ECHA
EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

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

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

CLH-O-0000001412-86-53/F

Adopted

12 March 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.
All attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website.

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Chemicals names: **linalool; (*S,R*)-3,7-dimethyl-1,6-octadien-3-ol; *dl*-linalool [1]**
coriandrol; (*S*)-3,7-dimethyl-1,6-octadien-3-ol; *d*-linalool [2]
licareol; (*R*)-3,7-dimethyl-1,6-octadien-3-ol; *l*-linalool [3]

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

Dossier submitter: **Sweden**

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GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29/07/2014	Germany	Manufacturer	Individual	1

Comment received

Please find our comments within the attached document "BASF_comments related to CLH_Linalool_78-70-6.pdf"

ECHA note: The attachment no.1 has been copied below.

We disagree with the proposal for harmonized classification of Linalool for skin sensitization in sub-category 1A as proposed by the Swedish Chemicals Agency, due to procedural concerns.

CLH Report	Comment
Page 9; Section 2.2; "the autoxidation is an intrinsic property of Linalool"	According to Article 2 (7) of Regulation (EU) No 1272/2008 a "*substance means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used…*" . The composition of linalool as referred in the CLH report includes a stabilizer preventing linalool to autoxidize. Therefore, autoxidation cannot be considered as an intrinsic property of linalool as specified.

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	Section 4	The studies in this section, cited to justify the proposed classification of linalool for skin-sensitization sub- category 1A have been performed with oxidation products / hydroperoxides. Thus according to Article 5(1) of Regulation (EU) No 1272/2008 " *Manufacturers, importers and downstream users of a substance shall identify the relevant available information … The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used*." In addition Article 8 (6) of Regulation (EU) No 1272/2008 states that "*Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.*" Therefore according to these articles, for classification of linalool as it is placed on the market, only studies on non-oxidized linalool should be taken into consideration. The oxidation procedure as described in the cited studies does not reflect how commercial products are handled daily. Therefore the mentioned studies do not reflect sound scientific basis and should be considered invalid for any conclusion regarding the sensitization of Linalool.	

Section 3 "It is also well-established that linalool is prone to autoxidation when it is exposed to air, which is very likely to occur in consumer products during storage or handling."	This statement is not relevant for the classification of Linalool itself. Consumer products containing linalool are mixtures and need to be classified themselves. According to Article 6 (1) of Regulation (EU) No 1272/2008 *"Manufacturers, importers and downstream users of a mixture shall identify the relevant available information on the mixture itself or the substances contained in it… The information shall relate to the forms or physical states in which the mixture is placed on the market and, when relevant, in which it can reasonably be expected to be used".* However according to Article 14 (1) a *"The classification of a mixture shall not be affected where the evaluation of the information indicates any of the following:* *(a) that the substances in the mixture react slowly with atmospheric gases, in particular oxygen, carbon dioxide, water vapour, to form different substances at low concentration;"* This means that consumer products have to be classified when they are placed on the market. Oxidation which might occur during inappropriate storage of consumer products is not in the scope of Regulation (EU) 1272/2008 and therefore does not justify a classification of linalool as skin sensitizer sub-category 1A.

[End of attachment no. 1]

Dossier Submitter's Response

Please see response to comment no 4 (DSM Nutritional Products AG). Please note that article 6(1) and 14(1) of CLP refer to mixtures and not to substances.

RAC's response

Noted. RAC has considered in the opinion the SID of the substance submitted for harmonized classification and labeling, including the relevance of the presence of additives (i.e. stabiliser), the normally anticipated conditions of use and storage of the substance in the market and the relevance of the various test materials used in the studies referred to in the CLH report with the SID of the of the substance to be submitted for harmonised classification and labeling.

Date	Country	Organisation	Type of Organisation	Comment number
31/07/2014	Switzerland	Givaudan International SA	Company-Downstream user	2

Comment received

ANNEX 2 – COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

Please find extensive comments in the attached document.

ECHA note: Page 2 and appendix 1 from attachment no.2 have been copied below.

Overview

The CLH proposal made by the Sweden is based on the hypothesis that Linalool may oxidise under relevant conditions of use and exposure and that this is a cause of allergic contact dermatitis in the general population. Closer inspection of the data shows that this hypothesis is not relevant to the qualities of Linalool in commerce. In addition it does not have a sound scientific basis, as it is mainly based on patch test data which have not been thoroughly validated and therefore cannot form the basis for relevance to classification. We disagree with the recommended classification in the dossier which we believe contains unsupported conclusions and is based on a narrative which appears biased to fit the above hypothesis.

The report proposal also contains many factual errors which are detailed in the page by page comments provided in Appendix 1.
Our main concerns with the classification proposal for Linalool are based on the following:

- Non classification for sensitization of Linalool used in commerce based on experimental evidence (animal and human)
- Non relevance of the information on oxidized Linalool to samples of commercial quality
- Concerns over the data used to support the hypothesis of relevance of oxidation of Linalool to human sensitization.

The following comments provided by Givaudan cover 3 areas:

1. Data supporting non classification of Linalool
2. General comments on the hypothesis and patch test information presented
3. Page by page comments on the CLH proposal

Givaudan are also supportive of the comments provided by IFRA.

Appendix I – Page by Page Comments on the CLH report

Comment				**CLH Dossier from MS Sweden**	**Comment**
comment 1	Page 5	Section A1.1 and subsequently in report	2nd paragraph	"CLH report shows that Linalool is autoxidised in air…."	This statement is misleading and not representative of qualities found within the supply chain. Autoxidation has only been shown under some strict experimental conditions.
	Page 9	Section A2.1	2nd paragraph	"It belongs to fragrances of special concern due to the high number of published cases of allergy in the scientific literature, 100-1000 cases (Opinion of the SCCS, 2012)"	This is untrue. The SCCS report only provides information on 17 reports of patch test positive reactions to Linalool; however in in no cases was

comment 2					evidence of clinical relevance to the patient provided. The SCCS report does provide more information on patch test reactions to oxidized Linalool, but as discussed in this document this is irrelevant to the current classification discussion. Despite the very frequent possible exposure to Linalool (actually around 80% of consumer products contain this ingredient since many decades), the lack of reports of allergic contact dermatitis to this substance support a conclusion that Linalool should not be classified as sensitizing.
	Page 11	Section A3	4th paragraph	"High frequency of sensitization in human"	
comment 3	page 9	Section A2.2	2nd paragraph	The autoxidation is an intrinsic property of linalool	This statement is misleading; the linalool as specified in the dossier gives the presence of an antioxidant in the substance identity. This specification shows no significant presence of peroxides.
comment 4	Page 9	Section A2.2	4th paragraph	"high frequencies of positive patch test reactions"	See comment 2linalool does not have a high frequency of positive patch tests. The frequency of reactions towards non-oxidised linalool is. Need to include information on the frequencies on positive patch tests with pure linalool in this section.
comment 5	Page 11	Section A3	2nd paragraph	"..apparently the low concentration of linalool used in products does not protect from skin sensitisation"	This comment has no basis for reference or fact. As discussed clinical data shown linalool to be a very rare to none sensitiser. Only data are available on oxidised material which remains an unproven hypothesis without relevance as discussed in this document.
comment 6	Page 11	Section A3	3rd paragraph	"…these recommendations are not frequently followed as shown by studies of consumer products on different European markets"	There are no references given to support this statement.
comment 7	Page 11	Section A3	Paragraph on animal data	"The hydroperoxide fraction of oxidized linalool was a strong sentiser in LLNA (Sköld et al., 2002, Sköld et al., 2004)."	This is not completely correct. Sköld et al., 2002 used the FCAT. Only Sköld et al tested in the LLNA.
comment 8	Page 12	Section A3	Paragraph on costs of allergy		The costs in this section refer to all contact allergies in the EU and are not specific to this material. Therefore relevance is low.
comment 9	Page 12	Section A3	3rd paragraph	"unsatisfactory self-classification of linalool by European Industry	We strongly disagree with the appropriateness of this classification (see also DSM position paper) and consequently we do not classify linalool as a skin sensitizer.
comment	Page 12	Section A3	4th paragraph	…"as a skin sensitizer in sub-category 1A"…	We strongly disagree with the appropriateness of this classification (see also DSM position paper)

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comment 11	Page 18	Section B2.2	Last paragraph	…"that linalool concentration in some cosmetic products have exceeded the recommended limits, being common up till a range of 130—280 ppm of product (Poulsen and Strandsen, 2011)	We disagree with this statement. There are no recommended use limits on Linalool.
comment 12	Page 19	Section B4.1 toxicokinetics			The interpretation of the data does not comply with the guidance and recommendations given e.g. by SCCS 2010 in their guidance document on in vitro dermal absorption studies.
comment 13	Page 19	Section B4.1 toxicokinetics			We consider it inappropriate to use data on substances which do not comply with the substance definition (Kitahara et al., 1993, Cal et al., 2001, Cal 2006b, Brandao et al., 1986)
comment 14	Page 19+20	Section B4.1		2nd and 3rd paragraph	The discussion is about toxicokinetics not about sensitization. Thus, these two paragraphs are unnecessary repetitions and can be deleted.
comment 15	Page 21	Section B4.1.1	1st paragraph	"it is known to have a very high skin penetrating capacity"	We disagree with this statement. As shown in the REACH Dossier and in the DSM position paper, a maximum of 4% of the applied dose is systemically available upon application on skin. The Gerberick paper cited does not present any skin penetration data.
comment 16	Page 20	Section B4.1.1		Hydroperoxides.. "As they penetrate the skin they readily form adducts to skin proteins, such as histidine, through a radical mechanisms (Kao et al 2011)	Kao et al 2011 did not indicate that the hydroperoxides are able to penetrate skin. Indeed there is to the best of our knowledge no dedicated study on dermal penetration of any form of oxidized linaool.
comment 17	Page 20	Section B4.1.1		Epoxides…"enzymatic (metabolic) activation of epoxides, involving CYP 2B6…, to electrophilic oxidation products such as 6,7-epoxy-linalool could be another pathway apart from autoxidation."…. "the epoxides could be formed from the hydroperoxides or serve as prohapten being activated in the skin upon entry"…	The discussion about epoxides is highly speculative. Epoxides were not found in the oxidized linalool mixtures and their occurrence in skin (being it by metabolic processes or by degradation of hydroperoxides of linalool) has to the best of our knowledge not been confirmed. The references given (Bergström et al 2007 or Merk et al 2007) have not tested linalool at all but give an overview on metabolic processes in the skin. Thus, we would recommend discussing metabolic processes of linalool in skin in the right perspective i.e. there is no scientific information on this.
comment	Page 20	Section B4.1.2	1st paragraph		Citations, references should be added to underpin the conclusions.

