Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

citral; 3,7-dimethylocta-2,6-dienal

EC Number: 226-394-6
CAS Number: 5392-40-5

CLH-O-0000001412-86-225/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CITRAL; 3,7-DIMETHYLOCTA-2,6-DIENAL

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 comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. 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. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: citral
EC number: 226-394-6
CAS number: 5392-40-5
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	1
Comment received				
Reliability scores are lacking which makes it challenging to assess the quality of the various and numerous studies.				
Dossier Submitter's Response				
Thank you for your comments. Reliability scores have not been assigned to each study cited in the CLH report but the robustness of the available information is reflected from Annex I. While it has been highlighted where robust study summaries/information is not available the reliability of all the studies cited could have been described with more clarity in the CLH report. Some general considerations about the reliability of the available animal and human data on skin sensitisation are given here: *Animal data:* The two first studies in table 9 of the CLH report (LLNA's reported by Bastetter et al., 2012 and Jung et al., 2012) are, respectively, considered to qualify for a reliability score of 1 ("Reliable without restriction") and 2 ("Reliable with restriction") according to the Klimisch criteria (Klimisch et al., 1997). All the remaining animal studies included in the CLH report have been cited from secondary literature, i.e. the SCCS opinion from 2012 on Fragrance allergens in cosmetic products, REACH registration data (public part) and literature reviews. A substantial part of those studies cited from secondary literature refer to unpublished data from the Industry. Such studies would be assigned a reliability score of 4 ("Not assignable") according to the Klimisch criteria as sufficient experimental details about the studies were not available.* *Human data:* The Klimisch reliability scores have been developed for assessment of experimental				

toxicological and ecotoxicological studies for regulatory purposes and are not always directly applicable for human data. Epidemiological studies and human case reports are e.g. observational in their nature, exposures and test conditions may vary and such types of studies are not likely to provide repeatable results. However, both diagnostic patch testing and human volunteer studies are conducted according to standardised guidelines and with well defined exposure conditions during the tests. The human data in the CLH report primarily include diagnostic patch tests and of human volunteer tests (HRIPT and HMT studies). The diagnostic patch test data are mostly reported in the open literature as peer reviewed articles. Most of these publications would be considered as "Reliable with restrictions" as they are based on a standardised methodology, standardised test series etc. and contain detailed information about the exposure regime, test conditions and results. Some of the older patch test data are, however, reported with very little or scarce information and the reliability of these would correspond to "not assignable" under the Klimisch scoring system. The volunteer studies are cited from secondary literature and refer to unpublished data from the industry. The reliability of the human volunteer studies would thus also be considered "not assignable".*

The proposed classification and potency assessment for citral is based on the total weight of evidence from animal and human studies. Even though the reliability is considered to be "not assignable" for many of the available studies the dossier submitter considers that the results collectively support a sub-categorisation of citral in category 1A. The animal data show moderate to strong sensitising effects of citral. The results of numerous patch tests with selected patients and the large number of positive cases provide substantial evidence of a high frequency of occurrence of skin sensitisation. Combined with an estimated low exposure it is concluded that a Category 1A classification is justified.

*During the public consultation confidential information and study reports has been provided for some of the unpublished animal and human studies cited in the CLH report (LLNA, HMT and HRIPT studies). Please see the answer given to comment no. 5 where this information is discussed further (althougn the studies cannot be commented in detail due to the confidential nature of the information). While further insight is gained about these studies and allows the dossier submitter to perform a more qualified assessment of the robustness and the reliability of these data, the information provided does not alter the overall assessment and conclusion on the classification of citral.

RAC's response

RAC agrees with the perspective of the Dossier Submitter that it is possible to characterise the hazard of citral by considering both the animal and human data. It is important to take all the available studies are taken into account. The additional information provided about some of the studies during the public consultation gives further reassurance about their validity. However, as the assessment does not rely on the findings of a limited number of key studies, detailed information on reliability of each individual study does not seem to be needed on this occasion.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany		Individual	2

Comment received

see attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 0_AS_Comment on CHL_CITRAL_V2.pdf

Dossier Submitter's Response
Thank you for your comments. Please find below our response to the issues raised: *1) Frequencies of sensitisation possibly giving rise to concern* Disagreement is expressed with the ECHA guidance with respect to limits set for assessing high versus low frequency of occurrence of skin sensitisation for various population/patient groups. In the context of responding to comments on the CLH proposal for citral it is not up to the dossier submitter (DS) to enter into a general discussion of the relevance of the guidance. The guidance document has been developed by experts (including dermatologists) and has been agreed by consensus by the authorities upon the formal consultation procedure described by ECHA. We believe that general comments on the guidance document an suggestions for revisions should be addressed to ECHA in the context of a guidance revision. Comments on the adequacy of the guidance document for the endpoint of skin sensitisation is thus, in our opinion, outside the scope of the concultation procedure for a CLH proposal. *2) Frequencies of sensitisation to fragrances* The author notes that the ECHA guidance does not give clues to choosing the suitable time period to be considered when using diagnostic patch test data to assess the frequency of sensitisation. Further, the author has shown examples of extrapolating positive patch test frequencies in patient studies to expected frequencies in the general population (by the "CE-DUR approach" which in previous publications has been shown to correlate relatively well with results from epidemiological population studies). Again the DS considers that these comments relate to general aspects of the guidance document rather than the actual CLH proposal. According to the guidance, when using human diagnostic patch test data for classification only one or two types of the information specified in table 3.2 may be sufficient for sub-categorisation. Thus, if high frequencies are observed in dermatitis patients (selected and/or unselected) and a high number of cases have been published this is considered sufficient to justify sub-categorisation (when the observed frequency of sensitisation is subsequently balanced with the estimated level of exposure). *3) Hazard versus risk: The role of exposure* With regard to the comment on the reliability of animal versus human data the dossier submitter considers that the evidence from the animal studies as well as the human data both confirm the sensitising properties of citral, but that the potency is best reflected from the human patch test data. In addition, indications of strong potency are also evident from some of the available animal studies. According to the classification criteria and guidance the evaluation of human data should be carried out with caution as the frequency of cases not only reflects the inherent properties of the substances, but also factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken (CLP section 3.4.2.2.4.2. and Guidance section 3.4.2.2.3.7.). In the case of citral 10 out of 11 published patch test studies with selected patients show relatively high frequencies of occurrence of skin sensitisation in studies including more than 3000 patients of both genders from different regions (in and outside) Europe [please also refer to the answer given to comment no. 7. Here it is discussed that if excluding the non-EU patch test studies 8 out of 8 studies with selected patients show sensitisation prevalence rates above 2%]. The patch tests are carried out under well-defined experimental conditions in accordance with international standards. The fact that full coherence between animal and human data is not observed should not be used as an argument to negate results from relevant and adequate human studies showing high frequencies of sensitisation in a large number of patients. For skin sensitisation the concentration limits for elicitation (and thus the use of

