Committee for Risk Assessment

RAC

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

14 September 2018

CLH-O-0000001412-86-224/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

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

EC Number: **203-377-1**

CAS Number: **106-24-1**

The proposal was submitted by **Denmark** and received by RAC on **8 September 2017.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Denmark has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **17 October 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **1 December 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Andrew Smith**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **14 September 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol	203-377-1	106-24-1	Skin Sens. 1A	H317	GHS07 Wng	H317			
RAC opinion	TBD	geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol	203-377-1	106-24-1	Skin Sens 1	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM	TBD	geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol	203-377-1	106-24-1	Skin Sens 1	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The sensitising properties of geraniol have been intensively studied in both animals and humans. Guideline and non-guideline studies in animals are available; the positive results of numerous local lymph node assays, Guinea pig maximisation and Buehler tests are directly applicable for classification and sub-categorisation. A large number of human patch tests are also available. Geraniol is a component of one of the standardised fragrance mixtures used in the European baseline series used for diagnostic patch testing. Follow-up testing with the single fragrance substances is done routinely in many clinics; the sensitising properties of geraniol are well documented. Results of historical human volunteer studies are also available for geraniol and provide supporting evidence for sub-categorisation.

All the available local lymph node assays (LLNAs) suitable for classification of geraniol show a moderate potency with EC values > 2%. Whereas one maximisation test indicates a moderate potency, the remaining Guinea pig tests only indicate positive, with no indication of potency, or negative results.

The human data provide substantial evidence of strong sensitising effects of geraniol, especially based on the results of patch tests with selected dermatitis patients. Human patch tests with geraniol show a high frequency of occurrence of skin sensitisation. There are data from thousands of unselected and selected patients, and well over 100 published cases. Although original study reports are rarely available, some of the older volunteer tests in humans (human repeat insult patch tests and maximisation tests: HRIPTs and HMTs) generally confirm the sensitising properties of geraniol and indicate a moderate potency.

There is widespread use of geraniol as a fragrance in cosmetics and other consumer products and a high tonnage is placed on the market (1000 - 10000 tonnes/annum). Although frequent or daily exposure to geraniol is anticipated, the overall exposure to geraniol is estimated to be relatively low based on information on how the geraniol is used in these products.

Overall, there is a high frequency of skin sensitisation in human patch tests (≥ 2.0% in 36 of the 56 patch tests with selected patients and ≥ 1.0% in 6 of 32 patch tests with unselected patients) and a high number of published cases, set against an estimated low exposure. In accordance with the CLP criteria and guidance, classification of geraniol as a strong skin sensitiser (Skin Sens. 1A) is justified on the basis of this human evidence.

Comments received during public consultation

Comments were received from 3 Member State Competent Authorities (MSCAs), a Downstream User company (DU) and a Manufacturer, 3 non-governmental groups of dermatologists and one expert individual. In all cases there was an agreement that geraniol should be classified as a skin sensitiser based on both animal and human data. However, differing perspectives were offered in relation to potency and sub-categorisation. The most challenging aspects related to the interpretation of clinical data and information on the extent of human exposure.

One of the commenting MSCA agreed with the Dossier Submitter (DS) that although the animal data indicated low or moderate potency, the clinical information and exposure assessment were typical of a high potency sensitiser. In their view a category 1A classification would have been appropriate. All 3 groups of dermatologists, including clinicians from across the EU, also supported the proposal to classify geraniol as a skin sensitiser in category 1A. In contrast, 2 further MSCAs were not convinced that a sufficiently clear case had been made to support this level of classification. They queried especially the DS's assertion that human exposure to geraniol had been low.

The expert individual, a clinician based in Germany, did not support classification in category 1A. He regarded the strength of the human evidence to be insufficient. He argued against use of the data from selected patients for hazard or risk assessment given the heterogeneous nature of the selection process. Of the fragrances in the standard series used for patch testing, he observed that geraniol had not given an especially high frequency of responses in non-selected patients; several substances had given higher response rates. When sensitising frequencies (clinical data) and exposure frequencies (volumes in consumer products) were compared for the standard series, as an indicator of risk, geraniol appeared not to be of high concern.

