and liver cells, see Table 10c, have shown the cytotoxic effects of linalool and lavender oil (Prasher *et al.*, 2004; Usta *et al.*, 2009). The major active component in lavender oil was found to be linalool. The mechanisms of cytotoxicity leading to cell lethality in the liver cells have revealed that linalool causes depletion of ATP production and glutathione (GSH) availability besides generating reactive oxygen species (ROS) in the mitochondria. Membrane damage was the proposed mechanism of cytotoxicity in human skin cells.

4.4.1.2.Human information

The human studies reported are diagnostic patch test studies. Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists. Studies of diagnostic patch testing is usually reported as positive patch test frequencies, e.g. number of patients having a positive patch test result in relation to the total number of patients tested, as well as the percentage of positives. It is important to note how patients or individuals have been selected for patch testing; if all patients at a clinic with suspected ACD are patch tested they are often called *consecutive* patients at the clinic. Sometimes more *aimed* patch testing is performed among patients from a certain work environment or where exposure to certain groups of allergens, such as preservatives, fragrances or pigments, is suspected. In aimed patch testing the frequency of positive patch test results is usually higher than among consecutively tested patients at a clinic. This needs to be considered when evaluating the results.

In studies chosen to be key studies the selection of tested individuals as well as the number of tested individuals is reported, the test substance is characterised and patch testing has been conducted according to international standards. International standards include standardisation of the application of patches, the reading of reactions and the interpretation of results.

<u>Unoxidized (pure) linalool</u>

Table 10a (i) describes eight patch test studies on unoxidised linalool. These studies show diagnostic patch test data from consecutive dermatitis patients from different European clinics (Germany, Austria and The Netherlands), from patients with known allergy to cosmetics, from a work place study as well as from a case report. Three of the studies were multicentre studies. The patch test concentrations used in them were 10% and 20%. The rate of positive patch test reactions was 0.2%-0.3% among consecutive dermatitis patients (Schnuch *et al.*, 2007; Uter *et al.*, 2010; de Groot *et al.*, 2000). Among patients with suspected cosmetics allergy 0-4% were patch test positive to linalool (van Oosten *et al.*, 2009; de Groot *et al.*, 1987; de Groot *et a*l., 1985) . In a work place study 15% of perfume fillers were patch test positive (Schubert, 2006). The higher rates of positive patch tests could be expected when there has been a selection of individuals for patch testing, such

as patients with suspected cosmetics allergy or workers in the cosmetics manufacturing industry. There is a case report with positive patch test to linalool (de Groot and Leim, 1983).

The studies presented show that the rate of positive patch test reactions in patients is lower for unoxidised linalool than for oxidised linalool.

Oxidized linalool

Five key studies, presented in Table 10a(ii), have identified oxidized linalool as a human skin sensitizer.

Autoxidation of linalool has been found to increase skin sensitization (Christensson, 2009). The major allergenic components are the hydroperoxides that accumulate after oxidation; they were identified as strong skin contact allergens to humans (Kao *et al.*, 2011; Christensson *et al.*, 2012). The aldehydes have also been identified to have skin sensitizing effects. This knowledge has been demonstrated by clinical findings. As shown in Table 12a (ii) a recent multicentre study in Sweden has shown 7.2% and 5.3% positive responses in 1004 and 1725 dermatitis patients tested with 11% and 6% oxidized linalool in petrolatum, respectively (Christensson, 2009; Christensson *et al.*, 2010). Buckley (2011) in the UK found positive patch test reaction among 2.3% of 483 dermatitis patients to 3% oxidized linalool in petrolatum. In a former multicentre clinical study that comprised 1511 patients in five European countries 1.3% of the patients were patch test positive to 2% oxidized linalool and 1.1.% of the patients were patch test positive to 0.5% of the hydroperoxide fraction (Matura *et al.*, 2005). In a recent international study involving 2900 dermatitis patients at nine centres in six countries Christensson *et al.*, (2012) demonstrated that the patch test positive rate was even increased to an overall prevalence of 6.9% (range 3-13%) as compared to the previous report 5.3% prevalence for the same 6% oxidized linalool used (Christensson, 2009; Christensson *et al.*, 2010). This rate is the highest rate ever recorded for an individual fragrance allergen. In a selected group of patients 3.5% of the patients were patch test positive to the hydroperoxide fraction, 0.5% (Christensson *et al.*, 2006).

Table 10 a (iii) presents two patch test studies from Europe and Japan and five case reports mainly on oxidized linalool, lavender oil and other products. Linalool has been identified as one of the main components in lavender oil (35-40%). An association between the allergenic properties of oxidized linalool and oxidised lavender oil was identified by Hagvall *et al.*, (2008). It was also verified, in combination with animal data, that lavender oil lacks protection against oxidation and that hydroperoxides are the major allergens.In a 9-years' study in Japan Sugiura *et al.*, (2000) reported an annual increase in the incidence of positive patch tests to lavender oil among patients suspected to have cosmetics allergy, from 1.1% in 1990 to 13.9% in 1998. A sudden steep increase in 1997 was concomitant with a marked increase of aromatherapy with lavender oil in Japan. A similar increase for nine other fragrances (linalool not included) was not observed. Five case reports demonstrate the relationship between the use of oxidized linalool in lavender oil or in other products and ACD and the following resolution of skin problems with avoidance of use.

4.4.1.3.Summary and discussion of skin sensitization

Linalool is labile to autoxidation while being exposed to air. Thus autoxidation is an inherent property of linalool. In its oxidized form it is a skin sensitizer, the hydroperoxides being the main agents initiating the allergic reaction in skin through radical mechanisms. The radical formation turns to deplete the antioxidant reserve in the skin so that further oxidative stress will continue and

sensitization progress will be aggravated. The result of the scenario has been well described in animal and human patch test studies.

The formation of hydroperoxides upon air exposure of linalool has been studied with the purpose to standardise the oxidised linalool for human patch testing and for the LLNA assay. Thus, after 10 weeks' air exposure of linalool the linalool content was reduced to 75% and the major hydroperoxide, 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol, was 4% (Sköld *et al*., 2004). After 25 weeks' air exposure the linalool content dropped to 61% and the major hydroperoxide was 15% (Christensson *et al.*, 2012). After 45 weeks the linalool content was 30% and the major hydroperoxide 15% (Christensson *et al.*, 2010). The major hydroperoxide constituted approximately 80% of the whole hydroperoxide fraction (Matura *et al*., 2005; Christensson *et al.*, 2012). .

Sometimes antioxidants are added to linalool in order to protect from autoxidation. However, even if this should be the case the addition of antioxidants do not appear to protect against autoxidation as demonstrated by the high prevalence of contact allergy to oxidized linalool in Europe. The preventive effect of antioxidants in terpenes was found to be hard 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. There are also studies showing some preservatives and antioxidants (such as α-tocopherol, vitamin E) themselves to be skin sensitizers and being able to promote the sensitizing property of the allergen in question (Bazzano *et al.*, 1996; Kohl *et al.*, 2002; Matsumura *et al.*, 2004; Biebel and Warshaw, 2006; Yazar *et al.*, 2010; SCCS, 2012). Studies on lavender oil have shown that linalool readily autoxidizes at the same rate when pure linalool or lavender oil, which contains 35-40% linalool, is exposed to air revealing the negligible effect of natural antioxidants that may be present in lavender oil (Hagvall *et al*,. 2008).

For pure linalool the reported frequencies of contact allergy in consequtively tested patients in European clinics have been 0.2%-0.3% (de Groot *et al.*, 2000; Schnuch *et al.*, 2007; Uter *et al.*, 2010). Corresponding frequencies for oxidized linalool were 0.83%-7.2% (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckley, 2011; Christensson *et al.*, 2012); thus the substance has been demonstrated to be a major cause of contact allergy in humans, especially in its oxidized form. The SCCS concluded in its opinion on fragrances (SCCS, 2012) that linalool in its oxidized form is 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. It was emphasized by the SCCS that the up to 1000 reported cases are only those cases that were published in scientific literature; thus it must be anticipated that the number of cases in the population is much higher.