special labelling requirements) specifically serve to protect already sensitised individuals. It is furthermore noted that the fragrance Hydroxyisohexyl 3-cyclohexene carboxaldehyde has been classified as a strong sensitiser (sub-category 1A) based on the same type of data; i.e. high prevalence rate of sensitisation seen in diagnostic patch tests in combination with an estimated low exposure although available animal data indicate moderate sensitisation potential.

The DS agrees that the guidance approach for sub-categorisation of skin sensitisers includes elements of risk when using human data (e.g. the use of data from sensitised patients integrated with exposure estimates, number of positive cases, etc.). However, we also consider that these comments are not directly related to the CLH proposal for citral but rather reflect general comments on the guidance approach. The approach for estimating relatively high or low exposure according to the guidance gives a rough indication of the expected level of exposure. As described in section 10.8.3 of the CLH proposal it is also important to consider that fragrances such as citral are placed on the market in high tonnages and have widespread use in consumer products such as cosmetics and cleaning products that are used on a daily or very frequent basis. It is thus not fully agreed that the CLH report mainly refers to exposure per product when estimating the exposure to citral. Besides the IFRA limits, product surveys and exposure assessment for workers and consumers (obtained from the Substance Evaluation for citral) are also taken into account confirming a relatively low exposure.

RAC's response

Thank you for the carefully considered comments.
As explained by the Dossier Submitter, it would be inappropriate to re-open a discussion about the supporting guidance to CLP during the assessment of this proposal.
Regarding exposure, RAC is aware of the need to consider carefully the nature, possible timing and frequency of the doses of citral that the patch tested patients may have been exposed to on their skin to induce their sensitised state.

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Sweden	The Swedish Contact Dermatitis Research Group	National NGO	3

Comment received

The Swedish Contact Dermatitis Research Group hereby responds to the open consultation regarding the proposal of harmonized classification and labelling of citral (3,7-dimethylocta-2,6-dienal, CAS number: 106-24-1) EC Number: 203-377-1. The Swedish Contact Dermatitis Research Group consists of elected members representing dermatologist and chemists with clinical experience in dermatology and allergology and broad competence within contact dermatitis.
This response was written by Professor Ann-Therese Karlberg on behalf of the Swedish Contact Dermatitis Research Group. They were agreed on by all members in the group. Professor Magnus Bruze declared conflict of interest and was not involved in the discussions.

Dossier Submitter's Response

Thank you for your comments and support. Please refer to the answer given under comment no. 10.

RAC's response

Noted; see also response to comment No. 10.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany		Individual	4
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment 0_AS_Comment on CHL_CITRAL_V2.pdf				
Dossier Submitter's Response				
Please refer to the answer given to comment no. 2 which addresses the same attachment as provided under comment no. 4.				
RAC's response				
Please refer to the answer given to comment no. 2 which addresses the same attachment as provided under comment no. 4.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany	BASF SE	Company-Manufacturer	5
Comment received				
Please see the attached documents ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH comments BASF SE final.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Confidential attachment final.docx				
Dossier Submitter's Response				
Thank you for your comments and for the provision confidential information and study reports for the LLNA's, the HRIPT's and the HMT's sponsored by RIFM (cited from the SCCS opinion in the CLH report). While the study reports are very useful in order to further assess the quality and reliability of the data a more detailed discussion of the information provided is not possible in this context due to the confidential nature of the data. However, some general remarks to the comments from BASF SE are provided below: *1) <u>Comments on animal data</u>* BASF SE has commented that 2 out of 3 LLNA's with EC3 values below or close to the cut-off value of 2% for sub-categorisation were performed with a combination of citral and various antioxidants which do not represent standard vehicles for LLNA testing. The reliability of these studies can thus not be confirmed. The DS notes that for the majority of the 10 LLNA studies reported by RIFM non-standard test conditions have to some extent been applied. In 6 out of the 10 LLNAs reported by RIFM anti-oxidants have been added to the test solutions. There are also other deviations from the standard test procesures described in OECD TG 429, e.g. with respect to the substance tested (air exposure of test substance prior to testing in some cases), lack of justification for the deviations from the standard test procedure with respect to the gender of the animals tested animals and vehicles used etc. However, looking across these 10 LLNAs it is noted by the DS that the results are relatively uniform taking normal biological and inter-laboratory variation into account (EC3 values ranging from 1.2-6.8%). If excluding those studies applying antioxidants and/or air exposed test substance then 3 of the LLNAs reported by RIFM remain with EC3 values of 1.2%, 4.6% and 6.3%, respectively (using EtOH:DEP as vehicles, either in a 1:3 or a 3:1 ratio). However, the 7 LLNAs deviating				

from the standard testing procedure with respect to the use of antioxidants and/or air-exposed test substance result in EC3 values in the same range (EC3 values of 1.5%, 2.1%, 3,7%, 4.6%, 5.3%, 5.8% and 6.8%). It was not possible for the DS to take the details of the study procedure and information on testing laboratory etc. into account in the weigth of evidence assessment for the CLH report as this information was not available (non-published information). After having gained access to the original study reports the DS considers that the 10 LLNAs reported by RIFM are "reliable with restrictions" and that collectively they confirm the sensitising properties of citral with a potency ranging from moderate (mostly) to strong.

