ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON EUGENOL; 2-METHOXY-4-(PROP-2-EN-1-YL)PHENOL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: eugenol; 2-methoxy-4-(prop-2-en-1-yl)phenol
CAS number: 97-53-0
EC number: 202-589-1
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	France	COSMED	Industry or trade association	1
Comment received				
The Consortium HE thanks the European Chemicals Agency for the opportunity to provide comments on the dossier proposing a harmonized classification and labelling for Eugenol, with the focus on the skin sensitization endpoint. We strongly disagree with the basis of the arguments and conclusion of Skin Sens. 1A (strong sensitizer) for Eugenol. Our rationale and comments are developed within this document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONSORTIUM HE- comments CLH REPORT EUGENOL.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	France	Laboratoire Puressentiel	Company-Manufacturer	2
Comment received				
We thank the European Chemicals Agency for the opportunity to provide comments on the dossier proposing a harmonized classification and labelling for Eugenol, with the focus on the skin sensitization endpoint. We strongly disagree with the basis of the arguments and conclusion of Skin Sens. 1A (strong sensitizer) for Eugenol. Our rationale and comments are				

developed within this document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Puressentiel-CONSORTIUM HE- CLH REPORT EUGENOL.docx
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	United Kingdom	<confidential>	Industry or trade association	3
Comment received				
<confidential> Consultation Response – eugenol – cas 97-53-0– August 2023 Thank you for the opportunity to give feedback on the proposals to amend the classification of eugenol under Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. <confidential> has some comments about this which we would like to set out. About <confidential>. As a respected trade association, <confidential> strives to support the development and advancement of the British fragrance industry and highlight the benefits of fragrance to health and well-being. <confidential> actively works with legislators as an advisory body and influences legislation through advocacy and policy. The Association works to protect the industry's future by setting a strict requirement for its members to comply with current legislation and industry standards that ensure consumer safety. ECHA note – An attachment was submitted with the comment above. Refer to public attachment <confidential> CLP Consultation Response eugenol – cas 97-53-0– August 2023.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2023	Switzerland	DSM-Firmenich	Company-Importer	4
Comment received				
Please find in the attached document the justification to classify Eugenol as SS1B, contrary to the current proposal of SS1A. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DSMFirmenich Comments to Public Consultation on CLH Proposal of Eugenol.pdf				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2023	Germany		MemberState	5
Comment received				
We support the dossier submitter's proposal of classifying eugenol as Skin Sens. 1A (H317) mainly based on the human patch test data showing high frequency of skin sensitisation occurrence in relation to relatively low exposure (estimated from surveys and assessments on consumer products from the Danish EPA and IFRA's standard limits on eugenol).				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2023	Switzerland	DSM-Firmenich	Company-Importer	6
Comment received				
Detailed comments are provided in the attached document and refer to the evaluation of the appropriate skin sensitisation class. The key points raised are: 1) All animal data support the classification of Eugenol as SS1B 2) The clinical patch test data on general population shows a prevalence of <0.2% which is below the threshold to consider an SS1A. 3) Data in consecutive/unselected patients overwhelmingly shows a prevalence of <1%. This is further affirmed by considering the most recent data as most relevant to the current clinical situation. A meta-analysis of all data also supports the SS1B conclusion. 4) Data from Van Oosten et al (2009) and Frosch et al (1995) both consider fully or partially groups of selected patients and this analysis should not be included in the consecutive/unselected patients section. 5) Data are reported for Vjanurug et al (2016) which are specific to Asia (Thailand) and therefore not relevant to consideration of classification in the EU. This is also the case for the An et al (2005) and (partially) Larsen et al (1996) studies which are included in the selected patients analysis. 6) Meta-analysis, considering total numbers from all reported studies in table 8 of the Proposal on consecutive/unselected patients shows an overall positive response of <1% for this group, supporting the SS1B classification. 7) The analysis of selected patients uses highly variable approaches, including several studies which use a highly targeted selection using FM prior to testing of Eugenol. The data includes studies where concentration and/or vehicle are unknown and/or date of testing is unknown. The majority of the data used is >20 years old and current relevance can be questioned. Interpretation of this data is problematic (see detailed comments below) and the weight of evidence considering the overall animal, general population and workplace data do not support an SS1A conclusion. 8) Workplace study data is limited to one study from Buckley et al (2002). The data reported are for a highly selected population – workers with contact allergy and positive to FM1 which already contains Eugenol, so reported numbers are unsurprisingly high. Overall, as reported in Buckley et al, 24046 workers in total were tested, pre-selected for dermatitis, and a total of 159 were found as patch test positive to Eugenol. This gives a positive response of 0.66% in workers with known dermatitis (low frequency). 9) Under exposure considerations an overall score of 0 is provided. This is not the case when considering worker and other consumer and non-consumer product exposures.				