Furthermore, from available epidemiological evidences it was extrapolated that the reported frequency of 5-7% of allergy to oxidized linalool in dermatitis patients corresponds to a prevalence of about 2% of the general population in Sweden: making it the third most important skin sensitizer following nickel and cobalt (Christensson, 2009; http://www.medicalnewstoday.com/releases/144041.php).

Regarding reported frequencies of contact allergy and case reports, it should be noted that they reflect what has been tested. As linalool is neither included in the baseline series for patch testing, nor in the Fragrance mix I or II it should be expected that a number of cases are not diagnosed and that the underestimation of the prevalence in the population is severe. Another source of missing cases is that patch testing has been conducted with pure linalool, which may not diagnose allergy to oxidized linalool. This has been demonstrated in the recent international study by Christensson *et al.*, (2012) where by using oxidized linalool in patch testing they have identified a large proportion of the patients that should have been missed by using pure linalool. According to Chemotechnique

Diagnostics AB, Malmö, Sweden (personal communication), patch test material with linalool hydroperoxides was not on the market until the beginning of 2012.

There are examples of other substances which have been assigned harmonized classifications as skin sensitizers due to the intrinsic property to autoxidise in air under the formation of potent skin sensitizing oxidation products. The pure substance itself is not, or only weakly sensitizing. Limonene is a fragrance terpene, similar to linalool, which autooxidizes to become a more potent sensitizer. In the same way rosin becomes sensitizing when exposed to air. Both have been assigned a harmonized classification as Skin Sensitizer 1 and R43, respectively. Similarly, linalool, which in the same way will be autoxidized to a potent sensitizer when exposed to air, should be assigned a harmonized classification as a skin sensitizer.

In the LLNA pure linalool was a weak sensitizer with an EC3 of 46.2% (Sköld *et al.*, 2004). However, after air oxidation the sensitizing properties increased as demonstrated by the same authors. After 45 weeks' air exposure the EC3 value was 4.8%. A mixture of the two major hydroperoxides, which were found to be the main allergens in oxidized linalool, had an EC3 of 1.6%. The hydroperoxides constituted 5% of the oxidised linalool after 10 weeks' of air exposure and 19% of the oxidized linalool after 45 weeks of air exposure. The content of unoxidized linalool was 75% after 10 weeks' air exposure and dropped to 30% after 45 weeks. The remaining percentage comes from the other oxidation products. Further, the same study has shown that only 4% of linalool remained unoxidized after 80 weeks of air exposure.

In FCAT oxidized linalool sensitized 33-87% of the animals, depending on the challenge concentration (Sköld *et al.*, 2002). Due to the test protocol with fixed intradermal induction concentrations, in this case 5.1%, it is not possible to conclude whether linalool is a strong sensitiser or not. However, the sensitivity of FCAT is comparable to that of the GPMT (Guinea Pig Maximisation Test) and the proportion of sensitised animals in FCAT was high. For comparison with GPMT, according to the criteria for sub-category 1A in the CLP at least 30% of the animals should be sensitised in GPMT at an intradermal induction concentration of 0.1% or less; or at least 60% of the animals at an intradermal induction concentration more than 0.1% but not more than 1%. Therefore it cannot be excluded that, based on the FCAT data, linalool is a strong sensitiser.

Guidance on the Application of the CLP Criteria

In Guidance on the Application of the CLP Criteria (version 4.0) November 2013 extensive guidance on how to evaluate human data for classification and subcategorisation of sensitisers has been introduced. Human data mainly originate from diagnostic patch testing, thus guidance is provided on how to use these data for classification purposes.

The following guidance values are given for categorizing sensitisers in sub-category 1A, based on human diagnostic patch test data and exposure data. For comparison, the actual values for linalool, oxidized linalool and the hydroperoxides are given in italics in the shadowed columns.

Human diagnostic patch test data	**Frequency, guidance values for sub-cat. 1A**	***Frequencies according to CLH proposal***		
		linalool	***oxidized 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%*
Work place 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	*100-1000 (SCCS, 2012)*		

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 sensitizer)	< 100 exposures (score 0)	≥100 exposures (score 2)	*anticipated score 2*

An additive exposure index of 1-4 equates to low exposure. For linalool the exposure index would be a maximum of 4, thus low exposure.

Taken together linalool meets the guidance values for being a sub-category 1A sensitizer.

4.4.1.4.Comparison with criteria

(i) Linalool is autoxidized when exposed to air, giving oxidation products with increased sensitizing properties. Thus linalool should be classified as a skin sensitizer according to Annex I, section 3.4.2.2 of the CLP Regulation (1272/2008/EC). The criteria in Table 3.4.2 states that if there is "evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons or if there are positive results from an appropriate animal test", then the substance shall be classified as a skin sensitizer.

<u>The following human and animal data meet the criteria for classification of linalool as a skin sensitizer:</u>

Human data

- Diagnostic patch test data, obtained from over eight dermatology clinics in Europe, showing positive patch test reactions to oxidized linalool in 0.83-7.2% of consecutively tested dermatitis patients (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckley, 2011; Christensson, *et al*, 2012);

- 1.1% of 1511 consecutively tested dermatitis patients and 3.5% of 29 selected patients were patch test positive to the hydroperoxide fraction of oxidized linalool (Christensson *et al*, 2006; Matura *et al.*, 2005); and

- 0.2%-0.3% of consecutively tested dermatitis patients were patch test positive to pure linalool in clinical studies (Uter *et al.*, 2010; Schnuch *et al.*, 2007; de Groot *et al.*, 2000) and 0-4% of selected patients were patch test positive to pure linalool (de Groot *et al.*, 1985; de Groot, 1987; van Oosten *et al.*, 2009). 15% of selected workers were patch test positive in a work place study (Shubert, 2006).

- Sensitization to linalool was also demonstrated by sensitization to oxidized lavender oil, one of its major components being oxidized linalool (Hagvall *et al.*, 2008); and

- a dramatic increase of sensitization to lavender oil was noted in Japan, from 1% to 14%, during the late nineties. It could be related to a concomitant marked increase of the use of specific products containing lavender oil (Sugiura *et al.*, 2000).

Animal data

- In the LLNA the EC3 value for linalool decreased with time of air exposure, demonstrating increased sensitizing potential. The EC3 value of pure linalool was 46.2% and after 45 weeks of air exposure 4.8%. The decrease in EC3 with time was due to the concomitant increase of allergenic hydroperoxides (Sköld *et al.*, 2004);

- a corresponding decrease of EC3 values in LLNA for lavender oil, with linalool as a major component, was noted when exposed to air. Pure lavender oil had an EC3 of 36%, while it decreased to 4.4% after 45 weeks of air exposure. A concomitant increase of hydroperoxides was demonstrated at 10 weeks (Hagvall *et al.*, 2008); and

- in FCAT oxidized linalool sensitized 33-87% of the animals, depending on the challenge concentration (Sköld *et al.*, 2002a).

  Classification as a skin sensitiser is also supported by the following evidence: the EC3 value in LLNA for a 5:3 mixture of the most potent oxidation products of linalool, the hydroperoxide fraction, was 1.6% (Sköld *et al.*, 2004).

(ii) According to table 3.4.2 “substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans”. Such substances shall be classified in sub-category 1A.

<u>The following human and animal data meet the criteria for classification of linalool in sub-category 1A:</u>

- Diagnostic patch test data, obtained from several dermatology clinics in Europe, showed positive patch test reactions to oxidized linalool in 0.83-7.2% of consecutively tested dermatitis patients (Matura *et al.*, 2005; Christensson, 2009; Christensson *et al.*, 2010; Buckley, 2011; Christensson *et al.*, 2012). These frequencies exceed the guidance values given in the CLP guidance for subcategory 1A;

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

- up to 1000 case reports are published in scientific literature, though being subject to a severe underestimation of the real number of cases in the population. The number of cases exceeds the guidance value given in the CLP guidance for sub-category 1A.