The DU did not support the DS, favouring classification in category 1 without a sub-category. Results of 10 mouse LLNAs showed geraniol to be a weak sensitiser, and this was supported by the Guinea pig tests. The mouse data were considered especially relevant because, as for human skin, several forms of cytochrome R450 known to oxidise geraniol to allergenic metabolites were active in mouse skin. Therefore, according to the DU, allergenic metabolites of geraniol would have been most likely produced under the conditions of the LLNA. Whilst some oxidation products or metabolites of geraniol were potent sensitisers when tested in the LLNA, these findings were not representative for exposure to geraniol itself because the tested concentrations would not have been generated in human skin. Similarly, according to the DU, the auto-oxidation of geraniol that had been found under extreme experimental conditions (> 10 weeks exposure to air) could not occur under conditions of normal storage, handling and use of geraniol-containing products.

Detailed comments provided by the Manufacturer of geraniol supported their view that data from the animal and human volunteer studies were consistent with the criteria for a category 1B classification. Four HRIPTs of mixed quality had shown no skin sensitisation reactions after repeated application of 2362, 3876 and 9690 µg geraniol/cm^2. Positive reactions had been seen in 4/221 volunteers exposed to dose levels of 5905 or 11810 µg/cm^2, but these could be attributed either to an individual being pre-sensitised or to irritant responses. Further, the tested concentrations were above the threshold for differentiating between sub-categories 1A and 1B.

Both the Manufacturer and DU regarded clinical patch test data to be unsuitable for hazard classification because the induction concentrations for all subjects were unknown. The Manufacturer accepted that the highly variable cumulative data on selected dermatitis patients indicated a high frequency of occurrence of skin sensitisation, as defined by CLP guidance (3.3% positive: 653/19800 patients). However, a meta-analysis for all the studies of unselected patients, including 2 new studies published in 2017 (see Additional Key Elements), met the criteria for low frequency. According to this analysis, the positive response rate was 0.44% (327/74381 patients tested).

The Manufacturer further commented on the DS's assessment that exposure of consumers to geraniol could be classed as low. Whilst the DS had indicated that frequent/daily exposure was anticipated amongst consumers due to widespread use and the high tonnage of geraniol, the

manufacturer suggested that the content of this substance in consumer products on the market leading to the induction of skin sensitisation had been under-estimated. The Manufacturer commented that it was not possible to know if those patients who had responded positively on patch testing with geraniol had mostly been induced by low concentrations. The reports showing the highest frequencies of positive patch test results in unselected patients were published before 2007. Although the International Fragrance Association (IFRA) had issued a limit of 1% on the content of geraniol in many consumer products in 2007, this would not have impacted on many of the products actually being used until some years later, and potentially as late as 2015.

The Manufacturer argued that the DS had not provided adequate justification for excluding from their analysis those current products and historical exposures to other products with > 1% content of geraniol.

The Manufacturer concluded that the low frequency of positive patch test results on unselected patients (0.44%) combined with clear evidence for a strong potential for high estimated exposure levels (> 1% in products) indicated that a classification in category 1B would be more appropriate than category 1A.

Analysis of further information received during the public consultation

The Manufacturer provided information on two relatively large, additional clinical studies of non-selected dermatitis patients.

In the first, patch testing was conducted in a single Danish clinic (Bennike *et al.*, 2017). Positive reactions to 1% geraniol were seen in 0.25% of patients (15/6004), tested between 2010 and 2015. The authors reported a steady to decreasing prevalence trend during this period.

In the second, clinical patch testing with 2% geraniol in Sweden produced positive responses in 0.4% of patients tested between 2009 and 2012 (8/2235), and 0.6% between 2013 and 2015 (14/2248) (Mowitz *et al.*, 2017).