10) Considering the points raised above, the overall evaluation does not support an SS1A classification and we conclude that SS1B would be more appropriate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DSMFirmenich Comments to Public Consultation on CLH Proposal of Eugenol.pdf
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	France	COSMED	Industry or trade association	7

Comment received

Key comments

a) Patch tests, general population data

Diepgen et al (2015) reported data from 3119 subjects from five different European countries from 2008 to 2011. The CLH report (Table 8) concludes that 0,2% tested positive to eugenol, showing a relatively high frequency of occurrence of skin sensitisation (Cf. Table below).

o However, the actual prevalence numbers of eugenol patch test positive responses are 6/3119 subjects, which is 0.19% and below the 0.2% threshold on general population to consider as high frequency of occurrence of skin sensitization.

o It is unclear why this prevalence of 0.19% has been rounded to 1 significant figure, whereas 2 significant figures have been used in some other reported data (although inconsistently).

b) Patch tests, unselected dermatitis patients

Frosch et al. (1995) reported prevalence of 1.2% from a study in 9 European centers of 1072 patients partly selected after being tested with Fragrance Mix. Van Osten et al. (2009) reported a prevalence of 1.3% on patients suspected of contact allergy to fragrances or cosmetics. These data have been considered with the category of unselected dermatitis patients (Table 8).

o The categorization of studies as "unselected patients" represents a bias because the CLH report recognizes that frequency of sensitization in patients selected after being tested with Fragrance Mix is higher than in unselected population. These results should therefore not be considered with the category of unselected dermatitis patients.

o In addition, data from Frosch et al. predates the publication in 1995 (patch test dates unknown) and are the oldest and probably least relevant data in this category.

o A more relevant and reliable meta-analysis of all data (excluding the 2 above-mentioned studies) shows a total of 168/24184 (0.69%) positive patch test results to eugenol in unselected dermatitis patients in data covering 2003 until 2016. This analysis supports a low/moderate frequency (<1%) of sensitization in unselected dermatitis patients (Cf. Table above).

c) Patch tests, selected dermatitis patients

There are further concerns with the data presented in this section:

o The relevance of data in patients allergic to Ketoprofen is questionable. In patients with photoallergic contact dermatitis to ketoprofen, it may be difficult to interpret whether the allergy is specific to eugenol.
o The data includes many studies where concentration and/or vehicle are unknown and/or date of testing is unknown.

d) Workplace studies
Workplace study data is limited to one study from Buckley et al, (2002). 24,046 workers in total were tested who were referred to the Institute due to dermatitis during a 15 year period. Of these 1813 had a positive patch test to FM1 which contains Eugenol, and a total of 159 were found as patch test positive to Eugenol. This gives a positive response of 0.66% (159/24,046) in workers who reported with known dermatitis.

o However, the CLH report does not consider the total of 24,046 patients included in this study to calculate the prevalence of allergy to eugenol in workers with known dermatitis. Only the 1112 patients tested with the single constituents of the Fragrance Mix were considered, which introduces a bias in the interpretation of the data.
o The response in selected workers with known exposure or dermatitis is therefore 0,66% supporting a low/moderate frequency (<1%) in this highly selected population (Cf. Table above).

e) Human exposure
Exposure data is reported as "low" weighting and assigned a score of 0 in the CLH report. This is based on expected exposure <1% in consumer products only and does not take into account potential for induction of sensitization coming from all sources.

o However, workplace exposure would be expected to have the potential to be "high" and the maximum concentrations in the IFRA standard limit for eugenol can be ≥1% in several consumer products such as fine fragrances, leave-on products applied to the face/hair/body or household care products with mostly hand contact (Cf. Table 10 of the CLH report).
o In addition, data use of oils, for example clove oil (which contains high levels of eugenol) as an antimicrobial and as a pain reliever for conditions such as toothache and muscle pain, would lead to the potential for "high" exposure.
o A compromise for the exposure concentration/dose between a low exposure (score 0) and high exposure (score 2) would be more relevant, as the concentration/dose of Eugenol cannot be reliably determined. A score of 1 would therefore be more appropriate (Cf. Table below).
Additional information

o Eugenol is considered as a weak sensitizer based on robust collective consideration of human, animal, in chemico, in vitro and in silico data (RIFM, 2022) with a weight-of-evidence-based Non-Expected Sensitisation Induction Level of 5900 µg/cm2 (NESIL) (RIFM, 2016) .

