Givaudan

Comments on the Proposal for Harmonized Classification and Labelling of Linalool for skin sensitization sub-category 1A

Linalool

EC No: 201-134-4

CAS No: 78-70-6

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Date: 25.07.14

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.

1. Data supporting non classification of Linalool

Extensive experimental data show that Linalool is not a skin sensitizer and this is recognized in the CLH report. Extensive data supporting the non-classification for sensitization of Linalool has been submitted by one major supplier to Sweden in 2012.

A review of clinical patch test data on Linalool concluded that when the underlying clinical and experimental data are analyzed, a clear cause-effect relationship has infrequently or rarely been established (Hostýnek and Maibach, 2003) despite widespread exposure and use.

The CLH report states on page 9 that the SCCS report that 100-1000 cases of allergy to Linalool have been published in the literature. 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 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.

Finally, the only 5 case reports on page 25 and 26 refer to use and patch testing of Lavender oil which is a complex mixture and not equivalent to Linalool. The use of neat Lavender oils is not advised due to irritancy potential, a warning obviously not followed in the reported cases. This information is therefore irrelevant to a discussion on classification of Linalool and should not be considered for a CLH report.

2. General comments on the hypothesis and patch test information presented

i. Information on oxidized Linalool is not relevant to samples of commercial quality

Throughout the report the argument is made that

a) since Linalool in principle can oxidize
b) and Linalool hydroperoxide is a sensitizer
c) therefore Linalool should be labeled equally as the hydroperoxide

This argument is made based on studies in which Linalool was

- placed in a flask open to air
- stirred every day 4 × for 1 h
- illuminated each day for 12 h
- the procedure was continued for 10 – 42 weeks (25 – 42 weeks in the majority of studies)

This is a valid scientific protocol to study maximal oxidation possible in any material. However classification and labeling refers to products put on the market. This oxidation procedure has **no**

relationship to how commercial products are handled. In this procedure, 19% of Linalool-hydroperoxide is formed.

A retrospective analysis of quality control data on 160 consecutive batches of commercial synthetic Linalool supplied from several sources and used in fragrance compounding by a large fragrance manufacturer indicates a typical level of <0.004% and an average peroxide content of 0.463 mM/L which equates to <0.01% (Givaudan, 2014).

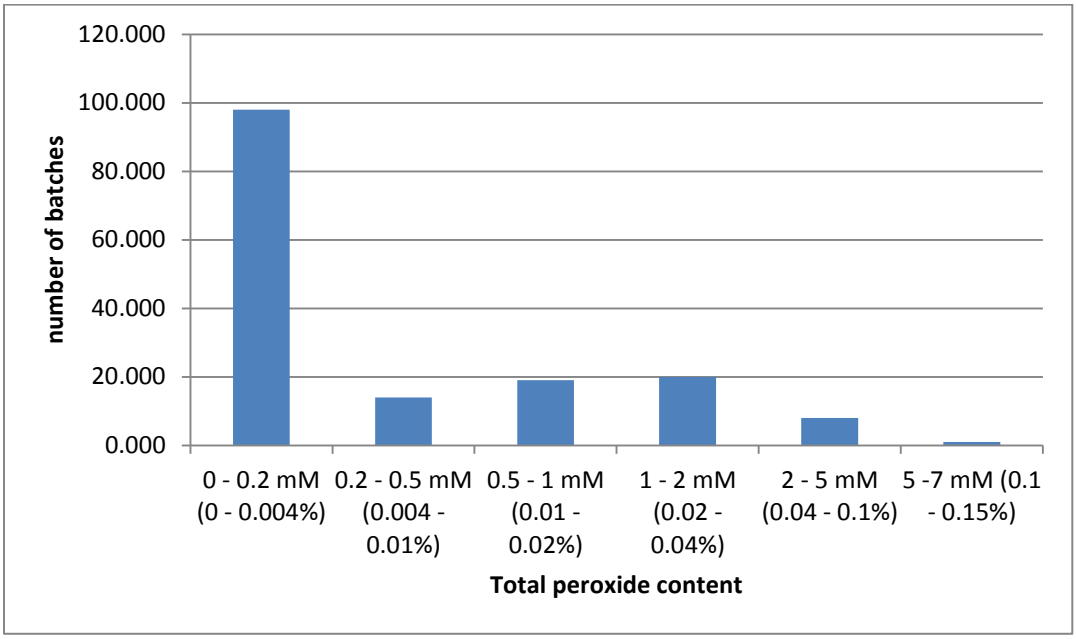

Figure 1. Total peroxide content in quality control on 160 consecutive commercial grade Linalool used for fragrance compounding

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 report showing sensitizing properties have been conducted with oxidized Linalool (see CLH 4.4.1.3). Therefore the use of data on artificially oxidized Linalool to describe commercially used Linalool is not appropriate.

ii. No data are presented on exposure

The CLH report does not mention or 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 (Rudback *et al.*, 2013; Rudback *et al.*, 2014) but methods were not applied to industrial products / industrial Linalool. The question is being addressed by the IDEA

prehapten 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 autoxidation.