The Manufacturer also provided further details (including study reports) of the various human volunteer repeated insult patch tests (HRIPTs) and human maximisation tests (HMTs) conducted with geraniol. This information is summarised in the table below.

Unless otherwise indicated, the HRIPTs involved nine 24h occluded induction applications (3 times a week for 3 weeks) followed approximately two weeks later by a 24h occluded challenge application to a virgin site. Reactions were read at patch removal and 48, 72 and 96 hours after application. The HMTs were conducted with occluded applications to the same site for five alternate-day 48–hour periods, followed 10-14 days later with a 48 hours occluded challenge application.

Generally, information on the age and ethnicity of the volunteers was not provided.

Additional information on the Human Repeat Insult Patch and Maximisation tests			
Study details	**Volunteer participants**	**Reactions**	**RAC Observations**
HRIPT 2% geraniol in 1:3 ethanol:Diethylphthalate (DEP)	110 (24 male, 86 female)	0/110	No evidence of sensitising potential.

HRIPT 5% geraniol in 1:3 ethanol:DEP	109 (20 male and 89 female)	1/109	The single positive response was not considered a case of sensitisation; subject did not respond when re-challenged 3 weeks later using occlusive and semi-occlusive patches
HRIPT 10% geraniol in 1:3 ethanol:DEP Reactions assessed at 24 and 72 h only	102 (30 male and 82 female)	3/112	None of the 3 respondents was considered to be a case of sensitisation. 1st: reacted to both geraniol and vehicle after first induction and reacted strongly at challenge to geraniol, solvent and saline control. 2nd: reacted to both geraniol and vehicle during last 2 induction applications, exhibited mild erythema during challenge; considered to be cumulative irritant response 3rd: comparable level of irritation seen at induction and challenge.
HRIPT 5% geraniol in alcohol SDA 39C Semi-occluded challenge.	40 (12 male and 28 female)	0/40	No evidence of sensitising potential. Relatively small group size limits statistical power of the study.
HRIPT 12.5% geraniol in alcohol SDA 39C Semi-occluded challenge.	41 (14 male and 27 female)	0/41	No evidence of sensitising potential. Relatively small group size limits statistical power of the study.
Modified Draize Procedure 10% "semi pure" geraniol in petrolatum 10% "semi pure" geraniol in alcohol Ten (48-72 h) occluded induction applications; 72 h occluded challenge 2 weeks later	104 73	0/104 2/73	This study reviewed data on 21 fragrance ingredients to compare the predictive potential of a Modified Draize Procedure (involving the use of high induction and challenge test concentrations) with the Maximisation test. Two volunteers responded positive to geraniol.
HMT 6% geraniol in petrolatum	24 (Japanese-American ethnicity)	0/24	Another test material (name not provided) gave a clear positive allergic result in 20 of the volunteers.
HMT *6% geraniol in petrolatum*	26 (Japanese-American ethnicity)	1/26	One volunteer responded positively to geraniol. Another test substance (name not provided) gave a clear positive allergic reaction in 7 of the volunteers.
HMT *6% geraniol (solvent not stated)*	25	0/25	No evidence of a sensitising potential.

Assessment and comparison with the classification criteria

Animal data

The sensitising potential of geraniol has been tested comprehensively in both Guinea pigs and mice. As shown in the following tables, limited reporting of the results from some of the Guinea pig studies makes it difficult to assess them against the CLP criteria. However, overall there does appear to be sufficient, reproducible evidence from both species to demonstrate that geraniol should be classified as a skin sensitiser. Where the data are sufficient to allow an assessment to be made, the potency of geraniol does not appear to be high.