2) Comments on human data

Diagnostic patch tests (clinical studies):
While patch test studies as such are considered as relevant and valid information according to the CLP classification criteria and guidance it lies in the nature of such clinical studies that detailed information of the actual exposure levels leading to induction of sensitisation for the patients tested are often/most likely not available. Instead the guidance establishes principles for deriving an exposure index leading to an assessment of relatively low or high exposure, respectively. The patch test data are conducted according to international standards and the results published in peer-reviewed journals. It is, on the other hand, hard to assess the adequacy and quality of studies which are not published and where more detailed information is not available.

HRIPT (volunteer studies):
Two of the HRIPTs reported are (according to information received in the public cons.) conducted at concentrations <500 µg/cm^2 and in these studies no sensitisation was observed in the 50 and 41 tested volunteers. Generally the results of the HRIPTs show that no sensitisation was observed at concentrations ranging from 0.5-1.2% (corresponding to ~388-1400 µg/cm^2) whereas high frequencies of positive reactions (48-63%) were seen in studies with higher concentrations (4-8%, corresponding to ~>3000 µg/cm^2). For most of these studies detailed study information is (still) not available.

HMT (volunteer studies):
All the HMTs reported are conducted at high concentrations (≥500 µg/cm^2). The tested persons are generally described as "healthy volunteers" but further information (besides age, gender and race) is not available and generally the level of details about the study is low. Except for one HMT (where no sensitisation was obserbed in 25 persons tested) the frequency of positive reactions is high ranging from 8-64% positive tests per study. The reactions are described as ranging from mild to very strong. The studies are conducted in the 1970'ies and no information is available about general exposure levels to citral at the time. In a substantial part of the studies only males were tested. The exact identity of the test substance is only vaguely described and is in some studies tested in the presence of antioxidants or with other variations of exposure. The HMT tests can not exclude that positive reactions could have occurred if concentrations lower than 500 µg/cm^2 had been tested. The results of the HMTs could indicate a dose-related response as the lowest response rate was observed at a dose of 2% whereas increasing response rates were observed when doses of 4%, 5% and 8% were used.

Whereas clinical diagnostic patch tests investigate elicitation reactions in dermatitis patients the HRIPT and HMT tests investigate whether sensitisation is induced in healthy volunteers. The endpoints and the history of the tested persons are thus very different in these types of human studies and it is not so surprising that diverging results are seen between these different types of studies. The diagnostic patch tests are still considered to be the key evidence for a sub-category 1A classification of citral as high frequencies of sensitisation are

observed in a high number of selected patients tested. As stated in the guidance only or two types of information generated in human diagnostic patch tests (either general population studies, selected dermatitis patients, unselected dermatitis patients, work-place studies or number of published cases) may be sufficient for sub-categorisation.

It is highly relevant to protect already sensitised persons from elicitation and the findings in patch tests should thus not be negated due to animal tests and other human evidence indicating "only" moderate sensitising potency. The potency assessment for sensitisers according to the CLP classification criteria is considered an important measure to prevent both induction of new allergies in humans as well as preventing elicitation in already sensitised persons. The concentration limits set for elicitation – and the subsequent labelling requirements – specifically serve to protect already sensitised individuals. The relatively high sensitisation frequency observed for citral in selected dermatitis patients supports sub-categorisation of citral as a Cat 1A sensitiser.

The reference in the comment to more recent publications (Bennike et al., 2017 and Mowitz et al., 2017) showing positive patch test frequencies in consecutive patients of 0.39% (2010-2015) and 1.2% (2009-2015) confirm the general picture observed for consecutive patients patch tested with citral, i.e. patch test frequencies in the range between 0-2%. (It is noted that in the latter publication the fragrance HICC was also associated with a positive patch test frequency of 1.2% in consecutive patients. HICC has a harmonised classification as a category 1A skin sensitiser based on high patch test frequencies >2% combined with an estimated low exposure).

3) Comments on exposure considerations

The exposure estimate reflected in section 10.9.3 in the CLH report (based on the CLP guidance, table 3.3) is considered a conservative estimate. While we don't have access to historic exposure data for the patients tested the DS considers that based on available data (e.g. information on measured concentrations in relevant products, exposure estimates conducted by KEMI for cleaning agents based on the REACH Registrant's exposure scenarios) the exposure to citral on concentration/dose level is estimated as low, i.e. a dose <1% / concentration < 500µg/cm^2 (score 0). Even though there are examples of products such as detergents, massage oils/eterical oils and air fresheners which may contain citral in concentrations >1%, citral is generally present in concentrations far below 1% in high-volume leave-on cosmetics and detergents products. It is considered speculative that non-IFRA compliant products/massage oils/aromatherapy should shift the overall weighting from relatively low to relatively high exposure for this parameter. The surveys conducted by the DK EPA in which the concentrations of citral have been measured in a range of cosmetic and household products were published in the period from 2002-2011 (and mostly before 2008). Thus, the measured concentrations relate to a time period before the current IFRA standards have actually been implemented and concurrent with many of the publications of the patch test data. As stated in the CLH proposal the measured concentrations in day-to-day cosmetic products and household products were generally in the range from 0-<0.06% with the exception of massage oils and air-fresheners. The scores designated for repeated exposure (score 2) and number of exposures (score 2) are considered as relatively conservative estimates by the DS. Even though citral is present in a large number and many types of consumer products with frequent use, a user pattern with more than one exposure on a daily basis and at least 100 exposures prior to induction is considered as reflecting a "worst case" exposure. On balance the DS considers that the estimated "relatively low exposure" is appropriate.