18	and 21				
comment 19	Page 20 and 21	Section B4.1.2	2nd paragraph		We question the relevance on the reported in vitro studies which are speculative.
comment 20	Page 21	Section B4.1.3		"Epoxides may also contribute to the allergic properties, though absorbed into the epidermis as intact prohapten and then activated via cytochrome P450 to become protein reactive. Later on they are likely to follow a similar immunogenic pathway to induce sensitization"	This statement is not clear and needs to be more precise. Usually, epoxides are formed from double-bond by cytochrome P450 enzymes and then react spontaneously. The relevance of epoxides is not clear to us in the context of linalool and this document. The whole summary presented here is speculative and needs revising based on our comments above.
comment 21	Page 22	Table 10a (i)			The table provides insufficient information to reach any conclusions. No information is provided on the severity of reaction or on clinical relevance to the patient allergy.
comment 22	Page 23 and 24	Table 10a (ii)			The data presented in this table are reviewed in the comments provided in this document and relevance to Linalool remains hypothetical.
comment 23	Page 25	Table 10a (iii)		Lavender oil and other linalool-containing products	These substances/preparations do not comply with the substance identity and thus are not relevant for the discussion about linalool under REACH.
comment 24	Page 27	Table, 3rd row		Lavender oil and other linalool-containing products	These substances/preparations do not comply with the substance identity and thus are not relevant for the discussion about linalool under REACH.
comment 25	Page 29	Table 10c			The relevance of this information is unclear. Skin irritation has been studied in detail and the mentioned in vitro data are not relevant (see also above).
comment 26	Page 29	Section B4.1.1.1	Last paragraph	"the aldehyde was found to be a moderate sensitizer… (Bezard et al. 1997)	To the best of our knowledge Bezard et al. 1997 did not study the aldehyde. They studied epoxides, furan and pyran derivatives as well as a hydroperoxide. Please correct.
comment 27	Page 31	Oxidized linalool	2nd paragraph	" as shown in Table 12a(ii) a recent multicenter study in Sweden has shown….	Table 12a(ii) does not exist
comment 28	Page 31	Oxidized linalool	2nd paragraph	"This rate is the highest rate ever recorded for an individual fragrance allergen."	Citation missing. Note our serious concerns over the patch testing of high levels of oxidised Linalool, equivalent to those that induce sensitisation in non-

					occluded animal studies.
comment 29	Page 31-32	Sections 4.4.1.3		"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 linalool administration on the antioxidant reserve under in vivo conditions has to the best of our knowledge not been shown. Thus, this is a theory only.
comment 30	Page 32		3rd paragraph	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).	Please be aware that the cited reference (Karlberg et al., 1994) is on limonene and not on linalool. Data to be considered are Kern et al. 2014 which indeed show adequate protection
comment 31	Page 31 and		Oxidized linalool, 3rd para		Irrelevant, lavender oil does not comply with the substance identity
	Page 32		3rd paragraph	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).	
comment 32	Page 32		5th paragraph	"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).	The conclusion on prevalence of about 2% in the general population is the personal opinion of Dr. Christensson and was expressed in an interview i.e. non-peer reviewed publication. We are not sure that such information is to be considered in this debate under REACH. We could not find in Christensson 2009 the respective information.
comment 33	Page 32		3rd paragraph	"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)."	The skin sensitisation potential of cited antioxidants is not relevant to this dossier. We are not aware of any publications that show that antioxidants can promote the sensitizing property of the allergen in question.
comment 34	Page 32		3rd paragraph	"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."	See comment above. Data do show adequate protection of Linalool.
comment 35	Page 33		2nd paragraph	"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	The relevance on classification and labelling for other substances not complying with the substance identity is irrelevant.

				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."	
comment 36	Page 33	Table 2nd row	Column frequencies according to CLH proposal, linalool	"2% anticipated by Christensson, 2009" as stated in the row "general population studies"	This figure is not correct: we could not find this information in Christensson 2009. See also comment 32 above.
comment 37	Page 33+34	Table	Columns on oxidized linalool and hydroperoxide fraction		These columns are not relevant. Linalool as defined does not autoxidize.
comment 38	Page 34	Table last row	Number of published cases	100-1000 (SCCS, 2012)	See earlier comment. The figure of 100 -1000 is for oxidized linalool not for linalool.
comment 39	Pages 34-36		Comparison of CLP criteria with linalool		The discussion about oxidized linalool and hydroperoxide fraction is irrelevant. Linalool as specified contains antioxidant and does not autoxidize. See also DSM position paper
comment 40	Page 35 page 22	1st bullet point Table, 5th row		"Shubert"	To be corrected into "Schubert"
comment 41	Page 35	2nd ,3rd and 5th bullet point			Discussion about lavender oil is irrelevant because it does not comply with the substance identity of linalool and needs to be deleted.
comment 42	Page 36	Section 4.4.1.5		"high frequency of positive patch test reaction"	Not correct, the frequency is low (see also comment 2)

Dossier Submitter's Response

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General response to comments from different submitters

A number of comments from different submitters have been provided on e.g. skin penetration of linalool, oxidation products in formulations on the market, standardized oxidation of linalool in the laboratory, lack of exposure data, questioning of the validity of clinical patch test data etc. In response to this the following needs to be considered and cannot be neglected.

The CLH proposal is mainly based on human diagnostic patch test data. Such patch testing is a sensitive and specific method to identify contact allergy to the tested substance. The patch test data have been collected and reported from several dermatological clinics in Europe, mainly during the 2000s. Diagnostic patch testing is standardized, as agreed by dermatologists; there are international guidelines on the application, reading and interpretation of patch test data. Patch testing has been performed with linalool as such, and later on with standardized oxidized linalool. The selection of tested patients has been given in the reports with positive patch test frequencies. Taken together, these collected data are a strong basis for classification of linalool as a skin sensitizer in sub-category 1A.

Since 2011, when criteria for discrimination between sensitisers and strong sensitisers (sub-categories 1A and 1B) were introduced in the CLP, there has been a need to clarify how human data could be used for classification and sub-categorisation of sensitisers. Therefore, the Guidance on the Application of the CLP criteria was updated in 2013 with guidance on how to evaluate human patch test data. Guidance values on patch test frequencies from differently selected groups were established in order to distinguish between sub-category 1A and 1B. The guidance values for exposure are based on concentration in products and anticipated use. - These guidance values were worked out in agreement by European dermatologists, member states and industry.

Thus, available human diagnostic patch test data as well as exposure data for linalool have been compared to the guidance values in the CLP Guidance. Exposure data are based on market surveys with analysis of linalool concentrations in products, as cited in section 2.2 of the CLH proposal, as well as the anticipated use of products.

Taken together, human patch test data and exposure data for linalool meet the criteria for sub-category 1A.

It should also be considered that The Scientific Committee on Consumer Safety in its Opinion 2012 concluded that linalool is an "established contact allergen in humans" and that oxidized linalool is "considered to be of special concern" due to the high number of reported cases of sensitization in scientific publications (although a severe underestimation of the real number of cases).

As linalool is extensively found in consumer products it's important, for the sake of protection of consumers that a correct and harmonised classification as a sensitizer in sub-category 1A is assigned to linalool.

Regarding Data supporting non classification of linalool

Linalool in its unoxidized form may cause skin sensitization (e.g. 0.2-0.3% positive patch test frequency in diagnostic patch testing) although the oxidized form is more potent due to the formation of allergenic oxidation products. Regarding the classification of linalool *in the form it can reasonably be expected to be used*, please see response to comment no 4 (DSM Nutritional Products AG).

Regarding General comments on the hypothesis and patch test information presented, i - iv.