Sub-category 1A is also supported by the following evidence: the EC3 value for a 5:3 mixture of the hydroperoxide fraction of oxidized linalool is 1.6% in the LLNA; moreover, 33%-87% of the animals were sensitized to oxidised linalool in the FCAT. These results do not exclude to refer linalool to sub-category 1A, see discussion under 4.4.1.3.

(iii) According to 3.4.2.2.2.1 human evidence for sub-category 1A can include "diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population or other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure".

The following data on exposure to linalool are evidence for the relatively low exposure of consumers to linalool:

- 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. 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. Taken together the exposure score for linalool is 4, which indicates low exposure according to the CLP Guidance.

4.4.1.5.Conclusions on classification and labelling

Linalool has the intrinsic property to autoxidize in air, making it a potent sensitizer. Therefore, it should be classified as a skin sensitizer based on human and animal data. It should be referred to sub-category 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. Sub-category 1A is also supported by animal studies on the oxidation products of linalool.

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.

<u>Human Data</u>

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: 3) all or randomly selected workers 4) 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	< 100 exposures	≥100 exposures	*anticipated score 2*

(irrespective of concentration of sensitiser)	(score 0)	(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)

The 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.

Additional key elements

Autoxidation procedure used in the literature

In the CLH report, 6 studies are using oxidised linalool in human patch test studies and 2 studies are using oxidised linalool as the test material in LLNA test in mice. The identity of the "oxidised linalool" used in each experiment and the experimental conditions used to prepare it are described below and summarised in a table below. It is the RAC's opinion that oxidised linalool is an artificial test material rather than a commercially available substance.

Matura et al., 2005

Preparation

To mimic the oxidation that takes place during handling and storage, linalool was air exposed in Erlenmeyer flasks, covered with aluminium foil to prevent contamination. It was stirred for 1 h, 4 times a day, as previously described.

Composition

A difference in the oxidation rates among the terpenes tested was found:
myrcene = caryophyllene > linalool.
The oxidised linalool was found to contain 30% linalool and 16% linalool hydroperoxide (7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol)
Oxidised samples of linalool (air-exposed for 45 weeks) were stored under nitrogen at –20°C, until test preparations were made.

Christensson *et al., 2010*

Preparation

According to Karlberg *et al.*, 1992 and Sköld *et al.*, 2004

Composition

After 45 weeks, the oxidation mixture of linalool contained only 30% linalool. At this time, the main oxidation products in the oxidation mixture were highly sensitising linalool hydroperoxides and non-sensitising ethers. At 45 weeks, the oxidation mixture contained 19% linalool hydroperoxides (15% of 7-hydroperoxy-3,7- dimethylocta-1,5-diene-3-ol and 4% of 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol), 20% of 2-(5-methyl-5-vinyltetrahydrofuran-2-yl) propan-2-ol and less than 4% of 2,2,6-trimethyl-6-vinyltetrahydro-2*H*-pyran-3-ol. It also contained 2,6-dimethylocta-3,7-diene-2,6-diol, 2,6-dimethylocta-1,7-diene-3,6-diol and 6-

hydroxy-2,6-dimethylocta-2,7-dienal .

Buckley, 2011

Hydroperoxides of linalool 2% in pet. (Petrolatum). MSDS Chemotechnique Diagnostics, Vellinge, Sweden

Christensson *et al.,* 2006

Preparation

Sköld *et al.* 2004

Composition
5:3 mixture of 7-hydroperoxy-3,7-dimetylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimetylocta-1,7-diene-3-ol.

Christensson *et al.,* 2009

Preparation

As in Nilsson *et al.* 1996. In Nilsson *et al.* 1996 reference to Karlberg *et al*., 1992 is made for the auto-oxidation procedure applied for limonene (room temperature and day-light).

Composition

After 45 weeks, the oxidation mixture of linalool contained only 30% linalool. At this time, the oxidation mixture contained 19% of linalool hydroperoxides.

Christensson *et al.,* 2012

Preparation

As in Karlberg *et al*., 1992 and Sköld *et al*., 2004

Composition

A maximum concentration of the major hydroperoxide (7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol) was observed in the oxidation mixture from about 20 weeks until 45 weeks of air exposure. After this time point, the degradation was the dominant process, and the concentration of hydroperoxide decreased. For the present study, a time point of 25 weeks was chosen, at which time the concentration of linalool was 61% and that of the major hydroperoxide was 14.6%. The concentration of remaining linalool in the oxidation mixture in the present study is twice as high as in oxidation mixtures previously used for patch

Sköld *et al.,* 2002

Preparation

Linalool sample was stirred in a flask (the top was covered with parafilm to prevent contamination and to reduce evaporation) *at room temperature* for 1h, 4 x / day, as previously described (Karlberg *et al*., 1992).

Composition

Linalool air-exposed for 10 weeks was used in the sensitisation experiment. During the 10-weeks period of air exposure, the amount of linalool decreased to about 80%. The GC analyses of the oxidised linalool revealed a complex mixture of compounds which was shown to contain alcohols and hydroperoxides. One of the major oxidation products was isolated from the oxidation mixture by flash chromatography and identified, using ^{1}H and ^{13}C NMR, as 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol **.**

Sköld *et al.,* 2004

Preparation

Linalool was air-exposed in an Erlenmeyer flask covered with aluminum foil to prevent contamination. It was stirred for 1 h, four times a day for 80 weeks, as previously described.

Composition

After about 30 weeks, 50% of the original compound was consumed, and after 80 weeks only about 4% remained (*cf.* figure below).

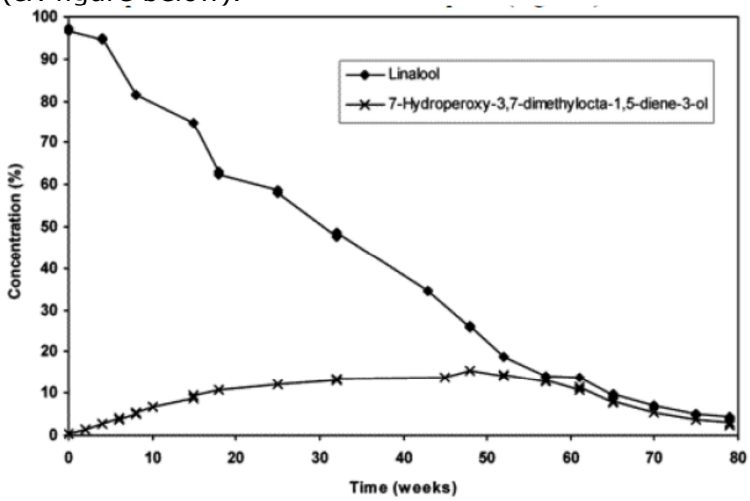


Figure A1: Concentrations of linalool and the major hydroperoxide (7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol) in air-exposed linalool, over time (Sköld *et al.*, 2004).