Although the estimated low exposure cannot be directly coupled to the specific exposure that has lead to induction of sensitization in the patients with positive patch tests it should

be kept in mind that the concentration limits for elicitation set out in the CLP regulation serves to protect already sensitized individuals.

4) <u>Reply to comments on Table 10 of the CLH report:</u>

- Heydorn et al., 2003: According to correspondence with one of the authors of this article (Mrs. Duus Johansen) the patients are considered to be selected based on their hand eczema.
- Van Oosten et al., 2009: These patients are considered to be unselected as not all the eczema patients are suspected of contact allergy to fragrances
- An et al., 2005: It is true that the article states that the patients tested were suspected of having (cosmetic) contact dermatitis but there is not much further description of the patient selection. The article states that parts of the patients tested have a past history of either contact dermatitis/atopic dermatitis/photosensitivity (24%, 6.4% and 2.8%, respectively) but there is no specific description of the remaining patients accounting for >50% of the tested persons. It is thus not entirely clear whether the patients should be considered selected or unselected. However (and as stated in comment no 7 below) this study is conducted in Korea and should possibly not be allocated the same weight as the European patch test studies as the positive patch test frequencies are ultimately compared with exposure estimates based on EU figures. Thus, it can be argued that the studies in patients from outside Europe should not be taken into account.
- De Groot et al., 2002 (2000): The DS agrees that the reference sould be cited De Groot et al., 2000 (and not 2002 as done in Table 10. In the reference list the year is stated correctly)
- Frosch et al:, 2005a and b: The DS regrets that the reference list lacks one of the Frosch et al 2005 publications (and the designation "a" or "b"). Both of the Frosch 2005 publications are, however, described in Annex I to the CLH report.

RAC's response

Thank you for the detailed comments, additional study information and information regarding the additional publications on the incidence of contact allergy. The results of the diagnostic patch tests are considered by RAC to be relevant for classification purposes. An assessment been made in accordance with the CLP guidance, relating the relatively high frequencies of positive results to an expert judgement abou the nature of the exposures that may have led originally to the induction of the sensitised state.

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	Finland	European Environmental and Contact Dermatitis Research Group (EECDRG)	International NGO	6

Comment received

EECDRG supports the Danish proposition to give citral the harmonised classification as a skin sensitiser in Category 1A

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EECDRG statement_to_Proposal for Harmonised Classification and Labelling of Citral 27112017.pdf

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted, thank you.

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	7
Comment received				

In the CLH report, the dossier submitter summarised the outcome of 21 animal studies on skin sensitisation conducted with citral. Conclusions on the substance's potency can be drawn from 19 studies. It is remarkable that 13 studies clearly point to sub-category 1B and only 4 studies to sub-category 1A. For further two studies with a sub-category 1B-outcome a more stringent sub-categorisation cannot be excluded. Based on these results and on the fact that "for most of the studies robust study information is not available to assess the quality more precisely" we agree with the dossier submitter's statement that „caution should thus be exerted in drawing firm conclusions on sub-categorisation based on the animal data alone" (see chapter 10.9.1, p. 29).

The CLH report also includes human data on skin sensitisation caused by citral, namely from diagnostic patch tests, human repeat insult patch tests, human maximation tests, case studies and an experimental study. We agree with the dossier submitter that "the key evidence for the assessment of the potency of citral in this classification proposal is the human data from diagnostic patch tests" (see chapter 10.9.2, p. 29).

From these patch test data convincing evidence for "high frequency" within the meaning of the CLP guidance is provided from tests with selected dermatitis patients: Taking eight studies into account (due to uncertainties regarding the "type" of patients we prefer not to consider the study results by Itoh et al. 1986 and 1988, Nishimura et al. 1984 and Ishihara et al. 1981), the prevalence rates for citral are consistently above 2 % (between 2.3 % and 16.7 %) and affect more than 250 patients.

In our opinion, however, it is debatable to assign "high frequency" also to those data that were collected in unselected patients. Only 5 out of 14 patch test studies show prevalence rates of □ 1 % with the highest rate reaching 1.7 % in patients who were tested in 1973 and 1974 (data collected by the North American Contact Dermatitis Research Group). The second largest prevalence rate amounts to 1.2 % and was identified by the Korean Society for Contact Dermatitis and Skin Allergy between 2002 and 2003. We think these two non-European studies should not be considered when evaluating the frequency for skin sensitisation elicited by citral in unselected patients. The reason is that this frequency is compared with exposure data which obviously refer to the European situation only. (If our impression of this issue is not correct, some further specifications on the scope of the presented exposure data (relevant for Europe only? or world-wide relevance?) would be highly appreciated and helpful). Moreover, the North American data are rather old. On the assumption that the North American und Korean data are not taken into account, there are only 3 out of 12 studies showing prevalence rates of no more than 1.0 %, 1.0 % and 1.1 %. We think that in light of these results it is questionable to assign "high frequency" for skin sensitisation elicited by citral based on patch test data from unselected patients.