Some specific response is given below – for the rest please see the General response to comments from different submitters above.

i) See response to comment no 4 (DSM Nutritional Products AG).

ii) See response to comment no 5 (IFRA).

iii) A structural alert for autoxidation is not sufficient to classify for sensitization. Human data or animal data are needed.

iv) Regarding the concentrations used for diagnostic patch testing in relation to the doses used for induction in animal tests or actual use concentrations in products, the following should be considered: Patch testing is a sensitive and specific tool for diagnosis of contact allergy to a particular substance. The concentration of a sensitizer in the standard patch has been screened out to be the optimal concentration to diagnose sensitization to a particular substance while not inducing sensitization to the same substance when patch testing. The patch test concentrations used are optimal also in the sense that eventual skin irritation properties should not interfere with the reading of the patch test. Thus the patch test concentration is not a threshold for elicitation, which may be much lower. Induction and elicitation reactions usually evolve from repeated exposure during a long time in contrast to a diagnostic patch test reaction which follows after a single exposure.

In a recently published article by Audrain H *et al*. (2014) “Allergy to oxidized limonene and linalool is frequent in the U.K.” Br J Dermatol 171, pp 292-297 the result of a multicenter study in the U.K. was reported, including 4731 patients. 5.9% had positive patch test reaction to hydroperoxides of linalool 1.0% in pet. (from Chemotechnique Diagnostics). 0.3% reacted to stabilized linalool 10.0% in pet., about half of them also reacted to the hydroperoxides. Irritation reactions were distinguished with strict criteria and amounted to 5.9% for the hydroperoxides of linalool and to 0.3% to stabilized linalool. The authors concluded that diagnostic testing with nonoxidised linalool is not useful. Instead they recommend patch testing with the oxidized form and, due to the high rate of positives found, that it should be included in the base line series for patch testing, whereby all patients at dermatological clinics with suspected ACD will be tested.

This study further strengthens the basis for classification of linalool as a skin sensitizer in sub-category 1A.

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RAC's response
All points raised by the industry have been taken into consideration by RAC. Regarding the validity of patch testing for classification purposes, RAC has followed the criteria set out in Reg. 1272/2008/EC and expanded in the Guidance on the Application of CLP criteria (v. 4.0, 2013). Furthermore, RAC has separately evaluated the results of each test material used in the studies referred to in the CLH report and has considered whether or not to include data on lavender oil in its decision-making process. In addition, and as mentioned in RAC's response above, RAC has considered the SID of the substance submitted for harmonised classification and labeling, including the relevance of the presence of additives (i.e. stabiliser), the normally anticipated conditions of use and storage of the substance in the market and the relevance of the various test materials used in the studies referred to in the CLH report with the SID of the of the substance to be submitted for harmonised classification and labeling.

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Date	Country	Organisation	Type of Organisation	Comment number
06/08/2014	Germany		MSCA	3

Comment received

The German CA supports the CLH proposal of the Swedish CA.
We support the assessment that linalool is a skin sensitizer in its oxidized form. Therefore we support the proposed classification of linalool as Skin Sensitizer 1A; H317.

Dossier Submitter's Response

Thanks very much for your support!

RAC's response

RAC has taken into consideration the German CA support for classification of linalool as Skin Sens 1A. RAC has considered the SID of the substance submitted for harmonised classification and labeling, including the relevance of the presence of additives (i.e. stabiliser).

Date	Country	Organisation	Type of Organisation	Comment number
06/08/2014	Switzerland	DSM Nutritional Products AG	Company-Manufacturer	4

Comment received

DSM Nutritional Products AG disagrees with the proposed harmonised classification and labelling for linalool made by the Swedish MS Authority. We take the opportunity to present in detail scientific argumentation for our conclusion that classification and labelling of linalool as skin sensitizer category 1a is not justified.

Therefore, we compile in the attached document the following data on linalool:
(i) Information already presented in the DSM REACH Dossier submitted in 2010 (REACH Dossier (2010), of which not all data was taken into account in the CLH report (2014): state of the art skin penetration data (Green et al. 2007) and/or information on the absence of skin sensitization in human volunteers (Harrison and Spey 2005, Belsito et al. 2008).
(ii) Additional information on mechanistic investigation on skin sensitization of linalool in laboratory animal (Khan & Dearman 2010). These investigations clearly show that linalool is not a skin sensitizer in laboratory animal. This information was only available after submission of the DSM REACH Dossier in 2010 but this information was submitted to the evaluating Member State Sweden in September 2012.
(iii) New information in peer reviewed scientific literature.

Thus, our conclusions presented here are based on those data already included in the REACH Dossier (2010) together with data newly available (please find details in attached document).
Substance identity

This document and the substance identity presented in the DSM REACH Dossier (2010) refers to linalool with a purity between > 96.7 and < 98.2 % (w/w). Linalool is stabilized with an antioxidant (additive), alpha-tocopherol, in a concentration range of > 0.02 to < 0.03 % (w/w) which is part of the substance identity according to the definition of a substance in Regulation (EC) No 1907/2006 Article 3(1) and Regulation (EC) No 1272/2008 Article 2(7)).

It is noticed that non-relevant data were used in the CLH report (2014) throughout the document: For example data on lavender oil containing linalool, artificially produced mixtures such as "oxidized" linalool or data on linalool hydroperoxides were used to justify the proposed classification and labelling as skin sensitizer category 1a. All these substances / mixtures fail to meet the specifications of the substance identity for linalool as placed on the market. This is not in accordance with Regulation (EC) No. 1272/2008 Article 8 (6) which states "Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used."

Thus, for the purpose of discussing the skin sensitization potential of linalool only such information

should be used which specifically addresses the substance linalool as given in the substance identity.
Reactivity of linalool upon air exposure
It is known that substances with allylic structural elements which are also present in linalool are prone to oxidation. Sköld et al. (2004) showed that pure non-stabilized linalool is degraded and that linalool hydroperoxides and degradation products thereof are formed: after 10 weeks 30% of the initial linalool were degraded.

The conditions used in these investigations are not realistic and do not reflect normal production and use conditions. Adequate protection by antioxidants or a combination of antioxidants and further stabilizers such as UV-filters and/or chelating agents prevent such oxidative degeneration both in the pure substance and in personal care products (DSM 2014, Kern et al. 2014). The substance identity of linalool therefore specifies an antioxidant for stabilization (section 2 in the attached document).
In the CLH report (2014) it is argued (based on a paper by Karlberg et al. (1994)) that the use of antioxidants does not adequately protect against oxidation. However, the Karlberg paper studied limonene and its degradation but not linalool. We do not agree that such argumentation is adequate and refer to newer data which specifically addresses the question of potential oxidative degradation of linalool in the presence or absence of antioxidant both as pure substance or in personal care formulations (DSM 2014, Kern et al. 2014). These documents show that linalool is effectively protected from oxidation even under prolonged and accelerated storage conditions.
Toxicokinetics and metabolism upon dermal exposure

According to our interpretation of the available data, the key study on dermal penetration of linalool is the study of Green et al. (2007) in which 14C-radiolabelled linalool was used and which was conducted in compliance with existing OECD guidelines on the conduct of an in vitro dermal penetration study (OECD 428 (2004)). This study was available in our REACH Dossier (2010) but not taken into account in the CLH report (2014). In contrast, published papers were used: The studies of Cal (2006a) or Cal & Sznitowska (2003) do not comply with the OECD 428 guideline (2004) because not all required samples were investigated. For details please refer to section 4.
Once applied to the skin, linalool quickly evaporates (see section 4.1, Green et al. 2007) from skin with only 7% of applied dose remaining after 1h. The available data on dermal absorption of linalool into the viable skin (epidermis and dermis) show that only a minor amount of the applied substance is absorbed being about 4% of the applied substance under non-occluded conditions within 24h.
We are in addition surprised about the use of data on other substances in the CLH report (2014). For example Cal et al. (2001) addressed limonene, diterpene, terpinolene, and eucalyptol, Cal (2006b) studied lavender oil, and Kitahara et al. (1993) did investigations with several terpenes but not with linalool. It is our opinion that such data should not be used when evaluating linalool.
Up to date we found no information whether any form of oxidized linalool once applied dermally is systemically available and/or whether oxidized linalool does penetrate through skin. The only information is that forms of oxidized linalool can induce skin sensitization upon dermal application (e.g. Sköld et al. 2002, 2004, Bezard et al. 1997). In addition, we have no evidence that any form of oxidized linalool can be formed by metabolism in the skin. Any conclusion that this occurs is highly speculative. We consider it therefore not justified to take such discussion into consideration.
Skin sensitization

Linalool was tested extensively with regard to skin sensitization potential in laboratory animal. Most of the data available show no sensitizing potential of linalool: Studies in guinea pigs (Sköld et al. 2002) showed no skin sensitization potential (negative result) for linalool. Some results of local lymph node assays (LLNA) may indicate weak sensitizing potential (Sköld et al. 2004, Basketter et al. 2002).

The concentrations being positive in the LLNA were always equal to 50% or higher (see Table 15 on page 32 in the attached dodument) and showed the typical behavior of a false positive result due to skin irritant properties as suggested by Basketter et al. (1998). A mechanistic investigation according to Gerberick et al. (2002) and Betts et al. (2007) was performed to investigate whether the positive responses in the LLNA were true or false positives. The results of this mechanistic LLNA performed showed that the positive responses seen in the standard LLNAs can be considered the result of skin irritant properties (Khan & Dearman 2010).