A detailed analytical study was recently made by Kern et al. (accepted for publication in Analytical and bioanalytical chemistry, manuscript may be supplied once available). This study could only detect trace amounts of the hydroperoxides even in significantly aged, oxygen-exposed perfumes. These levels are 3 – 4 orders of magnitude below the concentrations used in the patch tests, based on which the CLH proposal is made (Table 1) (Kern et al., 2014).

Without any evidence for relevant exposure or occurrence in products of oxidized Linalool, a preemptive regulation is inappropriate. Additional work is ongoing to provide further information in this area.

iii. Labeling approach based on forced oxidation studies would create a precedent requiring application to potentially hundreds of materials

If the argument of the CLH document is followed, then any chemical might be subjected to a 42 weeks forced oxidation, all labeling would then be done based on toxicological data for oxidation products from forced oxidation and not on the chemical as it is used in industrial practice.

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 affect C&L of an enormous number of chemical products.

Following this route for a precautionary principle ("who can guarantee that in rare cases an almost empty bottle does not start to oxidize?") is also not appropriate, as C&L should inform on risks in common practice, over labeling as proposed in this case, which later may be generalized to all molecules prone to oxidation under above exaggerated regimen, completely undermines the usefulness and relevance of the C&L approach.

iv. The diagnostic patch test on oxidized Linalool has not been thoroughly validated

The main argument presented supporting regulatory and action and re-classification is derived from the clinical studies by Christensson *et al. (Brared Christensson et al., 2013; Christensson et al., 2010)* (used throughout the report on pages 9, 11, 12, 20, 21, 23, 29, 31, 33, 34, 35). It is thus of utmost importance to understand what the clinical test informs us about and how it was developed and validated.

The logic applied to the data interpretation can be summarized as:

a) Can we find a sufficiently high concentration of Linalool hydroperoxide which triggers reaction when applied in a patch test to patients (Christensson, et al., 2010)?
b) Can we then find a high number of patients reacting to the selected concentration (Brared Christensson *et al.*, 2012)?
c) Positive evidence on b) then leads to the assumption that patients were frequently exposed to this specific hydroperoxide as the source of the patients reaction
d) The subsequent assumption that hydroperoxide was present in products used by the consumers

e) Therefore, based on these assumptions, the peroxide must come from Linalool added to and oxidized in the product and thus Linalool should be labeled equally to the Linalool hydroperoxide

In absence of exposure data (see above) this is a very weak and indirect argumentation chain which relies on several assumptions. This would only hold true if the patch test is very specific (i.e. the clinical test indeed serves as a 'biological detection system' for past presence of Linalool hydroperoxide) and clinical relevance to a patient's allergy (i.e. a link to exposure to commercial products containing oxidised Linalool) can be shown.

However, the diagnostic patch test reaction may also be unspecific and patient reactions observed may be due to a different inducing agent.

Thus if the test was not validated to detect the specific sensitivity it claims to report, this argument cannot be made. The following considerations and observation indicate that scientific validation of this clinical patch test is not yet given.

The concerns over the diagnostic patch test on oxidised Linalool and relevance to classification are detailed below:

a) No published case of relevant reaction to oxidized Linalool

To be sure the diagnostic patch test detects the disease it claims to detect we would need correctly identified positive cases with established relevance. Thus

- a patient reacts to a product he uses
- presence of relevant amounts of oxidized Linalool in this product needs to be shown
- ideally, to prove evidence, a fraction of the product containing the hydroperoxide is then also positively tested in the patient

This approach is widely accepted in the dermatological community and such evidence was presented for other relevant allergens (Bernard *et al.*, 2003; Gimenez-Arnau *et al.*, 2002), but not a single case is reported for oxidized Linalool.

b) Strong dose-response of frequency of patch test positives

A critical question is the dose used in the patch test. The study of Christensson (Christensson, et al., 2010) used increasing concentrations, with strongly increasing reactions to high doses (Figure 1). No evidence that this high dose detects a true problem rather than false-positives is available, so we currently cannot judge what it means. The high frequency of positive reactions (used throughout the CLH report as evidence for 1A labeling) is obtained at a high concentration which is actually higher than the concentration that in animal tests induces skin sensitization (Table 1).

This test concentration appears optimized to see many positive reactions and not to detect a problem of specific preexisting sensitization.