Regarding human exposure the dossier submitter comes to the conclusion that "the exposure to citral is generally considered to be low based on the current IFRA standard limits and supported by information of the actual concentration of citral in various consumer products reported in different surveys" (see chapter 10.9.3, p. 30). However, the CLH report also points to some exceptions:

- 5 out of 11 IFRA QRA product categories have recommended standard limits for citral ≥ 1 % (see table 11, p. 26);

- Specific consumer products on the Danish market contain citral in concentrations well above 1 %: massage oils (up to 3.25 %); eterical oils/scented oils (up to 78 %), air fresheners (up to 26 %), (see chapter 10.8.3, p. 27);

- Fragrance mixtures and scented oils for professional use may contain citral in concentrations above 1 % according to the Danish Product Register (see chapter 10.8.3, p.27).

It seems that these exceptions mainly refer to products not being intended for (long) skin contact (apart from massage oils). Thus, we also think it's justified to assume generally low skin exposure to citral (i. e. score 0 for concentration/dose in the meaning of the CLP guidance) and to calculate an additive exposure index of 4 when considering the frequency for exposure to citral.

Altogether, we support the proposal to classify citral in sub-category 1A even though our interpretation of the outcome of patch tests in unselected patients deviates from the dossier submitter's interpretation.

Dossier Submitter's Response

Thank you for your comments and support.

To follow up on the above considerations about the outcome of the animal and human data, respectively, the DS notes that there are other examples of sensitising substances where animal data indicate a moderate sensitisation potential whereas human data indicate a strong sensitising potential. This was e.g. the case for the fragrance substance HICC (Hydroxyisohexyl 3-cyclohexene carboxaldehyde) which has been classified as a category 1A sensitiser, primarily based on human patch test data combined with expected low exposure.

We agree that it is debatable whether the data from unselected patients indicate "high frequency of sensitisation). Of the 5 out of 14 patch test studies with unselected patients showing prevalence rates equal to or above 1% two studies origin from outside Europe (Korea and North America, respectively). As the exposure estimate refers to a European situation it can be argued that the non-European data should not be taken into account. That leaves only 3 out of 12 patch test studies with unselected patients showing prevalence rates equal to or higher than 1% (1.0%, 1.0% and 1.1%, respectively).

The key evidence for the assessment of the potency of citral is thus the human patch test data from selected patients which clearly indicate a strong sensitising potency of citral in 10 out of 11 patch test studies with selected dermatitis patients. It could be argued that the two studies by Itoh et al., 1986 and 1988 and Nischimura et al., 1984 as well the study by Ishihara et al., 1981 which are cited from Lalko and Api 2008, there is not much information about the origin of the patients nor the "type" of patients. It is likely that these studies do not concern European patients and that these studies should not be allocated as much weight as the remaning patch test studies on selected patients. If these 3 studies are not considered as key evidence that leaves 8 studies with selected dermatitis patients, all with sensitisation prevalence rates higher than 2.0%.

With regards to the exposure estimate we agree with your comments. Although some examples of consumer products are identified which contain citral in concentrations >1%, these are – with the exception of massage oils – not products that are intended for (long)

skin contact (e.g. air fresheners, aromatherapy products) or, in the case of eterical oils: undiluted use on skin.

RAC's response

Thank you for the detailed comments. RAC considers that the human exposure to citral is not clear, and that an arguement can be made that exposure to citral is high (or at least was historically, when sensitisation to citral was likey induced in the patients from the patch test studies).

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium	International Fragrance Association (IFRA)	Industry or trade association	8

Comment received

Chapter 10.7 SKIN SENSITISATION page 13
Chapter 10.8 SHORT SUMMARY AND OVERALL RELEVANCE OF THE PROVIDED INFORMATION ON SKIN SENSITISATION pages 23-25
Chapter 10.9 COMPARISON WITH THE CLP CRITERIA pages 27-30
Chapter 10.10 CONCLUSION ON CLASSIFICATION AND LABELLING FOR SKIN SENSITISATION page 32

ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA-comments-re-Citral-CLH-proposal final version.docx

Dossier Submitter's Response

Thank you for your comments addressing the estimated low exposure and the human data on which the CLH proposal is based.

1) Exposure considerations

The human data from diagnostic patch testing mainly include dermatitis patients with expected allergy to fragrances/cosmetics. As stated in the comments citral occurs in a range of natural food sources and essential oils. While such sources could contribute to the overall dermal exposure (on top of the exposure from e.g. cosmetics, detergents and other consumer products), long-term skin contact with food such as fruit and vegetables is not expected for the general population and dermal uptake of citral from such sources is expected to be negligible. Work related dermal exposure to citral through such natural sources could, however, occur to a higher extent in the food/gastronomy industry. The natural sources of citral such as fruit and vegetables would be expected to mainly contribute to systemic exposure trough dietary intake. While allergic contact dermatitis is a widespread problem known to affect a large percentage of the population it has only been documented for relatively few patients that other exposure routes than dermal contact have contributed significantly to their allergic disease[1]

[1)] Lampel and Silvestri, Contact Dermatitis 2014
https://link.springer.com/article/10.1007/s40521-014-0029-6

The exposure estimate in the CLH proposal indeed considers that citral has widespread use. This lies in the estimated repeated exposure frequency of ≥ once daily and ≥ 100 anticipated exposures of sensitised individuals to citral. However, the actual dose levels are estimated to be low based on findings/measured concentrations in relevant high-volume consumer/proff. products such as cosmetics, detergents and other fragranced products. The

product surveys conducted by the DK EPA in which the concentrations of citral have been measured in a range of cosmetic and household products were published in the period from 2002-2011 (and mostly before 2008). Thus, the measured concentrations relate to a time period before the current IFRA standards have actually been implemented. As stated in the CLH proposal the measured concentrations in day-to-day cosmetic products and household products were generally in the range from 0-<0.06% with the exception of massage oils and air-fresheners.