In addition, the purity of linalool was important in the LLNA studies: Linalool having been purified prior to the LLNA experiment produced lower responses than the non-purified quality (see Table 15

page 32, Basketter et al. 2002). In further studies, it was clearly shown that the linalool autoxidation products hydroperoxides and some of their subsequent degradation products (epoxides and α,β-unsaturated aldehydes as well as mixtures thereof) were skin sensitizing (positive) in both the LLNA and the Freund's Complete Adjuvant Test (FCAT) (Sköld et al. 2002, Sköld et al. 2004, Bezard et al. 1997). For details please refer to attached document in Table 16 on page 33, Table 17 on page 34. Overall, there are several reasons for the positive responses to linalool in the LLNA: (i) irritation properties of linalool at the higher concentrations, (ii) oxidation of the substance resulting in strongly sensitizing degradation products, (iii) a combination of (i) and (ii), and/or (iv) the use of a test item not complying with the relevant specifications.

Predictive human studies, amongst others a Human Repeated Insult Patch Test (HRIPT) on 135 healthy volunteers, also showed no skin sensitization potential (Harrison & Spey 2005). In the reported case studies (Schubert 2006; Schaller and Korting 1995), some patients showed positive patch test results with linalool; however, it is not clear whether the exposure of the individuals was only to pure linalool.

We are not aware on general population studies in terms of frequency of positive patch tests in the normal population. The CLH report (2014) gives a figure of 2%. However, this figure refers to oxidized linalool and not to linalool itself (see also sections 7.6 and 7.7 in the attached document). In diagnostic human patch tests there were only very few positive reactions in patients (see Table 19 on page 40). Overall only 28 patients out of 12132 consecutive patients reacted positively. Likewise, the SCCS (2012) also concluded that there are less than 100 positive patch tests reported on the basis of the same database as presented here. Even in selected patients only 8 out of 461 showed positive reactions.

Conclusion

Mixtures of linalool with other substances such as essential oils or artificially aged linalool as well as isolated other substances such as linalool hydroperoxide do not comply with the substance identity and consequently such information is not relevant for linalool as placed on the market.
In this document we have shown that linalool as specified in the substance identity does not autoxidize under normal production and use conditions. Antioxidants successfully prevent the oxidative degeneration.

Thus, we do not agree with the proposal of a harmonized classification and labelling of linalool as a skin sensitizer (CLH report (2014)) which is based on the argumentation that it may be potentially oxidized to known skin sensitizers whereas this oxidation step is unlikely to occur under normal production and use conditions.

The dermal absorption of linalool is low because the majority of a substance on the skin evaporates. Only about 4% of the applied linalool penetrates into the deeper skin layers. We are not aware of information on the metabolism of linalool in skin or on the extent of dermal absorption of linalool hydroperoxide or its degradation products. Thus, it should not be speculated about it.
We have shown that linalool is not a skin sensitizer in laboratory animals. Mechanistic investigations show that certain studies in mice (i.e. LLNAs) were false positive due to the skin irritant properties of linalool and/or the use of a test substance not being compliant with the test substance identity.
In terms of human data, studies in healthy volunteers showed not skin sensitizing properties and the overall frequency of patients reacting towards linalool is remarkably low also in consideration of its extensive use.

Based on the overall weight of evidence it is concluded that classification and labelling of linalool as skin sensitizer according to Guidance (November 2013) on the Application of the CLP Criteria of Regulation (EC) No 1272/2008 is not justified.

Dossier Submitter's Response

Regarding Identity.

The identity of linalool is given in the CLH proposal, Part A, section 1.1.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

Regarding the information for identification of hazardous properties, article 5.1 of the CLP says the following:

> "The information shall relate to the forms or physical states in which the substance is placed on the market and *in which it can reasonably be expected to be used*."

The addition of the wording in italics means that information relating to reasonably expected use should also be considered for hazard identification. In article 2, the definition of "use" is given:

> "25. 'use' means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation;".

Thus the definition of "use" is rather wide and the classification should include linalool during e.g. storage, consumption. It is not restricted to the moment the substance is placed on the market. The same reasoning should be applied to testing for classification in article 8.6:

> "6. Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and *in which it can reasonably be expected to be used."*

As a consequence, relevant data for hazard assessment of linalool are not limited to data on the form of linalool which is placed on the market. Also data originating from linalool which has undergone autoxidation, for example during storage and consumption, may be used as a basis for a harmonized classification of linalool.

As referred to in the proposal, a similar reasoning has been applied to rosin and limonene when they were given a harmonized classification as skin sensitisers under the Substance Directive. It was due to the inherent properties of limonene and rosin to oxidise to allergenic forms when in contact with air during normal handling and use.

In the CLH proposal some of the studies are cited as background or as support to the proposal, e.g. studies on lavender oil which may contain up to 40% linalool. Key studies are marked as such in Table 10.

<u>Regarding Reactivity of linalool upon air exposure</u>

According to the comment linalool is stabilised with α-tocopherol in order to prevent oxidation. The addition of antioxidants may though, as stated in 4.4.1.3 of the CLH dossier, be hard to control as many factors may operate at the same time. It may work initially but other reactions may prevent the antioxidant effect on linalool. Factors which may interfere with the antioxidant effect on linalool and on a mixture containing linalool are

-the properties of the antioxidant, i.e. its degradation to toxic/nontoxic compounds

-the dosage of the antioxidant

-purity of linalool/mixture containing linalool. Other components, ingredients or impurities, which are readily oxidized may interfere with the effect of the antioxidant on linalool

-the antioxidant is consumed itself while exerting the antioxidant effect.

It is argued that the oxidation studies on linalool are not valid. However, these studies are conducted under standardized conditions and the relationship of oxidation and sensitizing properties is clearly demonstrated (Sköld et al., 2004); thus the results are both clarifying and valid and should be considered.

In a recently published article, "Detection of potentially skin sensitizing hydroperoxides of linalool in fragranced products" by Kern S et al., Anal Bioanal Chem, 2014 Oct; 406(25):6165-78, the formation of hydroperoxides was studied in hydroalcoholic products, samples recalled from consumers and antiperspirant products. Results

indicated that levels of hydoperoxides in the formulated products investigated stem mainly from the raw material and was not formed during storage.

Taken together, it seems that stabilisers are not safe to protect linalool from being oxidized and giving rise to sensitization. The high frequency of positive patch test reactions to linalool and oxidized linalool in European dermatological clinics illustrates and confirms the allergenic properties of linalool and the presence of the more allergenic oxidation products. Therefore, the addition of a stabilizer to the manufactured linalool does not appear to safely prevent autoxidation.

Regarding Dermal penetration and metabolism.

In section 4.1 of the CLH proposal information on skin penetration of linalool and other monoterpenes are given, indicating skin penetrating properties of linalool. No statement is given that linalool should act as a sensitizer through a bioactivation mechanism in the skin.

Even though the study by Green et al. (2007) indicates poor skin penetration of linalool, all human patch test data on sensitization to linalool is a sign that linalool penetrates the skin and is further processed in the induction process for skin sensitization. Thus the study by Green et al. cannot be taken as a proof that linalool in all instances is not absorbed through the skin.

Regarding Skin sensitization

All human data on skin sensitization of unoxidised and oxidized linalool is collected in Table 10 of the CLH proposal. Key studies are marked as such. The quality of linalool in the cited studies is described as far as possible. Overall, it can be seen that patch test frequencies with oxidized linalool are higher than with the unoxidised form.

It is noted in the comment that the oxidation products of linalool are described as strong skin sensitisers, which is in agreement with the CLH proposal.

Regarding the HRIPT which is referred to in the comment, it is not used as a predictive test to explore sensitization properties of substances. It's rather used as a so called "confirmatory" test by industry before marketing of products. The exposure is not so intense and the number of subjects in the test is low. It would have been remarkable if one of the 135 volunteers turned out to be positive in this test, as the resulting positive frequency of 0.7% is relatively high in this context. The test result could be described as a positive frequency of < 0.7%.

In the table in 4.4.1.3 of the CLH dossier the *Number of published cases* should be 11-100 for non-oxidised and 101-1000 for oxidized linalool, as pointed out in the comment. In this context it should be noted that linalool is not included in the Fragrance mixtures I and II; therefore it is not included in standard testing for ACD (allergic contact dermatitis) and not routinely tested at dermatological clinics. Thus it could be expected that a number of cases of ACD for linalool are not diagnosed.

Animal data shows unoxidised linalool being a weak sensitizer, however oxidation increases this property. The comment suggests that the positive response to unoxidised linalool in LLNA is due to irritation. However, there is to our knowledge no established method to distinguish irritants, giving a false positive response in LLNA from true sensitisers. Therefore we would rather refer the weakly positive response in LLNA to a weakly sensitizing property of unoxidised linalool.

RAC's response

RAC appreciates the scientific input submitted by the industry. All new data on oxidative degeneration of commercial products have been taken into consideration. Regarding dermal penetration, no statement is given in the CLH report that linalool should act as a sensitiser through a bioactivation mechanism in skin. Therefore, relevant data are not discussed. The Khan & Dearman, 2010 study is not considered for classification purposes, although it is the only animal study with test

material on stabilised linalool. The implication of any irritant properties of linalool in a possible false positive result in LLNA has been considered by RAC, taking into account all available information and the OECD 429 Guideline. Furthermore, see also all RAC's responses above.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

Date	Country	Organisation	Type of Organisation	Comment number
07/08/2014	Belgium	IFRA (International Fragrance Association)	Industry or trade association	5

Comment received

IFRA does not approve the proposal made by the Swedish Authorities for a classification of Linalool as a skin sensitizer in sub-category 1A due to several procedural concerns and some general conclusions drawn in the above mentioned report (and the basis on which this took place).