Guinea pig studies		
Method (study date)	**Result**	**RAC assessment against CLP criteria**
Maximisation (1989) Induction: 0.1% (intradermal) Challenge: 10%	0/10 animals sensitised when solvent was acetone:PEG400 for occluded induction and challenge. "Sensitisation observed" in another group of 10 animals when solvent was acetone only. Response rate not specified. In preliminary studies, intradermal doses of 0.25% and 0.5% evoked an irritant response.	Not possible, as the number of animals responding with a positive result is unclear.
Maximisation (1977) Induction: 5% (intradermal) Challenge: 10%	3/6 animals sensitized 50% response rate	Classification as a sensitiser (low potency, but lacking data to exclude high potency)
Maximisation (1977) Induction: 5% (intradermal) Challenge: "sub-irritant"	"Sensitisation observed" (n=10) Response rate not specified.	Not possible; insufficient information.
Maximisation (1986) Induction: 10% (intradermal) Challenge: 10%	"Sensitisation observed" (n=10) Response rate not specified.	Not possible; insufficient information.
Buehler Induction: 25% Challenge: 2.5, 7.5 & 25%	0/20 animals sensitised	Not classified

Mouse studies		
Method (study date)	**Results**	**Assessment against CLP criteria**
LLNA (OECD TG 429) Eight tests conducted between 2001 and 2007	EC3: 22.4% - sensitising EC3: 4.4% - sensitising (test substance had been air-exposed for 4 weeks) EC3: 5.8% - sensitising	Classification, sub-category 1B (low or moderate potency)

	EC3: 11.4% - sensitising* EC3: 5.6% - sensitising EC3: 11.8% - sensitising EC3: 20.4% - sensitising EC3: 25.8% - sensitising	
Ex vivo LLNA –BrdU/Elisa (2014)	EC3: 13.1% - sensitising	Classification, sub-category 1B (low potency)

**This study was summarised twice by the DS – it seemed to them from the literature originally available that 2 different studies with identical methodology and results had been conducted.*

Human data

In a number of human volunteer studies the skin sensitisation potential of geraniol has been assessed. As summarised in the following table, these include Repeat Insult Patch tests (HRIPT), Maximisation tests and a modified Draize procedure. Although the conduct of such studies is not permitted for compliance with CLP for ethical reasons, it is possible to take account of such data as part of a weight of evidence analysis if it is available historically. The comparable findings from study to study provide some confidence in the results seen.

Human Repeat Insult Patch Tests		
Geraniol test concentration	**% Positive (No. positive/No. tested**	**Summary**
2% (2362 µg/cm^2)	0% (0/110)	Induction of sensitisation was seen in 3/7 studies (6/589 volunteers; 1%). All exposures were > 500 µg/cm^2 Various different solvents were used.
5% (plus 0.5% tocopherol) (5905 µg/cm^2)	0.9% (1/109)	
10% (11810 µg/cm^2)	2.7 % (3/112)	
5% (3876 µg/cm^2)	0 % (0/40)	
12.5% (9690 µg/cm^2)	0 % (0/41)	
10% (modified Draize procedure)	0 % (0/104)	
10% (modified Draize procedure)	2.7% (2/73)	

Human Maximisation Tests		
Geraniol test concentration	**% Positive (No. positive/No. tested**	**Summary**
6%	0 % (0/25)	Induction of senstisation was seen in 1/5 studies (1/125 volunteers; < 0.1%). All exposures were > 500 µg/cm^2
6%	0% (0/25)	
6% (4140 µg/cm^2)	0% (0/24)	
6% (4140 µg/cm^2)	3.8 % (1/26)	
6% (4140 µg/cm^2)	0% (0/25)	

According to CLP guidance, the exposure concentrations used in volunteer tests like these can contribute to an assessment of potency and the possible sub-categorisation of a sensitiser. High

potency, supporting sub-category 1A, is shown when exposures below 500 μg/cm^2 induce a positive response. Lower potency, supporting sub-category 1B, is shown when induction occurs at higher exposure levels. The small numbers of individuals who did respond in these studies were exposed to 4140-11810 μg/cm^2 geraniol, suggesting that sub-category 1B may be appropriate. However, it is not possible to know whether lower test concentrations could also have induced sensitisation in some volunteers. Thus, overall, these data do not provide unambiguous support for sub-categorisation.