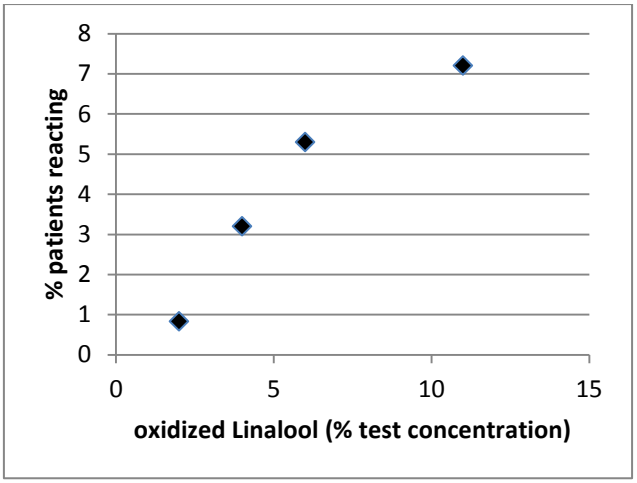

Figure 1. Dose response of patch test result in (Christensson, et al., 2010)

Table 1 provides information on exposure based on concentrations used in patch testing and those used to induce sensitization in animals and compares with concentrations found in (old) fragrances containing Linalool. The gap between patch test concentration and typical use concentration is a factor of 10'000.

Table 1: Exposure during patch tests and in (old) fragrances sampled from consumers

	Dose of hydroperoxide in test preparation	**Application area and amount**	**Dose per area**
LLNA [a] Dose inducing sensitisation (EC3)	16'000 µg/g (1.6%)	25 mg/cm^2	**400 µg/cm^2**
Patch test 2% oxidized Linalool (0.83% response)	3'800 µg/g (0.38%)	40 mg/cm^2	152 µg/cm^2
Patch test 6% oxidized Linalool (diagnostic level, ca. 6% positive response)	10'000 µg/g (1%)	40 mg/cm^2	**456 µg/cm^2**
Patch test 11% oxidized Linalool (7.2% response)	20'900 µg/g (2.09%)	40 mg/cm^2	836 µg/cm^2
Fine fragrance: (median of positive samples; with median matrix correction factor)[1)]	14 µg/g (0.0014%)	2.21 mg/cm^2 [2)]	0.031 µg/cm^2
Fine fragrance: (single sample of n=39 with highest content including matrix correction factor)	132 µg/g (0.0132%)	2.21 mg/cm^2 [2)]	0.29 µg/cm^2

[1)] Kern et al., Manuscript accepted for publication in Analytical and Bioanalytical Chemistry.
[2)] Api et al. 2008

c) Difficulty in reading the patch tests

The most recent study by Audrain et al. (Audrain et al., 2014), conducted independently from the Swedish Research group, but with identical test material, reported: "*It is the authors' consensus that interpreting and classifying terpene* (i.e. Linalool and limonene hydroperoxide patch test reactions, note added) *patch test reactions (particularly distinguishing irritant from allergic reactions) is more difficult than with other allergens, for reasons that are unclear."*

Thus while the Christensson studies indicate a clear cut result for the positives – this independent analysis indicates that the phenomenon might not be so easily identified (see also point d) below).

d) High frequency of doubtful/irritant reactions

Throughout the studies by Christensson et al. a high level of 'doubtful' reactions were observed (Brared Christensson, et al., 2012; Christensson, et al., 2010). The more recent, independent studies (not cited in the CLH report) by Audrain et al (Audrain, et al., 2014) reported similar frequencies of 'irritant' reactions. There is no consensus by the different authors obviously what is an irritant and what a doubtful reaction, which may be related to difficulty in exactly reading the reactions reported above. The frequency of positive and doubtful reactions in reported studies is provided in table 2 below.

Table 2: Frequency of positive and doubtful reactions in reported studies

Study reference	N patients	Target hydroperoxide	Hydroperoxide level in the patch test preparation	% of positives	% of doubtful / irritants
(Christensson, et al., 2010)	1693	Linalool-OOH	0.38%	0.83	1.9
(Christensson, et al., 2010)	2075	Linalool-OOH	0.76%	3.2	5.1
(Christensson, et al., 2010)	1725	Linalool-OOH	1.14%	5.3	6.4
(Christensson, et al., 2010)	1004	Linalool-OOH	2.1%	7.2	7.3
(Audrain, et al., 2014)	4731	Linalool-OOH	1%	5.9	7.3 [1)]
(Brared Christensson, et al., 2012)	2800	Linalool-OOH	1%	6.9	10.5
(Brared Christensson, et al., 2013)	2800	Limonene-OOH	0.33%	5.2	7.9
(Audrain, et al., 2014)	4731	Limonene-OOH	0.33%	5.0	7.3

e) Strong overlap of hydroperoxide sensitivity at population level

Comparing the positive and doubtful reactions vs. Linalool- and Limonene hydroperoxides in different study centers reported in the parallel studies on same 2800 patients (Brared Christensson, et al., 2013; Brared Christensson, et al., 2012), a strong correlation is seen (Figure 2). Thus at the population level the frequencies are related. This is not a proof that reactions are unspecific, as data at levels of individuals need to be evaluated. However it is a strong indication, that the reported

reactions may not indicate specific sensitization to Linalool hydroperoxides only, but rather to hydroperoxides in general, as at population level sensitivities correlate.