Please also refer to the answer given to comment no. 5 in this document under the sub-heading "Comments on exposure considerations"

2) Human data

While patch test studies as such are considered as relevant and valid information according to the CLP classification criteria and guidance it lies in the nature of such clinical studies that detailed information of the actual exposure levels leading to induction of sensitisation for the patients tested are often/most likely not necesarrily available. Instead the guidance establishes principles for deriving an exposure index leading to an assessment of relatively low or high exposure, respectively (c.f. comments on exposure assessment above). It is also noted that e.g. the fragrance Hydroxyisohexyl 3-cyclohexene carboxaldehyde has been classified as a strong sensitiser (sub-category 1A) based on the same type of data; i.e. high prevalence rate of sensitisation seen in diagnostic patch tests in combination with an estimated low exposure although available animal data indicate moderate sensitisation potential.

With regard to the comments on the HMT/HRIPT studies, please refer to the answer given to comment no. 5 under the sub-heading "Comments on human data"

Overall the DS disagrees with the conclusion that the data presented in the CLH dossier have failed to show sufficient justification for a category 1A classification.

RAC's response

Thank you for the detailed comments. As discussed in the response to other comments, RAC is aware of the need to consider carefully the nature, possible timing and frequency of the doses of citral that the patch tested patients may have been exposed to on their skin to induce their sensitised state. An assessment has been made in accordance with the CLP guidance, relating the relatively high frequencies of positive results to an expert judgement about the nature of the exposures that may have led originally to the induction of the sensitised state.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	France		MemberState	9

Comment received

The potency of citral to induce skin sensitisation is borderline between sub-categorisation 1A and 1B based on both animal and human data.

Animal data from LLNA indicate that citral is able to induce moderate to strong skin sensitisation. The range of EC3 values obtained in the LLNA studies (from 1.2 to 15%) is difficult to interpret as, in most of the studies, very limited information are available. Two out of the 14 reported studies show EC3 values below 2% and would therefore indicate subcategorisation 1A. Higher EC3 values have been observed with the solvent AOO than

with EtOH:DEP and EC3 below 2% has only been observed with EtOH:DEP. As detailed results are not available with most of the studies it is not possible to conclude if a higher background has been observed with AOO.

In the 6 M&K studies, only half of the studies have quantitatively reported positive responses. One of the studies met the criteria for category 1A (at the cut-off between 1A and 1B). Nevertheless, in studies using high intradermal doses, we agree that it is not possible to rule out that a high response could have been observed if lower intradermal induction doses had been used. The results of the Buehler study met the criteria for category 1A (borderline with 1B as the induction of concentration was 20%). Nevertheless, the results of the study is questionable as only a very low number of tested animals were used (n=5).

In the CLP criteria, no subcategorisation is proposed if data are insufficient to allow it. Although we agree that in case of numerous studies the higher potency should apply, a firm conclusion is not possible due to the lack of information on the quality of the studies and other missing information. Overall, based on animal data only, no subcategorisation could be set.

In human, we fully support the statement that there is a high frequency of occurrence of sensitization for citral in humans. Concentration of citral in patch test varies from 0.1% to 5%, 2% being the most reported. It is not clear why different concentrations were used in patch tests. Is there available information in the literature to explain the choice of the tested concentrations for patch testing? As citral is a skin irritant, maybe some reported reactions are related to irritation rather than sensitization when the concentration is above a certain value?
With regards to exposure considerations, it is reported in the CLH dossier that the majority of the products has concentration of citral below 1% but that for some products high concentration may be allowed (> 1%). If available it may be helpful to have concentration data of citral in products from other EU countries. Indeed, it is stated in the dossier that for example in Sueden, higher concentrations of citral compared to DK are found. As most of the incidence values from patch studies are from EU multicenters, exposure data may need to better reflect EU products. Moreover, the overall score of 4 proposed by the DS (table 12) may be debated with a score of 5 (1 instead of 2 for concentration/dose) and that would lead to the category "relatively high exposure".

Experimental studies show that citral could induce skin sensitisation at 2% but these data do not allow a conclusion below this concentration (e.g. 1%).

Overall, both animal and human data are borderline between category 1A and 1B. More information on citral in EU products may help to come to a conclusion.

Dossier Submitter's Response

Thank you for your comments.

The support of the observation of high frequency of occurrence of sensitisation for citral in humans is appreciated. With respect to the doses used in the various patch tests it is noted that the fragrance mix II (FMII), which contains citral, was first introduced in the European baseline series used for standardised patch testing in dermatological clinics in 2005. Citral is present in FMII in a concentration of 1%. When tested individually the recommended concentration for citral in pet. is 2% (Recommendation of the European Society of Contact Dermatitis), which is also the dose level most frequently reported in the available patch test studies.

The use of other test concentrations may in some of the cases possibly be explained by the time period of the study (prior to 2005) or that the study was performed outside EU and according to other recommandations/study protocols.

Regarding the comment on possible irritation reactions: When observing/reading the reactions in the patch tests a distinction the observations are graded according to the severity of reaction and reactions which are doubtful/possibly irritation reactions are given a specific note or score. It lies in the nature of an irritation reaction that such reactions will gradually decrease and are normally reversible. Sensitisation reactions are more severe in their nature. As an example the following description from the publication by Geier et al., 2015 is included for more clarity on how irritation reactions are distinguished from sensitisation reactions: *"In case of an allergen-specific sensitization, a positive reaction with erythema, infiltration and possibly papules (+), additionally vesicles (++), or even coalescing vesicles (+++) occurs, depending on the degree of sensitization. Patients, who are not sensitized, usually show no reaction at all; however, in some cases, irritant or doubtful reactions can occur, which are coded as 'ir' and '?', respectively"*.

We agree that it would have been very helpful to have exposure data from other EU countries but we have not been able to retrieve such data. That is why current IFRA recommandations have been included as an indication of the use of low concentration levels in high-volume fragranced products such as cosmetics and household products.