Details are provided in the attached comments.

ECHA note: The attachment no.4 has been copied below.

- Sensitizing properties of any substance not being a sensitizer as such but with the potential to get oxidized and form oxidation products/impurities with sensitizing properties, will very much depend on the degree to which the sensitizing impurities are formed.
- Analytical tools to collect information about exposure to oxidised form of terpenes are available but currently not validated.
- Research is ongoing to determine evidence for exposure to oxidized Linalool in the population or the occurrence of oxidized Linalool in products in the industrial supply chain. Analytical evidence suggests that Linalool oxidation does not readily occur in the supply chain.
- Artificial laboratory oxidation conditions for the preparation of the material used in patient diagnosis (patch testing), providing the basis for the arguments made around Linalool, have no relationship to how substances and commercial products are handled throughout the supply chain

It is therefore not possible to conclude on an adequate classification and labelling of Linalool based on the potential presence of oxidation products according to the principals as outlined in the CLP Regulation.

Procedural concerns:

We note that Article 5.1 of the CLP Regulation (1) explains that the "relevant available information" on which classification is to be based shall relate to "the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used". The ECHA «Guidance on the application of the CLP criteria» (2) provides more detail with regard to the meaning of "reasonably expected use" as "intended use or reasonably foreseeable conditions of misuse".

The autoxidation studies mentioned in the Swedish CLH report (3) involve the agitation (magnetic stirrer) of undiluted Linalool in the presence of air for long periods. It was reported that after 30 weeks only 50% of Linalool remained and after 80 weeks less than 5% remained. As such they constitute an intentional chemical transformation. On the other hand, "reasonably expected use" has been shown (4) to lead to a considerably lower degree of oxidation. The conditions used in the Swedish experiments cannot be considered as "intended use or reasonably foreseeable conditions of misuse". In fact, they constitute an intentional attempt (albeit justifiable in the context of a scientific investigation) to effect a chemical transformation of this substance. We have noted that the CLP Regulation would clearly exclude the attribution of the hazards of the products of an intentional chemical transformation process to the original substance used as a starting material in that process (e.g. the hazards associated with Acetic acid do not apply to or replace those of Ethanol from which it is made by intentional oxidation).

Furthermore, as the Swedish proposal is based on the potential formation of impurities, we note that Article 11 (1) of the Regulation states that "*Where a substance contains another substance, itself classified as hazardous, whether in the form of an identified impurity, additive or individual constituent, this shall be taken into account for the purposes of classification, if the concentration of the identified impurity, additive or individual constituent is equal to, or greater than, the applicable cut- off value in accordance with paragraph 3*" and believe that the characterization of these impurities and their hazard classification, already greatly advanced by Swedish scientists (5) should be completed and applied to the classification of different qualities of this substance.

The CLH report does not provide any evidence for exposure to oxidized Linalool in the population or the occurrence of oxidized Linalool in products in the industrial supply chain.

Currently no data are in the public domain indicating significant exposure of consumers or workers to oxidized Linalool. In absence of such data the assumption "Linalool = Linalool hydroperoxide" for C&L purposes is not justified.

This gap is recognized by the research groups having investigated the Linalool oxidation and attempts to develop methodologies were made (6, 7). As mentioned before, initial measurements (4) show no significant oxidation of Linalool as used commercially.

This question is also being addressed as an element of the IDEA project by the pre-hapten task force (http://www.ideaproject.info/eventsmanager/6/16/IDEA-Hydroperoxides-TF-Kick-off-meeting) including analytical experts from industry and the experts on Linalool (aut)oxidation.

In conclusion, without any evidence for exposure or occurrence in products, a pre-emptive regulation is inappropriate. Work is underway to fill this knowledge gap.

Concerns about general conclusions made and approaches taken in the CLH report:

The labelling approach taken in the Swedish CLH proposal recognizes that Linalool in its pure form should not be regarded a sensitizer.

What is of concern is the generalized conclusion that because of the potential of (aut)oxidation under certain experimental conditions with the subsequent formation of hydroperoxides (recognized as a sensitizer based on historical animal data) the substance itself should be regarded as and classified as a category 1A sensitizer. Many substances have the ability to become oxidized depending on the conditions of treatment and exposure. Some might form oxidation products which are sensitizers of various potency, others not.

The sensitizing properties of any substance not being a sensitizer as such but with the potential to be oxidized and form oxidation products/impurities with sensitizing properties, will very much depend on the degree to which the sensitizing impurities are formed, depending on susceptibility for oxidation, the environmental conditions etc. It is therefore not possible to conclude on an adequate classification and labelling of Linalool based on the potential presence of oxidation products according to the principles as outlined in the CLP Regulation.

If the argument of the CLH proposal is followed, then any chemical that under the appropriate oxidative conditions could form products with potential toxicological effects would need to be classified based on this state and not based on its form while used in industrial practice. This does not appear to be a sensible and proportionate approach.

In the REACH database of pre-registered substances, hundreds of chemicals likely contain a structural alert for autoxidation. Creating a precedent needs to be carefully evaluated as it will affects C&L of an enormous number of chemical products. Following this route for a precautionary principle ("who can guarantee that in rare cases the remaining in an almost empty container do not start to oxidize?") is also not appropriate, as C&L should inform on hazards in common practice. Over-labelling as proposed which may later be generalized to all molecules prone to oxidation under exaggerated regimen, completely undermines the usefulness and relevance of the C&L approach.

Concerns about interpretation of patch test data

Clinical (patch test) data play an important role in the argumentation used in the CLH proposal.

The patch test data on which many of the reports' conclusions rely, do not indicate the material to be a potent sensitizer that is inducing via its use in consumer products or workplace conditions but only shows that it (in a non-commercial form, specifically designed for diagnostic testing and not necessarily standardized composition) elicits reactions in a number of patients.

There are a lot of important questions around the patch testing with oxidized terpenes that need to

be adequately answered before deriving conclusions as drawn in the CLH proposal.

Without an agreed analytical method it is impossible to understand the amount of hydroperoxides delivered by patch tests to ensure that there is no active (sensitization) induction during the diagnostic procedure due to unrealistically high levels. In addition there remain questions about the stability of the patches and an investigation about the variability of the oxidation material presence over time would need to be carried out.
In addition, a diagnostic patch test could also be unspecific and patient reactions observed are concomitant reactions and therefore coming from a different inducing agent. This would not allow to generally link the positive patch test reactions with an induction caused by the presence of a specific oxidised material in a fragranced consumer product.

To answer these important questions in the framework of the IDEA project (http://www.ideaproject.info/), a series of workshops have been initiated. The first outcome of these is that an agreed and validated analytical method is required to reliably determine the levels of hydroperoxides in raw materials and finished consumer products. A project has already been initiated to achieve this.

Subsequently, it will be possible to determine with greater certainty to which extent a new classification should be established or other risk management measures should be taken. (Indeed the classification on its own would not be effective to protect consumers).
To achieve this objective, in the scope of the IDEA project, the scientific methods and their outcomes are planned for Spring 2016 with an investment estimated at 500,000€.

In light of the above arguments, IFRA does not approve the proposal made by the Swedish Authorities for a classification of Linalool as a sensitizer category 1A.

References:

(1) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
(2) Version 4 of November 2013: http://echa.europa.eu/documents/10162/13562/clp_en.pdf.
(3) E.g. Sköld M, Börje A, Matura M and Karlberg A-T (2002). Studies on the autoxidation and sensitizing cpacaity of the fragrance ingredient linalool, identifying a linalool hydroperoxide, Cont. Derm. 6(5):267-72.
(4) Kern et al (2014). Detection of potentially skin sensitizing hydroperoxides of linalool in fragranced products. Accepted in Analytical and Bioanalytical Chemistry.
(5) E.g. 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.
(6) Rudbäck J, Islam N, Nilsson U and Karlberg A-T (2013). A sensitive method for determination of allergenic fragrance terpene hydroperoxides using liquid chromatography coupled with tandem mass spectrometry. J Sep Sci 36, 1370-8.
(7) Rudbäck J, Ramzy A, Karlberg A-T and Nilsson U (2014). Determination of allergenic hydroperoxides in essential oils using gas chromatography with electron ionization mass spectrometry. J Sep Sci.

[End of attachment no. 4]

Dossier Submitter's Response

Regarding Procedural concerns

Please see response to comment no 4 (DSM Nutritional Products AG).

Regarding article 11.1 of the CLP we do not interpret the content of this article as applicable to the classification of linalool. The classification should relate to linalool with the identity as described in the CLH proposal and to *the forms in which it can reasonably be expected to be used*.

Regarding exposure evaluation, it is conducted by comparing exposure data with the guidance values provided in the Guidance on the Application of the CLP criteria. Exposure data for linalool originate from market surveys with

analysis of linalool content in products (Part B, section 2.2 of the CLH proposal) and anticipated use of products. Taken together these data are relevant for evaluation of exposure and for comparison with the criteria for low exposure.

Regarding Concerns about general conclusions made

There are, nota bene, high frequencies of positive patch test reactions to oxidized linalool reported from several European dermatological clinics. It means that exposure to oxidized linalool followed by sensitisation has taken place among individuals tested positive.

Please note that a structural alert for autoxidation is not sufficient to classify for sensitization. Human data or animal data are needed.