Table A1: Experimental conditions of autoxidation and composition of the oxidised linalool

Study	**Preparation**	**Period of air-exposure**	**Linalool**	**Peroxides**
Matura *et al.*, 2005	Linalool was air exposed in Erlenmeyer flasks, covered with aluminium foil to prevent contamination. It was stirred for 1 h, 4 times a day	45 weeks	**30%**	**16%** 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol
Christensson *et al*., 2010	Karlberg *et al*., 1992 & Sköld *et al*., 2004	45 weeks	**30%**	• **19%** linalool hydroperoxides: **15%** of 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol, **4%** of 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol • **20%** 2-(5-methyl-5-vinyltetrahydrofuran-2-yl) propan-2-ol • **< 4%** 2,2,6-trimethyl-6-vinyltetrahydro-2*H*-pyran-3-ol • 2,6-dimethylocta-3,7-diene-2,6-diol (traces) • 2,6-dimethylocta-1,7-diene-3,6-diol (traces) • 6-hydroxy-2,6-dimethylocta-2,7-dienal (traces)

Buckley, 2011	Commercial product (Chemotechnique Diagnostics, Vellinge, Sweden)		**0 %**	Hydroperoxides of linalool 2% in pet. According to the MSDS
Christensson *et al*., 2006	Sköld *et al*., 2004		Not reported	**5:3** mixture of 7-hydroperoxy-3,7-dimetylocta-1,5-diene-3-ol : 6-hydroperoxy-3,7-dimetylocta-1,7-diene-3-ol
Christensson *et al*., 2009	Karlberg *et al*., 1992	45 weeks	**30%**	**19%** linalool hydroperoxides
Christensson *et al*., 2012	Karlberg *et al*., 1992 and Sköld *et al*., 2004	25 weeks	**61%**	**14.6%** 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol
Sköld *et al*., 2002	Linalool sample was stirred in a flask (the top was covered with parafilm to prevent contamination and to diminish evaporation) *at room temperature* for 1h, 4 x a day	10 weeks	**80%**	A complex mixture of alcohols and hydroperoxides. Major oxidation product: 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol
Sköld *et al*., 2004	Linalool was air-exposed in an Erlenmeyer flask, covered with aluminum foil to prevent contamination. It was stirred for 1 h, four times a day	80 weeks	*cf*. figure above	*cf*. figure above

In conclusion, the composition of the test material used in studies in the CLH dossier referring to oxidised linalool consists of linalool 0-80%, linalool hydroperoxides 15-19% and various other components. The conditions under which autoxidation occurs comprise stirring air-exposed flasks for 1h, 4 x per day for 10-80 weeks at ambient temperature.

Human and animal data on the sensitisation properties of oxidised linalool, prepared as described above

Human studies

It should be noted that the human exposure to oxidised linalool has not been studied. Based on data provided by the DS, exposure to linalool is expected to be low. RAC assumes for classification purposes that, although linalool is also a natural constituent of herbs like lavender and coriander, the main source of oxidised linalool is linalool from consumer products that may undergo autoxidation. Therefore, the exposure to oxidised linalool is expected to be low. The studies are summarised below.

1. **Matura et al., 2005**

   Population: 1511 consecutively tested dermatitis patients in 6 clinics, of Copenhagen, Dortmund, Leuven, London, Malmo and Odense during 2002–2003
   Testing material: 2.0% of the oxidation mixture as described in the table above
   Prevalence: 20 patients (1.3%)
   RAC's opinion: *high frequency of sensitisation. The findings could provide evidence for classification as Skin Sens. 1A.*

2. **Christensson et al., 2010**

Population: Consecutive patients undergoing patch testing because of suspected allergic contact dermatitis (ACD)

Testing material: 2.0%, 4.0%, 6.0% and 11.0% of the oxidation mixture as described in the table above

Prevalence: 2.0% test mat. 14/1693 patients (0.83%), 4.0% test mat. 67/2075 patients (3.2%), 6.0% test mat. 91/1725 patients (5.3%), 11.0% test mat.72/1004 patients (7.2%)

RAC's opinion: *high frequency of sensitisation. (except for 2.0% test mat., low frequency). The findings could provide evidence for classification as Skin Sens. 1A.*

3. **Buckley, 2011**

Population: 483 consecutive patients

Testing material: 3% oxidised linalool as described in the table above

Prevalence: 11 patients (2.3%)

RAC's opinion: *high frequency of sensitisation. The findings could provide evidence for classification as Skin Sens. 1A.*

4. **Christensson et al., 2006**

Population: 29 colophonium-positive patients

Testing material: 0.5% the oxidation mixture as described in the table above

Prevalence: 1 patient (3.5%)

RAC's opinion: *high frequency of sensitisation. The findings could provide evidence for classification as Skin Sens. 1A.*

5. **Christensson et al., 2009**

Population: Consecutive dermatitis patients (n =20, 4 men and 16 women, mean age 41 years)

Testing material: 5.0%, 10.0%, 20.0% of the oxidation mixture as described in the table above

Prevalence: 5.0% test mat. 0.66%, 10.0% test mat. 0.94%, 20.0% test mat. 1.55%

RAC's opinion: *low frequency of sensitisation for 5.0 and 10% test mat., high frequency of sensitisation for 20% test mat. The findings could provide evidence for classification as Skin Sens. 1.*

6. **Christensson et al., 2012**

Population: 2900 consecutive dermatitis patients in Denmark, the United Kingdom, Singapore, Spain, Sweden, and Australia

Testing material: Oxidised linalool (as described in the table above) 6.0% in petrolatum (pet).

Prevalence: 6.9% (range 3–13% in the various)

RAC's opinion: *high frequency of sensitisation. The findings could provide evidence for classification as Skin Sens. 1A.*

<u>Animal studies</u>

Local Lymph Node Assay (LLNA)

7. **Sköld *et al*., 2004**

Table A2: Test results of the *Local Lymph Node Assay (LLNA)*

Test material	Concentration of the test material (pure linalool)	SI	EC3

Air-exposed linalool (10 weeks, as described above)	5%	1.4	9.4%
	10%	3.2	
	25%	12.7	
Air-exposed linalool (10 weeks, as described above)	2.5%	1.6	4.8%
	10%	6.4	
	25%	11.6	

A clear sensitisation effect is observed (SI>3) at concentrations > 10% with a linear dose-response. The EC3 values presented in the above Table, according to *RAC's opinion meet the criteria for classification for Skin Sens 1B.*

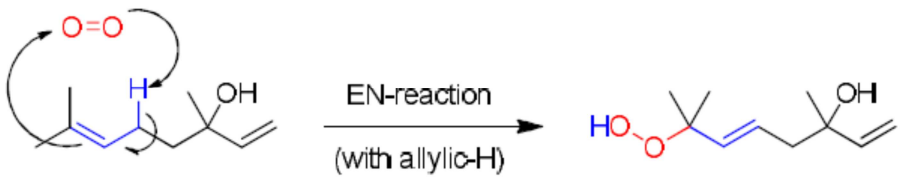
8. *Freund's Complete Adjuvant Test (FCAT) from* Sköld *et al*. (2002)

The animals induced with oxidised linalool became sensitised. A significant response was found at concentrations of 2.6, 5.1 and 10.3%, but not at 1.0%. At rechallenge, 5 of the control animals gave positive reactions when tested with 10.3% oxidised linalool, which suggests that these animals became sensitised at the first challenge testing. Furthermore, three reactions were seen at the rechallenge phase to the non-oxidised, unpurified linalool but the response was not significant. Therefore, RAC believes that sensitisation occurs to animals due to oxidised linalool exposure.

Study on the formation of peroxides in linalool with or without the presence of antioxidants

A company/manufacturer provided during PC a report on the formation of peroxides in linalool with or without the presence of alpha-tocopherol. A brief summary of this report is presented below.

The chemical reaction describing air oxidation of linalool is as follows:



linalool **linalool-peroxide**

Principle of the analytical method

This test measures organic and inorganic peroxides in aqueous solutions and organic solvents. Peroxidase transfers peroxide oxygen to an organic redox indicator. This produces a blue oxidation product. The peroxide concentration is measured semi-quantitatively by visual comparison of the reaction zone of the test strip with the fields of a colour scale.

Experimental conditions

Experiment 1:

Freshly prepared samples of Linalool (LL1=20 mL pure Linalool + 0 ppm alpha-tocopherol, LL2=20 mL pure Linalool + 1009 ppm alpha-tocopherol, LL3=20 mL pure Linalool + 208 ppm alpha-tocopherol) were stirred (350 rpm) in open glass bottles for 28 days under aerobic conditions at 40 °C. Semi-quantitative measurements of peroxide content were performed on a daily base within the first 2 weeks and then every second day by using MERCKOQUANT (max detectable concentration 25 mg/L) test stripes. The analytical determination of peroxides was stopped at the maximum detectable concentration of the test kit.