Further information from Danish EPA Product Surveys on measured concentrations of citral in various consumer products: An extract of the analysed content of citral in various consumer products on the Danish market is shown in the table below. The surveys are conducted in the period from 2002-2011 and further information can be found (in Danish) via this link: http://mst.dk/kemi/kemikalier/fokus-paa-saerlige-produkter/database-over-kemiske-stoffer-i-forbrugerprodukter/
An English search guide for the database on chemicals in consumer products can be found here: http://eng.mst.dk/media/mst/69132/Search%20guide%20-%20forbrugerdatabase%20-%20eng.pdf (using this guide the specific product surveys can be found in English at the website of the Danish EPA)

Extract of measured concentrations of citral found in various consumer products in surveys conducted in the period 2002-2011:
Note that for each product type/group, several products have typically been analysed. Note that the CLH report by mistake reports the content of citral in air-fresheners as 26%. The correct figure is 2.6%.

Product type (English translation)	**Citral content, ppm**
Massage oils	19-32500
Liquid soap	69-73
Shampoo	6-8
Eau de toilette	4-5
Deodorant spray	38,3-553,9
Deodorant stick	202,4
Deodorant roll-on	44,0
Eterical oils and scented oils	160-780000
Sex cream	40

Handsoap	5-13
Soap bubbles	27
Coloring pens, hobby articles	0,30-0,70
Coloring pens, toys/childrens articles	400
Animal care products	5
Stain removers	30-34
Scented balls	80-83
Air fresheners	200-26000
Cleaning products	0,0092-0,0160
Dishwashing detergents	0,0260-0,0501
Vinyl cleaner	0,03
Hand cream	3-52
Deodorant roll-on	<1-27
Day cream	<1-35
Bodylotion/cream	<1-47
Conditioner	<1
Facial spray/toner	<1-2

While that the patch test data do not allow a conclusion of the prevalence rates of sensitisation at doses below 2% the classification criteria/guidance for skin sensitisation allows for an overall assessment of the sensitisation potential when combining sensitisation frequencies from diagnostic patch tests with an estimate of either high or low exposure based on a scoring matrix. It is also noted that e.g. the fragrance Hydroxyisohexyl 3-cyclohexene carboxaldehyde has been classified as a strong sensitiser (sub-category 1A) based on the same type of data; i.e. high prevalence rate of sensitisation seen in diagnostic patch tests in combination with an estimated low exposure although available animal data indicate moderate sensitisation potential.

RAC's response

Thank you for your comments. RAC agrees that sub-categorisation is not possible based on the animal data.

With regards exposure, RAC agrees that assessment of the citral exposure to the population is key in assessing the significance of the high numbers of people who have responded positively on clinical patch testing. Whist the additional information provided by the Dossier Submitter is appreciated, it doesn't appear to be sufficient to demonstrate low exposure for the relevant time periods and geogrpahical locations. The possibility of high exposure (as defined in the CLP guidance) cannot be excluded.

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Sweden	The Swedish Contact Dermatitis Research Group	National NGO	10

Comment received

The Swedish Contact Dermatitis Research Group supports the proposal for harmonized

classification and labelling of citral (3,7-dimethylocta-2,6-dienal) as skin sensitiser 1A. A classification in sub-category 1A is justified based on the high frequency of occurrence of skin sensitisation observed in a large number of human patch test studies combined with a low estimated exposure to citral.
Citral was selected by the Scientific Committee on Consumer Safety as one of 12 established fragrance contact allergens of special concern, owing to the high absolute number of reported cases of contact allergy (>100) (SCCS 2012, SCCS (Scientific committee on Consumer Safety), opinion on fragrance allergens in cosmetic products, 26-27 June 2012).

Connection between citral and geraniol
It should be observed that there is a close connection between citral and geraniol ((2E)-3,7-dimethylocta-2,6-dien-1-ol) since citral is the reaction mass of the cis-trans stereoisomers geranial ((E)-3,7-dimethylocta-2,6-dienal) and neral ((Z)-3,7-dimethylocta-2,6-dienal). Geranial and neral have been identified as metabolites of geraniol (Hagvall L et al. 2008). A connection between contact allergy to geraniol and contact allergy to citral was shown in a study within the multicenter project IVDK (Information Network of Departments of Dermatology) an instrument of epidemiological surveillance of contact allergy (Uter W et al 1998). Concomitant reactions between citral and geraniol occurred most frequently among all fragrance allergens investigated since 83% of the dermatitis patients reacting to citral also reacted to geraniol (Schnuch A et al, 2007). This connection was also observed in a patch test study in which patients with positive reactions to citral, to a large extent, reacted to (both pure and oxidized) geraniol (Hagvall L, et al 2012). Thus, individuals allergic to citral can develop allergic contact dermatitis not only when exposed to citral but also when exposed to geraniol.

Sensitising potency of citral in the LLNA
The differences in sensitizing potency obtained for citral in the LLNAs depending on vehicle should be observed. In total 14 LLNAs are reported, four used AOO (acetone:olive oil 4:1) which is the standard and most commonly used vehicle in the LLNA while ten assays used mixtures of EtOH:DEP (ethanol:diethylphtalate) as vehicle. An increase in the sensitizing potency (decreased EC3 values) for citral was seen in the LLNAs using EtOH:DEP as vehicle compared to those using AOO as vehicle. Two of the LLNAs with EtOH:DEP vehicle gave EC3 values < 2 which renders a sub-classification of 1A. An experimental study has concluded that EtOH:DEP provides a suitable vehicle for use in the LLNA (Betts CJ et al 2007). It is well-known that the vehicle has an influence on the skin absorption of a compound and therefore also its sensitising potency. All experiments using EtOH:DEP were performed by the fragrance industry since this vehicle is considered more appropriate with regard to the exposure from fragranced consumer products. Based on this the results obtained from the LLNAs using EtOH:DEP as vehicle could be considered more relevant with regard to the risk of sensitisation in the population.