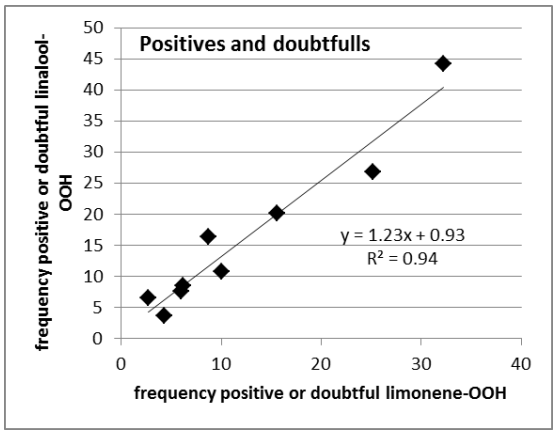

Figure 2. Correlation between frequencies of reactions to limonene-OOH and Linalool-OOH in different clinics, data taken from (Brared Christensson, et al., 2013; Brared Christensson, et al., 2012).

f) Data on cross-reactions/concomitant reactions at individual levels are available but currently not in the public domain

As indicated above, to resolve the case, data are needed at individual levels, including the doubtful and positives, to check how specific observed reactions are (i.e. whether the diagnostic patch test used as basis of the report has specific relevance for Linalool). These data are available for 2800 patients, but while the cross-reaction pattern with all other fragrance allergens are reported in full detail Table S1 ((Brared Christensson, et al., 2013), the cross-reactions between different hydroperoxides are specifically excluded from the publication, for unknown reasons, since these would be the most interesting data. Industry has made a request to the authors for these data, but currently they are not yet provided.

g) Different hydroperoxides can modify peptide side chains

A recent study showed that both Limonene- and Linalool-hydroperoxide can modify / oxidize tryptophan side chains in proteins (Kao *et al.*, 2014). Our data show that the same process happens also with an endogenous hydroperoxide of the skin (squalene hydroperoxide). Now, most interestingly, in a very recent report, evidence was presented that cross-reactions between different photosensitizers might be due to oxidative modifications of tryptophan side chains (Karlsson *et al.*, 2014). Interestingly enough, the same modifications occur in presence of different hydroperoxides and could also explain a mechanism of cross-reactions between hydroperoxides, putting again a question mark whether the high patch test concentrations really detect a Linalool-OOH specific effect.

Combining this evidence and the data in Figure 1 leads to the possible hypothesis that the observed patch test reactions to hydroperoxides indicate response to oxidative stress / oxidative protein modification in the skin rather than a specific reaction to oxidized Linalool.

Whilst this is a scientific discussion presenting an alternative hypothesis, it is relevant as the arguments of the CLH report are also only based on an hypothesis around the assumed specificity of the patch-test reactions.

h) Conclusion on the relevance of the patch tests

Based on the above evidence more research is needed to understand patch test results, which are appearing in the report to support the Swedish proposal.

- Relevance to detect cases of Allergic Contact Dermatitis (ACD) is not established
- Patch tests are conducted at high concentrations (levels which are sensitizing in the LLNA)
- Indications that results are not specific (follow up research needed). This may indicate general sensitivity to hydroperoxides/oxidative stress
- Gradual readings making interpretation difficult

Therefore classification of a material based on such an hypothesis would be incorrect.

3. Page by page comments on the CLH report are provided in Appendix I.

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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.
comment 2	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 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

Comment				CLH Dossier from MS Sweden	Comment
					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				CLH Dossier from MS Sweden	Comment
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 10	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)
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

Comment				CLH Dossier from MS Sweden	Comment
					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

Comment				CLH Dossier from MS Sweden	Comment
					processes of linalool in skin in the right perspective i.e. there is no scientific information on this.
comment 18	Page 20 and 21	Section B4.1.2	1st paragraph		Citations, references should be added to underpin the conclusions.
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

Comment				CLH Dossier from MS Sweden	Comment
					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				CLH Dossier from MS Sweden	Comment
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				CLH Dossier from MS Sweden	Comment
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	See comment above. Data do show adequate protection of Linalool.

Comment				CLH Dossier from MS Sweden	Comment
				oxidized linalool in Europe."	
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 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."	The relevance on classification and labelling for other substances not complying with the substance identity is irrelevant.
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	Page	Table	Columns on oxidized		These columns are not relevant. Linalool as defined

Comment				CLH Dossier from MS Sweden	Comment
37	33+34		linalool and hydroperoxide fraction		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)