Experiment 2:

Freshly prepared samples of Linalool (LL4=5 ml pure Linalool + 0 ppm alpha-tocopherol, LL5=5 mL pure Linalool + 200-300 ppm alpha-tocopherol) were stirred (ca 350 rpm) in glass bottles for 23 days under aerobic conditions at ambient temperature (20°C). Analytical measurements of peroxide content were performed on a daily base within the first 2 weeks and then every second day by using MQuant test stripes (max detectable concentration 100 mg/L).

Results

Linalool, which was not stabilised was shown to contain > 25 mg/L peroxide after 10 days of stirring at 40 °C but did not exceed 100 mg/L after 23 days (3 weeks) of stirring at ambient temperature, which is far below the recommended (by IFRA) maximum concentration of 20 mmol/L peroxide (H_2O_2) (corresponding to 680 mg/L H_2O_2). Formation of peroxides of linalool in the absence of alpha-tocopherol occurs slowly. Exposure to air for three weeks at ambient temperature results in a concentration of 0.5 mg/L peroxide in linalool in the presence of alpha-tocopherol >200 ppm, instead of ca. 30 - 100 mg/L without this stabiliser. The maximum concentration of peroxides detected in stabilised samples (200 ppm alpha-tocopherol) amounted to 2 mg/L after 4 weeks stirring at 40°C (*cf*. figure below).
The concentration of hydroperoxides present in linalool expressed in mg H_2O_2/L can be converted into µg linalool hydroperoxide/g linalool using the factor of 6.4 as explained below:

- x mg H_2O_2 / L = x (186.25 / 34) mg linalool hydroperoxide / L with 186.25 and 34 being the molecular weights of linalool hydroperoxide and H_2O_2, respectively.
- x L linalool = 860 g linalool with the density of linalool being 0.86 g/cm^3

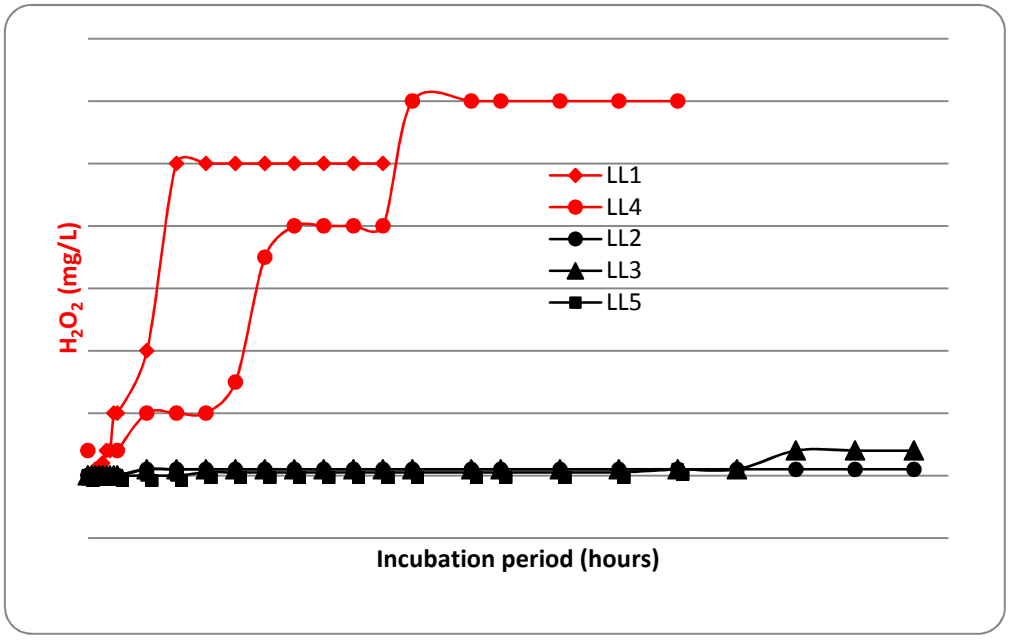


Figure A2: Maximum concentration of peroxides detected in stabilised samples

Formation of peroxide in Linalool samples (various volumes) with or without dl-*alpha*-tocopherol at different concentrations incubated for 23 and 28 days at 40°C (LL1=20 mL pure Linalool + 0 ppm alpha-tocopherol, LL2=20 mL pure Linalool + 1009 ppm alpha-tocopherol, LL3=20 mL pure Linalool + 208 ppm alpha-tocopherol) and at ambient temperature (LL4=5 mL pure Linalool + 0 ppm alpha-tocopherol, LL5=5 mL pure Linalool + 200-300 ppm alpha-tocopherol) (Figure produced by RAC).

Based on the above, the concentration of linalool hydroperoxides after 23 days does not exceed 0.019 % in comparison to hydroperoxide levels of 4% after 10 weeks in experiments reported (Sköld *et al*., 2004). In the presence of 200-300 ppm alpha-tocopherol, linalool hydroperoxides

does not exceed 0.00032% of linalool at ambient temperature after 23 days.

Formation of linalool oxidation products in consumer formulations

In a recent published manuscript by *Kern et al*. (2014) provided during PC by the industry, detection of potentially skin sensitising hydroperoxides of linalool in fragranced products was performed. The study focused on hydroalcoholic and antiperspirant formulations. Two categories of experiments were performed: those using fragrance formulations designed or selected to reflect typical contents of linalool in the commercial products and products recalled from consumers. In temperature stability studies, the products described above were stored in an oven at 45°C in order to accelerate the aging process by around 4-fold as compared to ambient temperatures, while control samples were stored at 5°C. All products were stored in parallel (i) in full bottles (ii) in half-emptied bottles which were opened only for sampling and (iii) in half-emptied bottles opened every 14 days (opened for *ca*. 1 min to allow for gas exchange) over the nine-month study period to maximize air exposure. The full experimental set-up was monitored for two months, which reflects a typical industry procedure for stability tests. Regarding products recalled from consumers, consumers were asked to bring in partly used samples of hydroalcoholic products stored in their homes for at least 2 years. 39 samples were obtained. These samples were then directly used for a detailed analytical investigation by GC-MS and LC-MS. Similarly, 29 partly used antiperspirants and deodorants and 5 fresh commercial samples were collected for analysis of linalool and linalool hydroperoxide.
In hydroalcoholic formulations, no significant degradation of linalool was observed during the monitoring period, independently of the presence of stabilising agents or the repeated opening of the bottles. The secondary oxidation products were detected below 6 µg/g in samples with synthetic linalool and around 300 µg/g of the formulation with natural linalool. These samples also contained detectable amounts of linalool-OOH as determined by GC-MS. No increase over time or due to temperature, exposure to air or absence of stabilising agents for the oxidation products was observed in both qualities of linalool. To investigate a scenario with higher oxidation risk, the study was prolonged for further seven months for the half-empty samples opened every second week (i.e. the samples with the highest oxidation risk). Linalool had still not significantly decreased below the starting level of 100000 µg/g after nine months. Linalool hydroperoxide (linalool-7-OOH), ranged 13-18 µg/g in the samples made from synthetic linalool and 82 - 97 µg/g in the naturally derived linalool samples. The secondary oxidation product (cis/trans linalool oxide – furanoide) was not detectable or only detected in traces in the synthetic linalool and it was found at around 80 – 150 µg/g in the samples made from naturally derived linalool. Similar to the results at the one and two months timepoints, neither the presence of stabilisers nor the storage temperature affected the stability of linalool and the detected levels of the hydroperoxide or secondary oxidation products were not modified.
Similarly, in complex hydroalcoholic fragrances no significant decrease of the initial theoretical linalool content could be detected, neither due to elevated temperature nor due to exposure to oxygen in partly filled and repeatedly opened bottles. Linalool hydroperoxide was detected in the range of around 2 µg/g (values were below LOQ), whereas the secondary oxidation products were not found. It should be noted that the hydroperoxides are surprisingly stable in fine fragrances stored at room temperature and at 45°C, denoting that potential accumulation of the hydroperoxide would not be masked by their limited temperature stability.
The stability of synthetic linalool and some characteristic fragrances in a typical pressurised aerosol antiperspirant stored at 45°C for either one or two months was also studied. For synthetic linalool, degradation was observed after two months (82% linalool remaining). Detailed analysis by GC-MS indicated the formation of a number of oxidation products, most prominently the formation of α-terpineol (6.2%), geraniol (1.5%) and a number of other terpenes, but no secondary oxidation products of linalool. For antiperspirants containing perfumes, the initial linalool content after two months remained unchanged and no oxidation products were detected by GC-MS.
To complement this study, aged commercial fragrances and antiperspirants/deodorants recalled from consumers and bought from stores were analysed by LC-MS in order to get a picture of the hydroperoxide content in products in daily use by consumers. Only products containing

linalool according to the INCI declaration were selected. Participants were asked to bring in at least 2 years old and partly emptied fragrances and some samples were considerably older. A total of 39 hydroalcoholic fragrances, 5 fresh commercial samples and 29 used products were analyzed. Results, as calculated by RAC, are summarized below.