Regarding Concerns about interpretation of patch test data

Diagnostic patch testing at dermatological clinics is conducted according to international standards as agreed among dermatologists, i.e. standardization of the application of patches, the reading of reactions and the interpretation of results. Reported positive patch test frequencies from such standadised testing is a good basis for evaluation of the epidemiology of contact allergens. Therefore such data cannot be neglected but need to be considered.

See also General response to comments from different submitters and point iv) under comment no 2 (Givaudan).

RAC's response

The comments made are noted and to a large extent they coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above. As a separate remark, positive patch tests in humans for oxidised linalool mean that the human population has been somehow exposed to oxidised linalool.

Date	Country	Organisation	Type of Organisation	Comment number
07/08/2014	France	PRODAROM	Industry or trade association	6

Comment received

PRODAROM, member of IFRA (International Fragrance Association), represents in France the manufacturers of fragrance materials. PRODAROM fully supports the IFRA general comments sent to ECHA in reply to this public consultation. In summary, PRODAROM does not approve the proposal made by the Swedish Authorities for a classification of Linalool as a skin sensitizer in sub-category 1A due to several procedural concerns and some general conclusions drawn in the above mentioned report (and the basis on which this took place).

• Sensitizing properties of any substance not being a sensitizer as such but with the potential to get oxidized and form oxidation products/impurities with sensitizing properties, will very much depend on the degree to which the sensitizing impurities are formed.
• Analytical tools to collect information about exposure to oxidised form of terpenes are available but currently not validated.
• Research is ongoing to determine evidence for exposure to oxidized Linalool in the population or the occurrence of oxidized Linalool in products in the industrial supply chain. Analytical evidence suggests that Linalool oxidation does not readily occur in the supply chain.
• Artificial laboratory oxidation conditions for the preparation of the material used in patient diagnosis (patch testing), providing the basis for the arguments made around Linalool, have no relationship to how substances and commercial products are handled throughout the supply chain.
It is therefore not possible to conclude on an adequate classification and labelling of Linalool based

on the potential presence of oxidation products according to the principals as outlined in the CLP Regulation.

Dossier Submitter's Response

Please see response to comment no 5 from IFRA.

RAC's response

Comments noted. For details see all RAC's responses to comments above.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	Belgium	Procter & Gamble NV/SA	Company-Downstream user	7

Comment received

We do not support the proposal for a harmonized classification of LINALOOL, CAS#: 78-70-6; EC#: 201-134-4, as a Skin Sensitiser Cat. 1A, H317. Our specific arguments which form the basis of this position are provided below under the heading "Any Other Hazard Classes or Endpoint: Skin Sensitisation".

Dossier Submitter's Response

As the comment is similar to comment no 15 from Cosmetics Europe, please see response to comment no 15.

RAC's response

Noted. For more details please see all RAC's responses above.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	Belgium	A.I.S.E.	Industry or trade association	8

Comment received

The CLH report from the Swedish Authorities propose a classification as skin sensitizer category 1 A for linalool based on the skin sensitisation properties of the oxidised linalool. A.I.S.E. generally supports comments provided by IFRA, in particular we would like to stress the following:

While it has been shown that linalool autoxidises under certain experimental conditions which cannot be considered to reflect normal conditions of storage, handling and use, with the subsequent formation of hydroperoxides being recognised as a sensitizer, there is no evidence provided that exposure of consumers or workers to oxidised linalool occurred in products as placed on the market. Linalool is typically present in a product matrix which contains anti-oxidants and the consumer products are stored in closed containers without excessive air exposure over several months.

This proposal is thus not in line with article 5.1 of the CLP regulation stating that the classification should be based on "the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used". In the absence of further evidence of possible formation of hydroperoxides of linalool during normal storage, handling and use by the consumer, it appears inappropriate to classify linalool on the basis of effects driven by its potential derivate, an impurity which may or may not be present in the parent substance. In line with the spirit of the legislation and with existing practices, the classification should focus on the intrinsic hazard of linalool as such.

In addition, we draw your attention to the fact that improvement of fragrance contact allergy diagnosis and risk assessment of fragrance allergens, including assessment of oxidation impurities for certain substances, is addressed by a multi-stakeholder research programme led by IFRA, and fully supported by A.I.S.E.: the IDEA project (International Dialogue for the Evaluation of Allergens). This project involves leading international scientists and is supported by DG Sanco. Since the

measurement of hydroperoxides in perfumes and diagnostic procedures are being improved, it is premature to address oxidised linalool impurities for harmonised classification of the parent substance. If there is a human health issue identified by the medical community, the broader question is how to best address it from a risk management and regulatory perspective as CLH appears not to be appropriate to solve it. It can be noted as well, that the Detergent Regulation already implies the mandatory label of allergenic substances on the packaging of detergents if added at concentrations exceeding 0,01% w/w - see Directive 2003/15/EC (7th amendment to Directive 76/768/EEC, Annex III, part I), it is also done on a voluntary basis for air-freshener via A.I.S.E. Product Stewardship Program.

Dossier Submitter's Response

Please see response to comment no 5 from IFRA.

RAC's response

The comments are noted and to a large extent they coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	Belgium	Cosmetics Europe	Industry or trade association	9

Comment received

Cosmetics Europe believes that the proposal for a harmonized classification of LINALOOL, CAS#: 78-70-6; EC#: 201-134-4, as a Skin Sensitiser Cat. 1A, H317 is not scientifically justified for the reasons provided.

Dossier Submitter's Response

Please see response to comment in no 15.

RAC's response

The comments made are noted and to a large extent they coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
30/07/2014	Netherlands	RIVM	MSCA	10

Comment received

Both human and animal studies with oxidized linalool result in sensitization, for which classification as Cat 1A is required. It is noted however, that, in contrast to the animal data, also in some of the human studies with unoxidized linalool, the guidance values for classification in sub-category 1A are fulfilled (2% in a general population study, 0-4% in selected dermatitis patients and 15% in selected workers with known exposure and dermatitis), as is shown in the table on page 33 and 34. We therefore agree to classify linalool as skin sensitizer Cat 1A; H317.

The main assumption in this proposal is that people are only exposed to linalool hydroperoxides formed from auto oxidation of linalool resulting in the human cases. However, there is no information whether there are other potential sources of linalool hydroperoxide exposure which could have resulted in human cases such as the use of the linalool peroxides themselves. Please provide information on the presence or absence of other potential sources of linalool hydroperoxides.

Dossier Submitter's Response

Thanks for your support to classify in category 1A.

We have not found any information on the formation of the two main hydroperoxides from other

substances than linalool when reviewing the documentation for the CLH dossier. To our knowledge they are also not marketed as such.

RAC's response

RAC has taken into consideration the Netherlands CA support for classification of linalool as Skin Sens 1A. RAC has considered the SID of the substance submitted for harmonised classification and labeling, including the relevance of the presence of additives (i.e. stabiliser).

OTHER HAZARDS AND ENDPOINTS – Skin sensitization

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Finland	Tukes	MSCA	11

Comment received

The Finnish CA supports the proposed classification and labelling as Skin Sens. 1A; H317 for Linalool. We agree that the criteria for classification in sub-category 1A are met by the well described human data present in the CLH report. We also see that reported animal studies support this classification, although in our view, the results alone would not be sufficient for the sub-categorisation. Finland would like to thank Sweden for this very clear, thorough and well justified CLH proposal.

Dossier Submitter's Response

Thanks very much for your support!

RAC's response

RAC has taken into consideration the Finnish CA support for classification of linalool as Skin Sens 1A. RAC has considered the SID of the substance submitted for harmonised classification and labeling, including the relevance of the presence of additives (i.e. stabiliser). With regard to animal studies with non-oxidised linalool, results point to classification as Skin Sens 1B.

Date	Country	Organisation	Type of Organisation	Comment number
01/08/2014	Belgium		MSCA	12

Comment received

We would like to thank Sweden for initiating a CLH proposal on Linalool.

We agree with the DS to consider the pure linalool as a weak sensitising. This is supported by the few dermatitis patients affected in the patch test studies presented in the dossier. The Schubert (2006) study indicates a high number of reactions (15,4%) but this can be justified by the small sample of workers (4/26 patients)

Generally, the human and animal studies indicate a clear sensitization following the exposure to oxidised linalool. We however question the subcategorization chosen by the DS for linalool as we consider the results not clear cut enough.

In the LLNA study (Shöd et al. 2004) with pure linalool, the EC3 value after 45 weeks is 4.8% due to the concomitant increase allergenic hydroperoxides. This value fulfils the criteria for category 1B. The other LLNA study (Hagvall et al. 2008) with lavender oil indicates a EC3 value of 4.4%, also fulfilling the criteria for category 1B. therefore both studies support the moderate potency with EC3-value >2%. Besides, this last study cannot prove that the observed sensitisation is related only to oxidised linalool as no quantification was performed according to the DS.

The FCAT study (Sköld et al. 2002) indicates a high number of response following intradermal induction at high concentration : 33.3% , 53.3% and 86.7% following the challenge concentrations 2.6%, 5.1% and 10.3%. Besides, no significant response was recorded for 1%. We therefore consider that it is not possible to conclude whether or not "linalool is a strong sensitizer ". On the other hand, this information may indicate a moderate potency.
Another uncertainty concerns the senzitisation observed following the exposure to the oil lavender

and the linalool content. There is no clear evidence in the Japanese study (Sugiura et al.2000) indicating that the positive patch tests to lavender oil among patients is due to oxidized linalool as no information on linalool content is given. We consider then that it is possible to establish a link between the oil lavender, its linalool content and the sensitization.
Finally, the scoring established by the DS are not so well substantiated in the dossier.
All in all, we consider that the effects presented in the dossier don't support so clearly the sub categorization 1A. Regarding the uncertainties of some information and the results observed, we are in favor of category 1B.