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Hagvall L, Baron J M, Börje A, Weidolf L, Merk H F, Karlberg A T. Cytochrome P450-mediated activation of the fragrance compound geraniol forms potent contact allergens. Toxicol Appl Pharmacol 2008: 233: 308–313
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Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the

literature. Contact Dermatitis 2007: 57: 1–10
Uter W, Schnuch A, Geier J, Frosch P J. Epidemiology of contact dermatitis: the information network of the departments of dermatology (IVDK) in Germany – a surveillance system on contact allergies. Eur J Dermatol 1998: 8: 36–40

Dossier Submitter's Response

Thank you for your comments and support.

We are aware of the link between citral and geraniol as geraniol can metabolise to geranial and neral, which constitute the components of citral. Please note that a separate CLH proposal for geraniol has also been submitted by the DK EPA.

We also agree that the LLNAs conducted with EtOH:DEP as a vehicle is considered more appropriate in relation to exposure to fragranced consumer products. However, please also refer to the answer given to comment no. 5 under the sub-heading "Comments on animal data".

RAC's response

Thank you for your comments. RAC notes the (potential) effect of vehicle on the results of the LLNA, however a number of studies conducted using EtOH:DEP gave EC3 values >2%. RAC considers that the animal data are variable, and on their own, cannot be used for sub-categorisation.

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany	European Society of Contact Dermatitis	Academic institution	11

Comment received

classification as 1A is supported

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ESCD statement_to_geraniol_citral(171129).pdf

Dossier Submitter's Response

Thank you for your comments and support.

RAC's response

Noted, thank you.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	12

Comment received

The Swedish Chemicals Agency agrees with the classification of citral as Skin Sens. 1A based on a high frequency of occurrence of skin sensitization to citral in humans, in combination with a relatively low exposure. Although the overall animal data suggest sub-category 1B, this cannot negate the extensive human diagnostic patch test data presented in the CLH proposal.

Animal data
It is difficult to assess the reliability of the different animal studies in the CLH-report, since no reliability scores have been assigned to them. However, the overall animal data for citral seems to point to subcategory 1B.

Human diagnostic patch test data
Frequency
In almost all (10/11) of the patch test studies with selected dermatitis patients the frequency is >2.0%. For unselected, consecutive patients a relevant part of patch test studies (5/14) have a frequency of >1.0%. The total number of published cases are >400. Thus, it can be concluded that there is a high frequency of occurrence of citral skin sensitization (in accordance with Table 3.4.2-2 of the Guidance on the application of the CLP criteria).

Exposure considerations
The CLP report for citral states that average concentrations found in consumer products (Danish EPA database) are generally below 1% but with some exceptions in for example massage oils (3.25%) and air fresheners (26%). IFRA standards for citral are also stated to be below 1% for most product categories, especially for those that can be expected to be frequently used by consumers. As consumer products containing citral are abundant it is anticipated that the repeated exposure would be > once/daily with >100 exposures in total. Considering the data above, the cumulative exposure score for citral is 4 (Table 3.4.2-3 of the Guidance on the application of the CLP criteria). A score of 1-4 translates to a relatively low exposure.

According to Table 3.4.2-4 of the Guidance on the application of the CLP criteria, the combination of a relative low exposure and a relative high frequency of occurrence of skin sensitization to citral fulfils the criteria for classification in subcategory 1A.

HMT and HRIPT data
All of the HMT studies were performed using concentrations of citral >500 µg/cm2. The lowest concentration used was >1000 µg/cm2 where about 8% of volunteers were sensitised. Since no test have been performed using concentrations below 500 µg/cm2, we agree with the DS that the results from the HMTs cannot be used in the weight of evidence assessment for sub-categorization of citral, but that they confirm the sensitising potential of citral. The HRIPT studies have been performed with concentrations of citral ranging from 388 to 3876 µg/cm2 resulting in few cases of sensitisation. In order to clarify the outcome of the HRIPTs we propose to evaluate and discuss these studies in more depth in the CLH-report, if it is possible to get access to the original study reports.

Dossier Submitter's Response

Thank you for your comments and support.

With regard to the comment on reliability scores, please refer to the answer given to comment no. 1.

With regard to the comments on the HRIPT studies the DS has received original study reports for two of these studies ("RIFM 2004b": 0% were tested positive of 101 volunteers and "RIFM 1971a": 0% were tested positive of 50 volunteers). Based on the information received, which e.g. clarifies the dose level used in the study "RIFM1971a", it seems that positive sensitisation reactions are seen with increasing doses in the available HRIPT (and HMT) studies. Please refer to the answer given under comment no. 5 for further information/discussion of both animal and human data, for which confidential study information was supplied in the public consultation.

RAC's response

Thank you for your considered comments. RAC agrees that the results of the HMT studies cannot be used for sub-categorisation. Further information on the HRIPT studies was provided during the public consultation and has been taken into consideration by RAC.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CITRAL; 3,7-DIMETHYLOCTA-2,6-DIENAL

PUBLIC ATTACHMENTS
1. IFRA-comments-re-Citral-CLH-proposal final version.docx [Please refer to comment No. 8]
2. 0_AS_Comment on CHL_CITRAL_V2.pdf [Please refer to comment No. 2, 4]
3. CLH comments BASF SE final.pdf [Please refer to comment No. 5]
4. ESCD statement_to_geraniol_citral(171129).pdf [Please refer to comment No. 11]
5. EECDRG statement_to_Proposal for Harmonised Classification and Labelling of Citral 27112017.pdf [Please refer to comment No. 6]

CONFIDENTIAL ATTACHMENTS
1. Confidential attachment final.docx [Please refer to comment No. 5]