The table below presents linalool, linalool hydroperoxide and linalool oxide concentrations in 39 hydroalcoholic commercial products studied recalled from consumers and their content in oxidation products over aging.

Table A3: linalool, linalool hydroperoxide and linalool oxide concentrations in 39 hydroalcoholic commercial products

	Linalool (µg/g product)	**Linalool hydroperoxide (µg/g product)**	**Cis/trans Linalool oxide (µg/g product)**	**%Linalool in the product**	**% Linalool hydroperoxide product**	**% Cis/trans Linalool oxide in the product**	**% hydroperoxide linalool in linalool**	**% linalool oxide in linalool**
Average	3073	17.1	30.5	0.299	0.00171	0.00305	0.574	1.105
maximal value	13924	132	216	1.39	0.0132	0.0216	3.11	8.81
Min	23,0	0	0	0	0	0	0	0
Std	2778	26.8	52.8	0.279	0.00268	0.00528	0.721	1.90
median	2429	6.0	6.0	0.240	0.0006	0.0006	0.293	0.304

Based on the above, it can be concluded that the concentration of linalool hydroperoxide in linalool found in aged hydroalcoholic commercial products does not exceed 3.1%, while the average test material in studies with oxidised linalool the relevant concentrations reached were up to 19%.
Linalool hydroperoxide was not detected in any commercial antiperspirants/deodorant sprays recalled from consumers, but the method has proven to have low recovery depending on the product matrices. After performing a standard addition experiment, the authors estimate the content of the hydroperoxide in these samples to be < 20 µg/g in the final product.

Auto-oxidation of linalool and its relevance to classification

Auto-oxidation procedure used in the literature

In the CLH report 6 studies are referred to, using oxidised linalool in human patch test studies and 2 studies using oxidised linalool as the test material in an LLNA test in mice. The identity of the "oxidised linalool" used in each experiment and the experimental conditions used to prepare it are described in detail in the Background Document. The composition of the test material "oxidised linalool" used in these studies consists mainly of linalool 0-80%, linalool hydroperoxides 15-19% and various other components. The conditions, under which auto-oxidation occurs, comprise stirring for 1h, 4 x per day of air-exposed flasks for 10-80 weeks at ambient temperature.

It is the opinion of RAC that oxidised linalool is an artificial research material rather than a naturally occurring commercial substance.

Human and animal data on the sensitisation properties of oxidised linalool, prepared as described above

It should be noted that the exposure to oxidised linalool has not been studied. Based on data provided by the DS, exposure to linalool is expected to be low. RAC assumes for the classification purposes that, although linalool is also a natural constituent of herbs like lavender and coriander, the main source of oxidised linalool is linalool from consumer products that may undergo autoxidation. Therefore, the exposure to oxidised linalool is also expected to be low.
The actual data of the human and animal studies are summarized in the Background Document. Based on these data, RAC is of the opinion that the human studies could provide evidence for classification of oxidised linalool as Skin Sens. 1A and that animal studies support this conclusion.

Study on the formation of peroxides in linalool with or without the presence of antioxidants

During PC, a company/manufacturer provided a report on the formation of peroxides in linalool with or without the presence of alpha-tocopherol using a less accurate, semi-quantitative, colorimetric method. A brief summary of this report is presented in the Background Document.
Based on the data of the company/manufacturer experiments, the concentration of linalool hydroperoxides after 23 days does not exceed 0.019 % in comparison to hydroperoxide levels of 4% after 10 weeks in experiments reported by Sköld et al., 2004. In the presence of 200-300 ppm alpha-tocopherol, linalool hydroperoxides does not exceed 0.00032% of linalool at ambient temperature after 23 days.

Formation of linalool oxidation products in consumer formulations

In a recent published manuscript by Kern *et al*. (2014) provided during PC by the industry, detection of potentially skin sensitising hydroperoxides of linalool in fragranced products was performed. Details are presented in the Background Document.
Based on these data, it can be concluded that the concentration of linalool hydroperoxide in linalool found in aged hydroalcoholic commercial products does not exceed 3.1%, while in an average test material of oxidised linalool studies the relevant concentration reaches even 19%.
Linalool hydroperoxide was not detected in any commercial antiperspirants/ deodorant sprays studied recalled from consumers, but the method has proven to have low recovery depending on the product matrices. After performing a standard addition experiment, the authors estimate the content of the hydroperoxide in these samples to be < 20 µg/g in the final product.

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
	Dose response is odd and/or weakly positive, only at high test concentration
Primary challenge reactions are weak and scattered	
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 EC 3 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 linalool as **Skin Sens. 1**
Schnuch *et al.*, 2007 2401 consecutive dermatitis patients in Germany	10% stabilised linalool	0.3% (7 positive patch test reactions – PPT: 6 +, 1++, 0+++, 1 follicular reaction, 12 IR or doubtful reactions)#	
Uter et al., 2010 985 dermatitis patients	10% stabilised linalool	0.2% (0.1% +, 0.1% ++/+++, max scoring +++, 0.81% irritant (IR) or doubtful reactions)	

(2005-2008)			
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).**

4.4.2. Respiratory sensitisation

Not evaluated.

a. Repeated dose toxicity

Not evaluated.

b. Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated.

c. Germ cell mutagenicity (Mutagenicity)

Not evaluated.

d. Carcinogenicity

Not evaluated.

e. Toxicity for reproduction

Not evaluated.

f. Other effects

Not evaluated.

D) ENVIRONMENTAL HAZARD ASSESSMENT

5.1.Degradation

Not evaluated.

5.2.Environmental distribution

Not evaluated.

5.3.Aquatic Bioaccumulation

Not evaluated.

5.4.Aquatic toxicity

Not evaluated.

5.5.Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Not evaluated.

5.6.Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Not evaluated.

6. OTHER INFORMATION

7. REFERENCES

Basketter DA, Wright ZM, Colson NR, Patlewicz GY and Pease CKM (2002) Investigation of the skin sensitizing activity of linalool. *Cont. Derm*. 47:161-4.

Bergström MA, Ott H, Carlsson A, Neis M, Zwaldo-Klöarwasser G, Jonsson CAM, Merk HF, Karlberg A-T and Baron JM (2006) A skin-like cytochrome P450 cocktail activates prohaptens to contact allergenic metabolites. *J. Invest. Dermatol.* 127:1145-1153.

BEUC (2005) The European Consumers Organization. Emission of chemicals by air fresheners-Tests on 74 consumer products sold in Europe.

Bazzano C, de Angeles S, Kleist G, *et al*, (1996) Allergic contact dermatitis from topical vitamin A and E. *Cont. Derm*. 35:261-262.

Bezard M, Karlberg A-T, Monelius J and Lepoittevin JP (1997) Skin sensitization to linalyl hydroperoxide:support for radical intermediates. *Chem. Res. Toxicol.* 10:987-993.