Four case studies from within the EU are summarised in the CLH report. They describe how positive patch test reactions to geraniol were seen in a 54-year old female bartender with chronic hand dermatitis, a 48-year old male metalworker with recurrent hand dermatitis, 3/7 patients who were referred to a clinic with sensitivity to farnesol, and 1/3 eczema patients. The patch test concentrations ranged from 1-20%. These studies are consistent with diagnostic patch test data available from various groups of selected and non-selected dermatology clinic patients.

The many reports of diagnostic patch tests available for geraniol provide supporting information to the classification assessment and may, potentially, steer the conclusion towards sub-categorisation. The studies date from the 1960s. Such tests are conducted according to standardised guidelines and with well-defined challenge conditions. The DS cited 56 reports of patch tests conducted on selected dermatitis patients. These patients included those suspected of having contact allergy to fragrances or cosmetic products and those from certain relevant occupational groups. The CLH report also included 32 publications summarising the results of similar patch tests conducted on non-selected (consecutive) contact allergy patients and a further 4 patch test studies. Data from unselected, consecutive dermatitis patients is more standardised than testing which is undertaken on a specific patient group. Additionally, 2 recent publications reporting incidence of contact allergy to geraniol in consecutive patients were provided through the public consultation (see above).

As shown clearly in the CLH report, there is no obvious trend related to the date of the study, the positive response rates being highly variable (range: 0-30%). In total, the data presented in the CLH report show 654 cases out of 20023 patients tested, a response rate of 3.3%. The studies with the higher response rates would appear to have selected particularly well for individuals who had been exposed and sensitised to geraniol before they attended the clinics. In accordance with the CLP criteria, these data overall show a "high frequency" of cases (response rate ≥ 2.0%).

The studies with non-selected (i.e. consecutive) patients showed much less variable positive response rates, ranging from 0-4.6%. Again, there were no obvious trends relating to the date of study. It is noted that 4 of the 32 studies reported by the DS used geraniol that had been air-exposed for 10 weeks; these studies showed some of the highest response rates (0.6, 0.9, 2.3, 4.6). It is possible that this aged material was more potent as a sensitiser than geraniol itself, possibly due to oxidation, but this is circumstantial and the findings are not definitive. Overall, taking into account data provided in the CLH report and the public consultation, there has been a positive response rate of approximately 325 reported cases/74400 patients tested (approx. 0.45%). This meets the criteria for "low frequency" according to the CLP guidance (< 1%). Only 6 of the individual studies with non-selected patients met the criteria for "high frequency" (rates were 1.1, 1.2, 1.7, 2.3, 4.1 and 4.6%).

As it is not possible to establish the induction doses encountered by those patients who responded positively to geraniol, the CLP guidance describes principles for deriving an exposure index leading to an assessment of relatively high or low exposure for a substance that can be matched against patch test data to inform on potency and sub-categorisation.

Geraniol is a fragrance that is used widely in consumer products found on the EU market. It is imported in amounts of 1000-10,0000 tonnes/year and the registered categories for use for

consumers are cosmetics and a variety of household and professional cleaning products. Individuals can be exposed to geraniol from many different sources.

In 2007, IFRA established maximum recommended limits of geraniol in leave-on cosmetic products between 0.3 - 5.5%, depending on product category, between 5.0-8.6% in rinse-off cosmetic products, and of 2.5% for non-cosmetic consumer products with direct skin contact. However, it is not clear how quickly or completely products on the market came to adhere to these recommendations. In 2012, the Scientific Committee on Consumer Safety (SCCS) considered a number of surveys on the presence and content of certain fragrances in consumer products, based mostly on labelling information. Geraniol was found present in 12-49% of the products covered; the SCCS concluded that exposure to geraniol is foreseeable in daily life. Further surveys have shown geraniol to be present in deodorants, soaps, shampoos, conditioners, lotions and creams, and also cleaning agents, stain removers and air care products. A Danish database (2017) generally describes low levels of geraniol in consumer products marketed currently and in the past, although up to 23% was found in certain massage oils. A further database, a Danish register of hazardous substances in professional products, reports concentrations below 0.1% in the majority of cleaning products, but above this value in fragrance mixtures and scented oils.