Dossier Submitter's Response

The proposal to subcategorise linalool in 1A is based on human diagnostic patch test data from consecutively tested patients in European clinics, the number of published case reports and the relatively low exposure. See section 4.4.1.4 (ii) and (iii) in the dossier.
These data are compared to the guidance values in Guidance on the Application of the CLP criteria (November 2013). See end of section 4.4.1.3 in the dossier where relevant data are tabulated.
From this follows that classification in sub-category 1A is appropriate.

The subcategorisation is supported by animal data, i.e. a low EC3 value in LLNA on the hydroperoxide fraction of oxidised linalool and a high frequency of sensitisation in FCAT.

RAC's response

RAC has taken into consideration the Belgium CA support for classification of linalool as Skin Sens 1B. RAC has considered the SID of the substance submitted for harmonised classification and labeling, including the relevance of the presence of additives (i.e. stabiliser). With regards to animal studies with non oxidised linalool, results point to classification as Skin Sens 1B. The study of Hagvall et al. on Lavender oil is not considered relevant for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
06/08/2014	Switzerland	DSM Nutritional Products AG	Company-Manufacturer	13

Comment received

We disagree with the proposed harmonised classification and labelling of Linalool. Detailed comments are provided under general comments and the attached document.

*ECHA note: The attachment no.3 (*DSM comments CLH proposal_Linalool 2014.pdf) *has been provided separately.*

Dossier Submitter's Response

Please see response to comment no 4.

RAC's response

All comments made by DSM have been taken into consideration.

Date	Country	Organisation	Type of Organisation	Comment number
06/08/2014	Germany		MSCA	14

Comment received

1) Linalool is a sensitising fragrance that is not directly reactive. It requires previous activation making it a potent sensitizer. Pure linalool is a weak sensitizer, but can be activated to a more potent sensitizer via simple chemical transformation - air oxidation (autoxidation). The autoxidation in air is an intrinsic property of linalool. Autoxidation is a free radical chain reaction in which hydrogen atom abstraction in combination with addition of oxygen forms peroxyl radicals. The reaction shows selectivity for positions where stable radicals can be formed.

The classification proposal of linalool is based on human and animal data. The human studies reported are mainly diagnostic patch test studies. The skin sensitisation potency of linalool was

investigated using unoxidized (pure) linalool, oxidized linalool and lavender oil, of which linalool is a major component. In the animal studies pure (unoxidized) linalool, oxidized linalool, unoxidised lavender oil and oxidized lavender oil were investigated.

It was shown that the skin sensitization potential of linalool is closely related to oxidation and the primary oxidation products, the hydroperoxides, are the main allergens. Thus the skin sensitizing properties of oxidized linalool have been demonstrated in humans and in tests with animals. Conclusion: The presented human and animal data of linalool are sufficient for classification of linalool as skin sensitizer of sub-category 1A in accordance with CLP Regulation.

2) The generic concentration limits (GCL) for classifying mixtures containing sensitizing chemicals of the sub-category 1A is ≥ 0.1%. Given the availability of data on the content of linalool in different products and results from the patch tests, it would be of value to specifically address in the report if this GCL is sufficiently protective or specific concentration limits (SCL) should be considered.

Dossier Submitter's Response

1) Thanks very much for your support.
2) Thanks for this comment. Regarding human data it has not been possible to deduce the concentration needed for induction of sensitisation. The actual exposure concentrations seem to vary between a few ppm up to 0.38%, according to published studies. No more specific data are, to our knowledge, available which would allow setting an SCL.
   It is also difficult to deduce such thresholds from animal data as different assumptions have to be made in order to extrapolate to humans.
   Taken together, we are not able to set an SCL based on available data; even though the need for an SCL for linalool cannot be excluded.

RAC's response

RAC notes the comment regarding a SCL.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	Belgium	Cosmetics Europe	Industry or trade association	15

Comment received

• Animal data on pure (non-oxidised) LINALOOL indicates that the substance is not a skin sensitizer (EC3 was 46.2%). LINALOOL is considered to cause skin irritation (provisionally classified as H315) and when tested at concentrations having irritant potential, only a very weak allergic response was seen in mice which were administered pure LINALOOL. Additionally, no clear dose-response relationship was established (Sköld, M., Börje, A., Harambasic, E., Karlberg, A-T. 2004). Therefore, pure LINALOOL is not considered as a sensitizing substance and does not have to be classified as such based on the criteria of Annex I of 1272/2008/EC and Annex VI of 67/548/EEC.

• LINALOOL does not have a structural alert for sensitisation.

• An OECD SIDS report (2002) concluded that LINALOOL is not considered to be a sensitizer. It was not a skin sensitizer in a guinea pig test. This conclusion was further supported by a host of patch test challenges performed in Dutch allergy clinics in which < 1% of subjects reacted positive to LINALOOL. LINALOOL has also been patch tested on 2401 patient in some German dermatological clinics from January 2003 to December 2004. Only 0.3% of these patients reacted positively to LINALOOL. The authors thus considered LINALOOL as being a very rare allergen apparently turn into allergen after substantial oxidation (Schnuch et al, 2007). The substance was considered to be of 'extremely weak potency' in an assessment of human sensitization potency and, in comparison with allergenic potency based on mouse LLNA data, LINALOOL was also considered to have 'weak' potency.

• Pure LINALOOL is not a sensitizer while hydroperoxides and other oxidation products have shown sensitizing properties. The two major oxidation products of LINALOOL were identified as 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol. In guinea pig sensitization studies, LINALOOL of high purity gave no reactions, while LINALOOL that had been oxidized for >10 weeks sensitized the animals. It was concluded that autoxidation of LINALOOL is essential for its sensitizing potential (Sköld et al., 2002). However, the single mouse

LLNA result indicating that > 10 weeks air exposed, oxidized LINALOOL may be a strong skin sensitizer (EC3 value of 1.6%) is unrealistic and not relevant for regulatory classification purposes. The two major hydroperoxides present after extensive air exposure of LINALOOL were isolated and mixed before testing together in a procedure which has no relevance for human exposure.

• Such qualities of linalool and the data derived from them do not represent any normal or naturally occurring situation during cosmetic product use. Storage and packaging conditions, quality standards for essential oils and ingredients as well as the stability of the finished product (using antioxidants) are all designed to avoid peroxidation. The classification proposal for linalool is therefore not appropriate.

• Auto-oxidation can occur with LINALOOL – however the extent to which it occurs is much lower than what has been studied under extreme experimental conditions of prolonged air exposure (>10 weeks exposure to air). LINALOOL is typically present in a product matrix which either contains anti-oxidants or is stored in a closed container without excessive air exposure. These are the conditions of normal storage, handling and use of LINALOOL-containing products.

• Diagnostic Patch Test data are not suitable for hazard classification – they cannot be used for quantification of thresholds for induction as they do not provide any dose response data (they can be used for elicitation threshold studies). Further, patch test data with oxidized LINALOOL (after 10, 25 and 45 weeks of air exposure) creates an experimental situation which is not relevant for the normal handling and use of products containing LINALOOL by consumers. Evidence from well-controlled animal studies is typically more reliable for use in classification than evidence from clinical patch test results designed for diagnostic purposes and prevalence evaluations.

• 6% oxidized linalool used in a multicenter study on consecutive eczema patients elicited a high rate of positive reactions - 6.9% (Christensson et al, 2012); it was however difficult to determine the clinical relevance and the unusually high rate of doubtful reactions (9.2%) suggests that the test material might have been irritant thus giving rise to false positive patch test reactions.

• An IFRA Industry "Specification" exists already for LINALOOL since 2008 which limits the peroxide level to 20mmol/l for product use. The IFRA guidance also recommends that antioxidants (e.g. BHT) are added at the time of production of the raw material.

Dossier Submitter's Response

Please note: the response points below refer to the comment points in the same order as they appear in the comment box above.

- We consider pure linalool to be a weak sensitizer based on animal data from LLNA (Sköld *et al*., 2004; Basketter *et al*., 2002; Ryan *et al.*, 2000).
- Linalool has been demonstrated to be prone to autoxidation, thereby making it a strong sensitiser.
- Data presented here seem to relate to unoxidised linalool. However both human and animal data demonstrate that autoxidation of linalool increases the sensitizing capacity.
- The LLNA on a 5:3 mixture of the two major hydroperoxides illustrates their high sensitizing capacity (EC3 1.6%). As the hydroperoxides are present in oxidized linalool, this LLNA study is relevant as support to the classification of linalool as Skin sens. category 1A, see section 4.4.1.4 i) and ii) of the dossier.
- Even though precautionary measures are made during manufacturing and in the supply chain it is obvious that oxidation of linalool takes place. This is illustrated by the high frequency of positive diagnostic patch tests reported from European dermatological clinics. See also General response to comments from different submitters in Comment no 2 (Givaudan).