Biebel KA and Warshaw EM (2006) Allergic contact dermatitis to cosmetics. *Dermatol. Clin.* 24:215-232.

Brandáo FM (1986) Occupational allergy to lavender oil. *Cont. Derm.* 15(4):249-250.

Bruze M, Svedman, Andersen KE, Brynzeel D, Goossens A, Johansen JD, Matura M, Orton D and Vigan M (2012) Patch test concentrations (doses in mg/cm^2) for the 12 non-mix fragrance substances regulated by European legislation. *Cont. Derm.* 66:131-136.

Buckley DA (2007) Fragrance ingredient labelling in products on sale in the U.K. *Br. J. Derm*. 157: 295-300.

Buckley DA (2011) Allergy to oxidized linalool in the UK. *Cont. Derm.* 64(4):240-241.

Bäcktorp C, Wass JRTJ, Panas I, Sköld M, Börje A and Nyman G (2006) Theoretical investigation of linalool oxidation. *J Phys. Chem. A*110:12204-12212.

Cal K (2006a) How does the type of vehicle influence the in vitro skin absorption and elimination kinetics of terpenes? *Arch. Dermatol. Res.* 297:311-315.

Cal K (2006b) Skin penetration of terpenes from essential oils and topical vehicles. *Planta Med*. 72(4):311-316.

Cal K, Janicki S and Sznitowska M (2001) *In vitro* studies on penetration of terpenes from matrix-type transdermal systems through human skin. *Int. J. Pharm.* 224:81–88.

Cal K and Krzyazaniak M (2006) Stratum corneum absorption and retention of linalool and terpinen-4-ol applied as gel or oily solution in humans. *J. Dermatol. Sci.* 42:265-267.

Cal K and Sznitowska M (2003) Cutaneous absorption and elimination of three acyclic terpenes-*in vitro* studies. *J. Controlled Release* 93:369-376.

Casabianca H, Giraff JB, Faugier V, Fleig F and Grenier C (1998) Enantiomeric distribution studies of linalool and linalyl acetate. A powerful tool for authenticity control of essential oils. *J. High. Res. Chrom.* 21:107-112.

Chemotechnique Diagnostics AB (2012) Safety Data Sheet H-031.Vellinge, Sweden.

Christensson JB (2009) Clinical and experimental studies on oxidized fragrance terpenes as contact allergens. PhD Thesis, University of Gothenburg, Gothenburg, Sweden. 55 pp.

Christensson JB, Andersen KE, Bruze M, Johanson JD, Garcia-Bravo B, Arnau GA, Goh C-L, Nixon R and White IR (2012) Air-oxidized linalool-a frequent cause of fragrance contact allergy. *Cont. Derm*. 67:247-259.

Christensson JB, Forsström P, Wennberg AM, Karlberg A-T and Matura M (2009) Air oxidation increases skin irritation from fragrance terpenes. *Cont. Derm.* 60(1):32-40.

Christensson JB, Matura M, Bäcktorp C, Börje A, Nilsson JL and Karlberg A-T (2006) Hydroperoxides form specific antigens in contact allergy. *Cont. Derm.* 55(4):230-237.

Christensson JB, Matura M, Gruvberger B, Bruze M and Karlberg A-T (2010) Linalool-- a significant contact sensitizer after air exposure. *Cont. Derm.* 62(1):32-41.

de Groot AC (1987) Contact allergy to cosmetics:causative ingredients. *Cont. Derm.* 17:26-34.

de Groot AC, Coenraads P J, Bruynzeel DP, Jagtman BA, van-Ginkel CJW, Noz K, Van Der Valk PGM, Pavel S, Vink J and Weyland J W (2000) Routine patch testing with fragrance chemicals in The Netherlands. *Cont. Derm.*42:184-185.

de Groot AC and Frosch PJ (1997) Adverse reactions to fragrances. *Cont. Derm.* 36:57-86.

de Groot AC and Liem DH (1983) Facial psoriasis caused by contact allergy to linalool and hydroxycitronlellal in after-shave. *Cont. Derm.* 9:230-232.

de Groot A C, Liem D H, Nater J P and van Ketel W G (1985) Patch tests with fragrance materials and preservatives. *Cont. Derm.* 12:87-92.

de Groot AC, Weyland JW and Nater JP (1994) *Unwanted effects of cosmetics and drugs in dermatology*, 3rd edn. Amsterdam, Elsevier.

Eggert T and Hansen OS (2004) Survey and emission of chemical substances from incense. Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemical Substances in Consumer Products, No. 39, Copenhagen, 136 pp.

Fenn RS (1989) Aroma chemical usage trends in modern perfumery. *Perfumes & Flavorist* 14:3-10.

Frosch PJ, Pilz B, Andersen KE, Burrows D, Camarasa JG, Dooms-Goossens A, Ducombs G, Fuchs T, Hannuksela M, Lachapelle JM, Lahti A, Maibach HI, Menne T, Rycroft RJG, Shaw S, Wahlberg JE, White IR and Wilkinson JD (1995) Patch testing with fragrances: Results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Cont. Derm.* 33:333-342.

Gerberick G F, Kern P S, Schlatter H, Dearman R J, Kimber I, Patlewicz G Y and Basketter D A (2005) Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods *Dermatitis* 16:157-202.

Glensvig D and Ports J (2006) Mapping of perfume in toys and children's articles, Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemical Substances in Consumer Products, No. 68, Copenhagen, 73 pp.

Hagvall L, Sköld M, Bråred-Christensson J, Börje A and Karlberg A-T (2008) Lavender oil lacks natural protection against autoxidation, forming strong contact allergens on air exposure. *Cont. Derm.* 59(3):143-150.

http://www.medicalnewstoday.com/releases/144041.php (2009) Widely used fragrance ingredients in shampoos and conditioners are frequent causes of Eczema.

IFRA, International Fragrance Association. 2009. 38th Amendment, IFRA Standard. October 14 2009.

Jager W, Buchbauer G, Jirovetz L and Fritzer M (1992) Percutaneous absorption of lavender oil from a massage oil. *J. Soc. Cosmet. Chem.* 43: 49.

Kao D, Chaintreau A, Lepoittevin J-P and Giménez E (2011) Synthesis of Allylic Hydroperoxides and EPR Spin-Trapping Studies on the formation of radicals in iron systems as potential initiators of the sensitizing pathway. *J. Org. Chem.* 76:6188-6200.

Karlberg A-T, Bergström MA, Börje A, Luthman K and Nilsson JLG (2008) Allergic Contact Dermatitis- Formulation, Structural Requirements, and Reactivity of Skin Sensitizers. *Chem. Res. Toxicol.* 21(1):53-69.

Karlberg A-T, Magnusson K and Nilsson U (1994) Influence of an antioxidant on the formation of allergenic compounds during autoxidation of d-limonene. *Ann. Occup. Hyg.* 38:199-207.

Kern P S, Gerberick G F, Ryan C A, Kimber I, Aptula A and Basketter D A (2010) Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. *Dermatitis* 21:8-32.

Kitahara M, Ishiguro F, Takayama K, Isowa K and Nagai T (1993) Evaluation of skin damage of cyclic monoterpenes, percutaneous absorption enhancers, by using cultured human skin cells. *Biol. Pharm. Bull.* 16: 912.

Kohl L, Blondeel A and Song M (2002) Allergic contact dermatitis from cosmetics- Retrospective analysis of 919 patch-tested patients. *Dermatol.* 204:334-337.

Larsen JR and Andersen TT (2006) Survey of liquid hand soaps, including health and environemental assessments. Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemical Substances in Consumer Products, No. 69, Copenhagen, 76 pp.

Magnano M, Silvani S, Vincenzi C, Nino M and Tosti A (2009) Contact allergens and irritants in household washing and cleaning products. *Cont. Derm.* 61:337-341.

Matsumura T, Takada T, Iijima M (2004) Widespread contact dermatitis from tocopherol acetate. *Cont. Derm.* 51:211-212.

