Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol

EC Number: 203-377-1
CAS Number: 106-24-1

CLH-O-0000001412-86-224/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GERANIOL; (2*E*)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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: geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol
EC number: 203-377-1
CAS number: 106-24-1
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	1
Comment received				
Reliability scores for the various studies are missing in the CLH report.				
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:* Among the 16 animal studies cited in the CLH report 11 of the study results 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.* The remaining five animal studies (references: Hagvall et al., 2007, Ulker et al., 2014, Klecak et al., 1977) are considered to quality for a reliability score of 2 ("Reliable with restriction") according to the Klimisch criteria (Klimisch et al., 1997). *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 geraniol 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 geraniol in category 1A. The animal data show moderate sensitising effects of geraniol. 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. 9 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 geraniol.

RAC's response

RAC agrees with the perspective of the Dossier Submitter that it is possible to characterise the hazard of geraniol 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 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
30.11.2017	Belgium	Procter & Gamble	Company-Downstream user	2

Comment received

Procter & Gamble (P&G) opposes the proposal for a harmonised classification and labelling of the substance, Geraniol. Arguments are presented in the Attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment FINAL Geraniol - supporting arguments to avoid H317 1A_Comments from PG_30 Nov 2017.pdf

Dossier Submitter's Response
Thank you for your comments, your position is noted. *<u>Comment on transformation/metabolisation of geraniol in LLNA/human studies and interpretation of results</u>* As stated in the CLH report geraniol has been shown to autooxidise to other substances with increased sensitising capacity. The CLH report also describes that the results of the studies using air-exposed geraniol (air-exposure for 10 weeks or more, both animal and human studies) are not considered directly applicable for the purpose of classification as the air-exposure is considered to produce more reactive metabolites/oxidation products with increased sensitisation capacity. In other words these tests do not reflect the identity of the actual test substance (geraniol) tested under standard conditions but rather its metabolites produced under conditions that enhance transformation. The comments from P&G refer that CYP metabolism in the skin may produce more allergenic metabolites (ref: Hagvall et al., 2008). The DS considers that the LLNA (and human testing) provides for the possibility to detect both pro-haptens and pre-haptens under normal testing conditions. This implies that the result of a test – whether it is an LLNA, a human patch test or other test – also covers any biotic or abiotic transformation of the test substance that may occur during the test. The final result (the magnitude of the reponse obtained) will thus reflect the properties of the tested substance as well as any transformation products that may be produced under the standard test conditions. The DS notes that classification of substances refer to the properties of the test substance as such, and is generally not based on the properties of the substance when present in a mixture e.g. including anti-oxidants, solvents and other substances which may or may not impact properties such as the solubility, the level of skin penetration etc. of the substance. Such data may, however, be used as supporting evidence in some cases. *Comment on suitability of diagnostic patch test data* The DS disagrees that diagnostic patch test data are not suitable for hazard classification. The classification criteria and guidance describes how such data can be used for classification, even though dose-response data will often not be available from this kind of testing. Please also refer to the answer given to comment no. 9 on this issue. *<u>Comment on on-pack listing</u>* Classification of strong sensitisers in category 1A will provide better labelling information to consumers as the concentration limits for classification and elicitation are more stringent than for category 1 or 1B sensitisers. Identification of the most potent sensitisers does thus aim at providing the users with information on the presence of such substances at even lower product concentrations (for mixtures under the scope of CLP).
RAC's response
The comments from P&G are noted. The guidance to CLP indicates how diagnostic patch test data may be used for hazard classification.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	France		MemberState	3
Comment received				
Identity and physico-chemical properties				

France is the eCA for the biocidal active substance geraniol. The assessment of the substance is still ongoing. Data reported in CLH report is different from that provided in the biocidal dossier. Nevertheless, conclusion on hazards properties of the substance geraniol are similar.
Dossier Submitter's Response
Thank you for your comments. It is not clear from your comment exactly which data in the CLH report that are different from those of the biocidal dossier.
RAC's response
Noted; no action taken.