In characterising the nature of the exposure of EU citizens to geraniol in order to make a comparison with the numbers of positive patch tested individuals, RAC is mindful that there is much uncertainty about the nature of the products that may have induced sensitisation, the periods during which the induction occurred, and the concentrations encountered by those individuals in which sensitisation was induced. Although according to the DS the IFRA guidelines have helped to reduce exposure, it is possible that patients may have been exposed to consumer products containing unrestricted concentrations of geraniol well into 2015 (according to comments received from industry during the public consultation).

RAC finds this general information to be relevant for the assessment of skin exposure to geraniol of sensitised patients before they became symptomatic. In accordance with the CLP guidance, RAC makes the following conclusions about the nature of the exposures encountered.

Consumer exposure to geraniol (skin)			
Exposure data	**Indicator of relatively low exposure**	**Indicator of relatively high exposure**	**Assessment by RAC**
Concentration/dose at induction	< 1.0% < 500 µg/cm^2	≥ 1.0% ≥ 500 µg/cm^2	The content of geraniol in many consumer and professional products appears to have decreased significantly in recent years; surveys suggest that current levels may generally be very low. However, it also appears that higher content levels (≥1.0%) will have prevailed during the periods when most of the contact allergy patients were induced to geraniol. *Conclusion: Some uncertainty: overall, relatively high exposure*
Repeated exposure	< once/daily	≥ once/daily	Given the wide range of consumer products shown to contain geraniol, repeated exposure every day seems very likely. *Conclusion: Relatively high exposure*
Number of exposures (irrespective of the concentration of the sensitiser)	< 100 exposures	≥ 100 exposures	Given the types of consumer and professional products shown to contain geraniol, it is highly likely that individuals will have been exposed 100s of times. *Conclusion: Relatively high exposure*

This assessment contrasts with the view of the DS, who concluded that concentration/dose levels at induction were relatively low.

In accordance with the CLP criteria, this assessment of relatively high skin exposure indicates that geraniol should not be regarded as a high potency skin sensitiser in spite of the high number of positive patch test results reported.

Conclusion

RAC concludes that geraniol should be classified as a skin sensitiser. This is justified by a considerable volume of animal and human data.

Although there are some indicators of possible high potency (most notably the very high numbers of positive patch test results in clinics, and the number of published cases), other data suggest geraniol has low or moderate potency (e.g. local lymph node assays). Human volunteer studies have also tended to indicate low to moderate potency, although the possibility of high potency cannot be excluded completely given the nature of these studies. Further, although the numbers of positive patch tests are undoubtedly high, the exposures responsible for inducing the sensitised state in these individuals also may have been relatively high – it is not entirely clear. Given this uncertainty about the potency of geraniol, RAC concludes that no sub-categorisation is warranted for this endpoint.

Overall, RAC concludes that classification as **Skin Sens. 1; H317 (may cause an allergic skin reaction)** is warranted for geraniol.

The available data are not sufficient to support the establishment of a specific concentration limit. Furthermore, the data do not suggest that geraniol has an extreme potency. Overall, an SCL is not justified.

Additional references

Bennike, Zachariae and Johansen (2017). Non-mix fragrances are top sensitizers in consecutive dermatitis patients – a cross-sectional study of the 26 EU-labelled fragrance allergens. *Contact Dermatitis*, 77, 270-279.

Mowitz, Svedman, Zimerson, Isaksson, Pontén and Bruze (2017). Simultaneous patch testing with fragrance mix I, fragrance mix II and their ingredients in southern Sweden between 2009 and 2015. *Contact Dermatitis*, 77, 280-287.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).