Matura M, Sköld M, Börje A, Frosch P, Goossens A, White IR, Bruze M, Menne' T, Andersen KE and Karlberg A-T (2004) Contact allergy to oxidized fragrance terpenes. *Cont. Derm.* 50:146-147.

Matura M, Sköld M, Börje A, Andersen KE, Bruze M, Frosch P, Goossens A, Johansen JD, Svedman C, White IR and Karlberg A-T (2005) Selected oxidized fragrance terpenes are common contact allergens. *Cont. Derm.* 52(6):320-328.

Meesters RJ, Duisken M and Hollender J (2007) Study on the cytochrome P450-mediated oxidative metabolism of the terpene alcohol linalool: indication of biological epoxidation. *Xenobiotica* 37(6):604-617.

Merk HF, Baron JM, Neis MM, Obrigkeit DH and Karlberg A-T (2007) Skin: Major target organ for allergic reactions to small molecular weight compounds. *Toxicol. Appl. Pharmacol.* 224:313-317.

National Toxicology Program, Department of Health and Human Services, National Institute of Environmental Health Sciences, NIH, USA. http://ntp-server.niehs.nih.gov/.

Nilsson J, Carlberg J, Abrahamsson P, Hulthe G, Persson B-A and Karlberg A-T (2008) Evaluation of ionization techniques for mass spectrometric detection of contact allergenic hydroperoxides formed by autoxidation of fragrance terpenes. *Rapid Commun. Mass Spectrom.* 22:3593-3598.

OECD SIDS Linalool CAS No.:78-70-6. SIDS Initial assessment Report for SIAM 14, 26-28 March 2002, Paris, France (2004) UNEP Publications. 157 pp.

Prashar A, Locke IC and Evans CS (2004) Cytotoxicity of lavender oil and its major components to human cells. *Cell Prolif.* 37:221-229.

Peiser M, Tralau T, Heidler J, Api J, Arts HE, Basketter DA, English J, Diepgen TL, Fuhlbrigge RC, Gaspari AA, Johansen JD, Karlberg AT, Kimber I, Lepoittevin JP, Liebsch M, Maibach HI, Martin SF, Merk HF, Patzek T, Rustemeyer R, Schnuch A, Vandebriel RJ, White IR and Luch A (2011) Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. *Cell Mol. Life Sci.* 69:763-781.

Ports J and Fuhlendorff R. (2003) Mapping of chemical substances in air fresheners and other fragrance liberating products. Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemical Substances in Consumer Products, No. 30, Copenhagen, 17 pp.

Poulsen PB and Schmidt A (2007) A survey and health assessment of cosmetic products for children. Danish Ministry of the Environment, Environmental Protection Agency (EPA). Survey of Chemical Substances in Consumer Products, No. 88, Copenhagen, 220 pp.

Poulsen PB and Strandsen M (2011) Survey and health assessment of cosmetic products marketed as “non-preserved”. Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemical Substances in Consumer Products No.11, Copenhagen, 1168 pp.

Rastogi SC (2002) Contents of selected fragrance material in cleaning products and other consumer products. Danish Ministry of the Environment, Environmental Protection Agency (EPA), Survey of Chemicals in Consumer Products, No. 8, Copenhagen, 29 pp.

Rastogi SC, Johansen JD, Frosch P, Menné T, Bruze M, Lepoitteven JP, Dreier B, Andersen KE and White IR (1998) Deodorants on the European market: Quantitative chemical analysis of 221 fragrances. *Cont. Derm.* 38(1):29-35.

Rastogi SC, Johansen JD, Menné T, Frosch P, Bruze M, Andersen KE, Lepoitteven JP, Wakelins S and White IR (1999) Contents of fragrance allergens in children's cosmetics and cosmetic-toys. ***Cont. Derm.*****41(2):84-88.**

Rastogi SC, Heydron S, Johansen JD and Basketter DA (2001) Fragrance chemicals in domestic and occupational products. *Cont. Derm*. 45(4):221-225.

Redeby T, Nilsson U, Altamore TM, Ilag L, Ambrosi A, Broo K, Börje A and Karlberg A-T (2009) Specific adducts formed through a radical reaction between peptides and contact allergenic hydroperoxides. *Chem. Res. Toxicol.* 23:203-210.

RIFM Expert Panel, Belsito D, Bickers, D, Bruze M, Calow P, Greim H, Hanfin JM, Rogers AE, Saurat JH, Sipes IG and Tagami H (2008) A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. *Food Cem. Toxicol.* 46:S1-S71.

Ryan CA, Gerberick GF, Cruse LW, Basketter DA, Lea L, Blaikie L, Dearman RJ, Warbrick EV and Kimber I (2000) Activity of human contact allergens in murine local lymph node assay. *Con. Derm*. 43:95-102.

SCCNFP. The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (1999) Opinion concerning Fragrance Allergy in Consumers. A Review of the Problem. Analysis of the Need for appropriate Consumer Information and Identification of Consumer Allergens, adopted 8 December 1999. *SCCNFP/0017/98* Final 1999.

SCCS. The Scientific Committee on Consumer Safety (2012) Opinion on Fragrance Allergens in Cosmetic Products, 26-27 June 2012. SCCS/1459/11, European Commission.

Schaller M and Korting HC (1995) Allergic airborne contact dermatitis from essential oils used in aroma therapy. *Clin. Exp. Dermatol.* 20:143-145.

Schnuch A, Uter W, Geier J, Lessmann H and Frosch PJ (2007) Sensitization to 26 fragrances to be labelled according to current European regulation, Results of the IVDK and review of the literature. *Cont. Derm*. 57:1-10.

Shubert H-J (2006) Skin diseases in workers at a perfume factory. *Cont. Derm.* 55:81-83.

Sköld M, Börje A, Harambasic E and Karlberg A-T (2004) Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. *Chem. Res. Toxicol*. 17(12):1697-1705.

Sköld M, Börje A, Matura M, and Karlberg A-T (2002) Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hydroperoxide. *Cont. Derm.* 6(5): 267-72.

Sköld M, Börje A, Matura M, and Karlberg A-T (2002) Sensitization studies on the fragrance chemical linalool, with respect to auto-oxidation. Cont. *Derm.* 46(Suppl. 4):20.

Sköld M, Hagvall L and Karlberg A-T (2007) Autoxidation of linalyl acetate, the main component of lavender oil, creates potent contact allergens. *Cont. Derm.* 58:9-14.

Sugiura M, Hayakawa R, Kato Y, Sugiura K and Hashimato R (2000) Results of patch testing with lavender oil in Japan. *Cont. Derm.* 43:157-160.

Tran TC and Mariott PJ (2007) Characterization of incense smoke by solid phase microextraction-Comprehensive two-dimensional gas chromatography (GC x GC). *Atmosp. Env*. 41:5756-5768.

Usta J, Kreydiyyeh S, Knio K, Barnabe P, Bou-Moughlabay Y and Dagher S (2009) Linalool decreases HepG viability by inhibiting mitochondrial complexes I and II, increasing reactive oxygen species and decreasing ATP and GSH levels. *Chem. Biol. Interact*. 180(1):39-46.

Uter W, Geier J, Frosch P J and Schnuch A (2010) Contact allergy to fragrances: current patch test results (2005 to 2008) from the IVDK network. *Cont. Derm.* 63:254-261.

Van Moerbeke D (Ed.) (1999) European allergy white paper. UCB Institute Allergy, Brussels.

Van Oosten EJ, Schttelaar M-LA and Coenraads PJ (2009) Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. *Cont. Derm.* 61:217-223.

Wijnhoven SWP, Ezendam J, Schuur AG, van Loveren H and van Engelen JGM (2008) Allergens in consumer products. National Insitute for Public Health and the Environment (RIVM), Report 320025001. Bilthoven, 119 pp.

Yazar K, Johnsson S, Lind M-L, Boman A and Lidén C (2010) Preservatives and fragrances in selected consumer-available cosmetics and ingredients. *Cont. Derm.* 64:265-272.