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_GERANIOL_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 geraniol 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 geraniol, 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 geraniol 36 out of 56 published patch test studies with selected patients show relatively high frequencies of occurrence of skin sensitisation in studies including a very large number of patients of both genders from different regions (in and outside) Europe. 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 geraniol 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 geraniol 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 geraniol. Besides the IFRA limits, product surveys 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 geraniol 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	5
Comment received				
The Swedish Contact Dermatitis Research Group hereby responds to the open consultation regarding the proposal of harmonized classification and labelling of geraniol ((2E)-3,7-dimethylocta-2,6-dien-1-ol, 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. The response was agreed upon 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. Please refer to the collective answer given under comment no. 8.				
RAC's response				
Noted; see also response to comment No. 8.				

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany		MemberState	6
Comment received				
Substance ID In IUCLID Section 1.1 Identification – Type of substance it was claimed that the substance is a multi-constituent substance. But since geraniol has a very high purity and other constituents are not present the substance should be classified as a mono-constituent substance. Reliability of studies: To compile this CLH report, the SCCS opinion on fragrance allergens from 2012 was used while an additional search in the open literature has been done for the period from January 2009 until November 2016. No reliability scores have been attributed to the studies taken from the SCCS opinion. The CLP Guidance recommends to apply the Klimisch code (1. Reliable without restriction; 2. Reliable with restriction; 3. Not reliable; 4. Not assignable) the weight of evidence assessment. Without any information on the studies' reliability it is hardly possible to weight the information.				
Dossier Submitter's Response				
Thank you for your comments. We apologise for the confusion about the substance ID. We agree that geraniol shall be considered a mono-constituent substance as it consists only of one constituent substance of high purity. (In the REACH registration dossier for geraniol some conflicting information is, however, found on the substance ID). On the comment on the reliability studies, please refer to the answer given to comment no. 1 from the Swedish MSCA.				

RAC's response
RAC agrees with the perspective of the Dossier Submitter that it is possible to characterise the hazard of geraniol 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 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.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany		Individual	7
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment 0_AS_Comment_on_CHL_GERANIOL_V2.pdf				
Dossier Submitter's Response				
Please refer to the answer given to comment no. 4. This answer addresses the same attachment as provided here under comment no. 7.				
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 geraniol 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	8
Comment received				
The Swedish Contact Dermatitis Research Group supports the proposal for harmonized classification and labelling of geraniol ((2E)-3,7-dimethylocta-2,6-dien-1-ol) as skin sensitiser 1A. According to the sub-categorisation decision table stated in the guidance (ECHA 2015) the combination of relative low exposure and relative high frequency of occurrence of skin sensitization in human to geraniol justifies this classification of geraniol (CLH report for geraniol, Table 3.42-d, p 33). Geraniol 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). It should be noted that geraniol is a prohapten and a prehapten (SCCS 2012, Hagvall L et al. 2008, Casati S et al. 2016). This means that geraniol is bioactivated in the skin as well as activated outside the body by air oxidation. In both cases skin sensitisers are formed of which the aldehydes geranial and neral (which in turn are the reaction mass of the fragrance material citral) are formed via both activation ways. The present proposal covers				

only geraniol as a prohapten.
References
Casati S, et al. Ability of non-animal methods for skin sensitisation to detect pre- and pro-haptens: Report and recommendations of an EURL ECVAM expert meeting; EUR 27752 EN; doi:10.2788/01803
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
SCCS 2012, SCCS (Scientific committee on Consumer Safety), opinion on fragrance allergens in cosmetic products, 26-27 June 2012

Dossier Submitter's Response

Thank you for your comments and support.

We agree that geraniol is both a pro-hapten and a pre-hapten.

Animal tests such as the LLNA and human studies such as patch tests implicitly cover any biotic and abiotic transformation that may occur during the test. The CLH report describes that the studies cited in which air-exposed geraniol is used (air-exposed 10 weeks or more prior to testing) are not considered directly applicable for classification as the increased sensitisation potential observed in these studies is considered to reflect an enhanced transformation into more reactive metabolites/oxidation products prior to the testing. However, the response obtained under standard conditions in LLNAs or patch test studies will, to some extent, also reflect any transformation of the substance that may occur during standard exposure conditions.