- Obviously autoxidation and sensitization takes place; positive patch test frequencies to oxidized linalool of up to 7.2% has been reported from European dermatological clinics among consecutively tested patients.
- Diagnostic patch test data should be used for classification according to the CLP criteria and the Guidance on the Application of the CLP criteria. See also General response to comments from different submitters in Comment no 2 (Givaudan).
- In the study by Christensson et al., 2012, the positive patch test frequency to oxidized linalool was 6.9%. The positive reactions were carefully distinguished from doubtful and irritant reactions (9.2%) according to the international ICDRG guidelines; thus the 6.9% could be referred to allergic reactions.
- Noted. Reference to the peroxide limit by IFRA is made in section 3 of the CLH proposal. Obviously the recommendations made by IFRA have not been sufficient to prevent the formation of sensitizing oxidation products of linalool in products on the market.

RAC's response

We appreciate the summary of the scientific data submitted by the industry. The comments are noted and to a large extent coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	Belgium	Procter & Gamble NV/SA	Company-Downstream user	16

Comment received

Animal data on pure (non-oxidised) LINALOOL indicate that the substance is not a skin sensitizer (EC3 was 46.2%). LINALOOL is considered to cause skin irritation (provisionally classified as H315) and when tested at concentrations having irritant potential, only a very weak allergic response was seen in mice which were administered pure LINALOOL. Additionally, no clear dose-response relationship was established (Sköld, M., Börje, A., Harambasic, E., and Karlberg, A-T., 2004). Therefore, pure LINALOOL is not considered as a sensitizing substance and does not have to be classified as such based on the criteria of Annex I of 1272/2008/EC and Annex VI of 67/548/EEC.

LINALOOL does not have a structural alert for sensitisation.

An OECD SIDS report (OECD SIDS, UNEP Publications, 2002) concluded that LINALOOL is not considered to be a sensitizer. It was not a skin sensitizer in a guinea pig test. This conclusion was further supported by a host of patch test challenges performed in Dutch allergy clinics in which < 1% of naïve subjects reacted positive to LINALOOL. The substance was considered to be of 'extremely weak potency' in an assessment of human sensitization potency and, in comparison with allergenic potency based on mouse LLNA data, LINALOOL was also considered to have 'weak' potency.

Pure LINALOOL is not a sensitizer while hydroperoxides and other oxidation products which may occur following autoxidation have shown sensitizing properties. The two major oxidation products of LINALOOL were identified as 7-hydroperoxy-3,7-dimethylocta-1,5-diene-3-ol and 6-hydroperoxy-3,7-dimethylocta-1,7-diene-3-ol. In guinea pig sensitization studies, LINALOOL of high purity gave no reactions, while LINALOOL that had been oxidized for >10 weeks sensitized the animals. It was concluded that autoxidation of LINALOOL is essential for its sensitizing potential (Sköld, M., Börje, A., Matura, M. and Karlberg, A-T., 2002). However, the single mouse LLNA result indicating that > 10 weeks air exposed, oxidized LINALOOL may be a strong skin sensitizer (EC3 value of 1.6%) is unrealistic and not relevant for regulatory classification purposes. The two major hydroperoxides present after extensive air exposure of LINALOOL were isolated and mixed before testing together in a procedure which has no relevance for human exposure. Such data do not represent any normal or naturally occurring situation during consumer product use.

Autoxidation can occur with LINALOOL – however the extent to which it occurs is much lower that what has been studied under extreme experimental conditions of prolonged air exposure (> 10 weeks exposure to air). LINALOOL is typically present in a product matrix which either contains anti-

oxidants or is stored in a closed container without excessive air exposure. These are the conditions of normal storage, handling and use of LINALOOL-containing products.

Diagnostic Patch Test data are not suitable for hazard classification – they cannot be used for quantification of thresholds for induction as they do not provide any dose response data (they can be used for elicitation threshold studies). Further, patch test data with oxidized LINALOOL (after 10, 25 and 45 weeks of air exposure) creates an experimental situation which is not relevant for the normal handling and use of products containing LINALOOL by consumers. Evidence from well-controlled animal studies is typically more reliable for use in classification than evidence from clinical patch test results designed for diagnostic purposes and prevalence evaluations.

An IFRA Industry "Specification" exists already for LINALOOL since 2008 which limits the peroxide level to 20mmol/l for product use. The IFRA guidance also recommends that antioxidants (e.g. BHT) are added at the time of production of the raw material.

LINALOOL is subject to on-pack listing since many years for certain consumer products sold in Europe. LINALOOL was identified by the SCCS in 1999 as a Fragrance Allergen in humans which should be listed on the label of cosmetics and household cleaning products if present above specific threshold limits. This is informative for the consumer as it allows individuals to be aware of the presence of LINALOOL above these cut off levels in their products.

Dossier Submitter's Response

As the comment is similar to comment no 15 from Cosmetics Europe, please see response to comment no 15.

RAC's response

We appreciate the summary of the scientific data submitted by the industry. The comments are noted and to a large extent coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above.

Date	Country	Organisation	Type of Organisation	Comment number
08/08/2014	United States	Firmenich, S.A	Company-Importer	17

Comment received

Firmenich does not support the proposal made by Swedish Authorities to classify Linalool (CAS#: 78-70-6; EC#: 201-134-4) as a skin sensitizer Cat. 1A, H317.

Linalool does not have a structural alert for sensitization nor does the animal or human data on pure (non-oxidised) linalool suggest that it is a skin sensitizer.

Autooxidation of Linalool can occur with Hydroperoxides and other oxidation products demonstrating sensitizing properties. However, this has been in studies where Linalool was subjected to unrealistic conditions. For example, in the majority of studies, Linalool was placed in a flask open to air; stirred every day four times for one hour; illuminated each day for twelve hours with the procedure continuing for ten to forty-two weeks (twenty-five to forty-two weeks in the majority of studies). The extent to which natural autoxidation of Linalool and the formation of peroxides occurs is much lower than what has been studied under these extreme experimental conditions. This in no way is representative of how Linalool (as a raw material or present in commercial products containing Linalool) is handled throughout the entire supply-chain. In commercial qualities of Linalool utilized for fragrance compounding, total peroxides have been demonstrated to be <0.01%. Additionally, an IFRA industry Specification Standard exists for Linalool which limits the peroxide level to 20 mmol/L for product use and recommends that antioxidants (such as BHT) be added at the time of production. Furthermore, Linalool is typically present in a product matrix which either contains anti-oxidants or is stored in a closed container preventing air exposure.
CLP Article 8 (6) states that "Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used." All cited tests in the CLH report showing sensitizing properties have been conducted with oxidized Linalool Therefore the use of data on artificially oxidized Linalool to describe commercially used Linalool is not appropriate.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

The CLH report also does not provide any evidence for exposure to oxidized Linalool in the population or the occurrence of oxidized Linalool in products in the industrial supply chain.
Patch test data in the report supporting Sweden's proposal require further examination with respect to their relevance and interpretation and using such data for hazard classification is not appropriate.

Taking into consideration that Linalool itself is not considered a strong sensitizer, on-pack labeling requirements already exist within the European Union and the additional lack of data demonstrating significant exposure of consumers or workers to oxidized Linalool, there is no justification for this proposal to classify Linalool as a skin sensitizer Cat. 1A, H317 under ECHA's Guidance on the Application of the CLP criteria.

Dossier Submitter's Response

Regarding the representativeness of clinical patch test data with oxidized linalool in relation to the actual concentrations in products: It should be noted that the patch test concentration is the *optimal concentration derived for the purpose of diagnosing ACD*. It may certainly differ from the concentrations found in products, see response to comment no 2, point iv), Givaudan. Therefore the concentration of hydroperoxides (1% since 2012, Chemotechnique Diagnostics) in patch testing with oxidized linalool may be higher than what can be found in products.

Regarding exposure to linalool in products and the relevance of patch test data: All reported positive patch test frequencies from dermatological clinics in Europe to oxidized linalool is a strong indication that exposure to oxidized linalool in products has taken place. The diagnoses, made by dermatologists in accordance with international guidelines cannot be dismissed. Therefore linalool, in the form it can reasonably be expected to be used should be classified as proposed in the CLH dossier.

RAC's response

We appreciate the new input with regard to a maximum level of linalool peroxides allowed and the use of antioxidants in the final products given by the industry. The comments made are noted and to a large extent coincide with comments made by other stakeholders from the Industry sector. For more details, see all RAC's responses above.

ATTACHMENTS RECEIVED: 4

1. BASF_comments related to CLH_Linalool_78-70-6.pdf. *Comment is copied under comment no.1.*

2. Comments on Linalool CLH proposal - Givaudan.docx. Page 2 and Appendix I of the attachments are copied under comment no. 2.

3. DSM comments CLH proposal_Linalool 2014.pdf submitted by DSM Nutritional Products AG, Switzerland. Refer to comment no. 13.

4. Linalool IFRA General Comments related to the CLH report for Linalool Final 7-8-14.pdf submitted by IFRA (International Fragrance Association), Belgium. Comment is copied under comment no. 5.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LINALOOL

Confidential attachments received: 2

1. Peroxide Formation Linalool_DSM 2014-07-30.pdf, refer to comment no. 4 and 13. *The report submitted as confidential information is regarded as intellectual property which has not been published yet.*

2. Kern et al_Linalool in products_preprint.docx , refer to comment no. 2. *The attached paper has been accepted for publication in the journal of Analytical and Bioanalytical Chemistry but is not yet publically available. Therefore this is submitted confidentially to respect the copyright agreements of the journal.*