RAC's response

Thnak you for the background information about the work of the SCCS.
RAC agrees with the response provided by the Dossier Submitter to the comments about haptens and the potential for gerniol to be oxidised if left in the open air.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany	BASF SE	Company-Manufacturer	9

Comment received

Please see the attached documents

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH comments_Geraniol (CAS 106-24-1)_BASF SE.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Geraniol_Confidential attachment.doc

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) *Comments on animal data*

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 5 LLNAs reported by RIFM are "reliable with restrictions" and that collectively they confirm moderate sensitising properties of geraniol as also concluded in the CLH dossier.

With regard to the comment on the increased sensitisation capacity of geraniol via autoxidation and metabolic activation the CLH report states that the experiments conducted with air-exposed geraniol (air-exposed for 10 weeks or more) are not considered directly applicable for classification. This is due to the enhanced conditions for transformation into reactive metabolites/oxidation products of geraniol which leads to uncertainty about what substance(s) that have actually been tested. However, the results of standardised animal tests or human patch testing with geraniol (without previous air-exposure) will in their nature reflect any metabolism or oxidation that may occur during the test. This is considered relevant for classification as it reflects the processes happening under normal skin exposure to the substance.

2) Comments on 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 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.

The HRIPT and HMP studies are generally conducted at concentrations exceeding 500 µg/cm2 and generally few positive reactions were observed in these studies. As reflected from the information received some of the reactions may be attributed to irritation rather than sensitisation. 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 geraniol 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 geraniol in selected dermatitis patients supports sub-categorisation of geraniol 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 0.26% (2010-2015) and ~0.5% (2009-2015) confirm the general picture observed for consecutive patients patch tested with geraniol, i.e. patch test frequencies in the range between 0-4.6% and mostly below 1%. (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, and mixture composition information from the Danish Product Registry) the exposure to geraniol 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 geraniol in concentrations >1%, geraniol is generally present in concentrations far below 1% in high-volume leave-on cosmetics and detergent 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 geraniol have been measured in a range of cosmetic and household products were published in the period from 2002-2011 (and by far most products have been analysed before 2007). 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-<0.15% with the exception of massage oils and air-fresheners. Furthermore, information from the Danish Product Registry indicate that concentrations of geraniol in chemical mixtures for professional use (e.g. detergents, cleaning products) are generally below 0.1% except for products such as concentrated fragrance mixtures/scented oils. 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 geraniol 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) Reply to comments on Table 9 of the CLH report:

- Kiec-Swierczynska & Krecisz, 2000: When writing the CLH dossier we were in doubt about whether the patients should be regarded as selected or unselected. However the patients are considered to be selected patients based on suspected work-related eczema.
- Malanin & Ohela, 1989: The total number of patients tested was 1967 and 14 patients (0.7%) had positive reactions to geraniol (by mistake table 9 in the CLH report states that 14 out of 200 patients reacted to geraniol. A total of 200 out of 1967 reacted to either the fragrance mix and/or its individual components). The paper does not reveal

further details about the patients, but they were (apparently) not selected based on positive reactions to the fragrance mix as all patients were tested both with the fragrance mix and its individual components. There is no information that the patients are selected specifically based on suspected allergy to e.g. fragrances or cosmetics, but as further details are not available this study should not be allocated a lot of weight due to this uncertainty. (In Annex 1 to the CLH report the study is by mistake listed as "selected patients" but should be listed as "consecutive").

- Cronin, 1978: The reference cites patch test data from 1984 so we agree that the correct year of publication can't be 1978. However, we only have access to an old scanned copy of the publication which indicates "Allergy to cosmetics. Acta Dermato-Venereologica, Stockholm 1978, Suppl. 134: 77-82" in the header.

RAC's response

The detailed comments and additional study information provided by BASF SE are noted. As discussed in response to several other comments, the results of the diagnostic patch tests are considered by RAC to relevant for classification purposes. An assessment has been made in accord with the CLP guidance, relating the relatively high frequencies of positve 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
30.11.2017	Belgium	Procter & Gamble	Company-Downstream user	10

Comment received

P&G does not support the proposed harmonised classification of Geraniol as H317, Skin Sensitiser, Cat 1A. Our arguments which support our position that Geraniol should not be classified as a Cat 1A Skin Sensitiser are summarised

ECHA note – An attachment was submitted with the comment above. Refer to public attachment FINAL Geraniol - supporting arguments to avoid H317 1A_Comments from PG_30 Nov 2017.pdf

Dossier Submitter's Response

Please refer to the answer given under comment no. 2. This answer addresses the same attachment as provided here under comment no. 10.

RAC's response

The comments from P&G are noted.
The guidance to CLP indicates how diagnostic patch test data may be used for hazard classification.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	France		MemberState	11

Comment received

Skin sensitization: Based on the animal data, human data and IFRA data, a classification Skin Sensitisation of category 1B should be proposed. However, based on Danish national data, a classification Skin sensitisation 1A is proposed. This classification is very restrictive. Therefore, could you please more argue the low exposure to geraniol of the population?

Dossier Submitter's Response

Thank you for your comments.

We consider that classification in category 1A is justified, mainly based on the results obtained in human patch test studies when seen in combination with an estimated low exposure. While it would have been very helpful to have further exposure data, incl. data from other EU countries, we have not been able to retrieve such data. The approach for estimating relatively high or low exposure according to the guidance gives a rough indication of the expected level of exposure. The estimate is based on product surveys referred by SCCS and the Danish EPA, which have measured the concentrations of geraniol in a range of cosmetic products as well as e.g. detergents and air-fresheners.

Danish EPA Product Surveys: An extract of the analysed content of geraniol 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 geraniol 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.

Product type (English translation)	**Geraniol content, ppm**
Hand soap	1-1200
Soap bubbles	< dg
Coloring pens	2-11
Scented balls	3
Lipcare products	3-725
Animal care products	3-360
Stain removers	18-120
Scented balls	390-430
Air fresheners	410-8900
Brown soap	0,0086
Wood soap	0,0103
Cleaning products	0,0843
Wet wipes	0,0069
Dishwashing detergents	0,0070-0,1454
Fabric softeners	0,0018
Hand cream	10-640
Deodorant roll-on	15-600
Day cream	<1-460
Bodylotion/cream	<1-4
Conditioner	8-51
Facial spray/toner	1-16
Massage oils	37-230000

Body shampoo/shower gel	3-9
Liquid soap	180
Shampoo	2-61
Eau de toilette	33-34
Deodorant spray	23,9-399,0
Deodorant stick	103,1
Deodorant roll-on	48,6

Data from the Danish Product Registry on the concentration of geraniol in mixtures for professional use furthermore support that low concentrations (mostly <0.1%) of geraniol are used in mixtures such as: cleaning products, adsorption/absorption products, anti-frost products, biocides, bleaches, impregnation products, cosmetics, lubricants, glue, paint, polishes, fabric softeners. Product concentrations of geraniol >1% are generally only found in concentrated fragrance mixtures (presumably used as ingredients in other mixtures) and scented oils/massage oils, whereas concentrations well below 1% have been measured in a range of every-day use products (confidential data, details cant be disclosed). The use of air-fresheners and scented oils/massage oils with concentrations >1% is considered to be less usual/frequent compared to daily use cosmetic and household products.

As described in section 10.8.3 of the CLH proposal fragrances such as geraniol 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.

RAC's response

RAC agrees that assessment of the genariol 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
29.11.2017	Germany		Individual	12

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.

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany		MemberState	13

Comment received

According to the CLP Regulation, the Murine Local Lymph Node Assay (LLNA) is the first-choice method for in vivo testing and only exceptional circumstances should another test be

used. LLNA is the REACH Annex VII-endorsed in vivo method. This assay has been validated internationally and has been shown to have clear animal welfare benefits and scientific advantages. The LLNA is designed to detect the potential of substances to induce sensitisation as a function of lymphocyte proliferative responses induced in regional lymph nodes (induction phase) (see Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance Version 6.0 July 2017). Scientific evidence indicates that labelling of geraniol as Skin Sens. 1B is appropriate as a result of the outcome of several LLNA in vivo studies.

Human data can be used in a weight of evidence approach. Sensitisation potential of geraniol in humans has been recorded in several studies. A concern represents indeed the eczema patients where it is shown high frequency of occurrence. It is worth to mention that the tests performed in humans have differences in sensitivity while there are a number of limitations that could be associated with the human data such as the fact that a lot of data originate from older studies. There is not a well standardized protocol. The intrinsic potency of chemical skin sensitizers in humans requires experimental studies of not acceptable ethics. The intra-species variability of human susceptibility to skin sensitization might influence the results. In addition, in some of the studies, too low or too high concentrations might have been used for testing, that would lead do false negative or positive results. Overall, the data obtained from animal studies and the evidence available from the human studies are sufficient to classify geraniol as skin sensitizer sub-category 1A.
Nevertheless, regarding the exposure considerations, the estimated additive exposure index might also indicate a relatively high exposure that would lead to sub-categorisation decision Category 1 or case by case evaluation.

Dossier Submitter's Response

Thank you for your comments and support.

With regard to the last comment on exposure considerations you may also refer to the answer given to this topic under comments no. 9 and 11.

RAC's response

Thank you for the carefully considered comments.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	14

Comment received

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

Animal data
The animal data for geraniol point to subcategory 1B.

Human diagnostic patch test data
Frequency
In the majority (36/56) 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 (4/32) have a frequency of >1.0%. The total number of published cases are >900. Thus, it can be concluded that there is a high frequency of occurrence of geraniol skin sensitization (in accordance with Table 3.4.2-2 of the Guidance on the application of the CLP

criteria).

Exposure considerations
The CLH report for geraniol states that average concentrations found in consumer products and products used by professional workers (Danish EPA database) are generally below 1% but with some exceptions in for example air fresheners (23%), fragrance mixtures and scented oils. IFRA standards for geraniol are higher than the concentration measured in products and are below 2-3% for most product categories used by workers and consumers. As products containing geraniol are abundant it is anticipated that the repeated exposure would be >1 once/daily with >100 exposures in total.

In our exposure consideration, the Swedish CA has relied on actual measured data of geraniol in products on the market. Therefore, considering also the data above, the cumulative exposure score for geraniol 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 geraniol fulfils the criteria for classification in subcategory 1A.

Dossier Submitter's Response
Thank you for your comments and support.
RAC's response
Thank you for the carefully considered comments.

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	Finland	European Environmental and Contact Dermatitis Research Group (EECDRG)	International NGO	15

Comment received
EECDRG supports the Danish proposition to give geraniol 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 Geraniol 27112017.pdf
Dossier Submitter's Response
Thank you for your comments and support.
RAC's response
Thank you for the carefully considered comments.

PUBLIC ATTACHMENTS
1. 0_AS_Comment_on_CHL_GERANIOL_V2.pdf [Please refer to comment No. 4, 7]
2. CLH comments_Geraniol (CAS 106-24-1)_BASF SE.pdf [Please refer to comment No. 9]
3. FINAL Geraniol - supporting arguments to avoid H317 1A_Comments from PG_30 Nov 2017.pdf [Please refer to comment No. 2, 10]
4. ESCD statement_to_geraniol_citral(171129).pdf [Please refer to comment No. 12]
5. EECDRG statement_to_Proposal for Harmonised Classification and Labelling of Geraniol 27112017.pdf [Please refer to comment No. 15]

CONFIDENTIAL ATTACHMENTS
1. Geraniol_Confidential attachment.doc [Please refer to comment No. 9]