o The sub-categorisation of category 1B (moderate sensitizer) for eugenol is supported by new approach methods (NAMs), such as the in vitro tests GARDpotency (OECD 442E) and SENS-IS1, to predict the hazard and potency of potential skin sensitizers as part of the weight of evidence.

o Evaluation of human data must be carried out with caution because human data are not normally generated in controlled experiments with volunteers for the purpose of hazard classification but are usually derived from case-control or other, less defined studies.
As an example, a recent retrospective analysis (Dittmar et al., 2018) over 20 years shows

that 30 to 40% of weakly positive patch test reactions were not reproduced on retesting (Dittmar et al, 2019; Bennike et al, 2019) , .

o Some of the human skin test results may be false positives, occurring due to the irritation potential of eugenol applied for several days under occlusion (Lefevre et al, 2021) .

Conclusion on sub-categorisation for skin sensitisation

o The animal data convincingly place Eugenol as Skin Sens. 1B.

o Human data present some issues on interpretation but the largest and most recent studies confirm a low frequency of reactions.

o Exposure data indicate repeated and frequent exposures where concentration and dose from all sources of exposition cannot be reliably determined.
The rationale for a Skin Sens. 1B for Eugenol is done according to table 3.4 in the guidance on the application of the CLP criteria and summarized in the table below:

To conclude, based on overall weight of evidence and the data available a Skin Sens. 1B classification would be the most appropriate.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONSORTIUM HE- comments CLH REPORT EUGENOL.pdf

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Germany	Information Network of Departments of Dermatology (IVDK), Institute at the University Medical Center Göttingen, Germany	Academic institution	8

Comment received

Ladies and Gentlemen,

in the CLH report, Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2: eugenol (CAS 97-53-0), Version 2 of 03.05.2023, classifying eugenol as skin sensitizer category 1A is proposed.

A closer look at the cited human studies on skin sensitization (section 10.7.3.2 of the CLH report) reveals that on several occasions, data have not been interpreted adequately. In these cases, the study setting has not been considered in sufficient detail. On some other occasion, the lacking accuracy of the data, resulting from small sample size, was not adequately considered.

When reviewing the cited studies, I came to the conclusion that the dossier submitter's CLH

proposal, i.e. classifying eugenol as a skin sensitizer category 1A is not appropriate.

In my opinion, there is no scientifically justified basis for marking eugenol as skin sensitizer 1A. Labelling with 1B would correct.

This conclusion and its rationale are explained in the attached comment.

I kindly ask you to consider my thoughts when deciding on the categorization of eugenol as skin sensitizer.

Kind regards,
Prof. Dr. med. <confidential>, IVDK

ECHA note – An attachment was submitted with the comment above. Refer to public attachment <confidential> IVDK comment on CLH report Eugenol 05-03-2023.pdf

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Belgium	The International Fragrance Association (IFRA)	Industry or trade association	9

Comment received

IFRA agrees with the fact that based on available human and animal data Eugenol warrants the classification as skin sensitiser but disagrees with the classification proposal of category 1A.
The CLH report itself states that the animal data rather support 1B than 1A (page 26 and 27 of the CLH report). This is also confirmed on the bottom of page 20 of the dossier, stating that 'Diagnostic patch test data are generally seen as the primary source of clinical information on the occurrence of skin sensitization and are considered to represent the most important data in relation to this dossier.'
Next to exposure considerations, the key argument to support a classification of 1A by the Dossier Submitter (DS) is therefore the human data cited in the CLH dossier. Our comments consequently focus on these data, which need to be carefully looked at, as many of them from our perspective, are not suitable for deriving the classification, as described in the attachment.
If epidemiological and clinical data are suitable to add to the weight of evidence regarding the classification as skin sensitiser, they should:
- provide information on the frequency of sensitization at present, and not cover a period beyond the past 5 years. Historical data beyond the 5-year interval are of no relevance.
- provide data on unselected patients or the general population. Studies in selected patients (such as breakdown tests in FM I positives) must be excluded.
Thus, a) frequency of sensitization and b) level / frequency of exposure are considered in more detail in our comments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA Position on proposed classification Skin Sensitization 1A for Eugenol Final August 16 2023.pdf

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	United Kingdom	<confidential>	Industry or trade association	10
Comment received				
<confidential> does not support the Skin sensitisation 1a classification that has been proposed by Denmark. <confidential> supports the work that has been done by the Lead Registrant. <confidential> also supports the comments submitted by IFRA Global. Conclusion on classification From our perspective the data presented in the CLH dossier do not support a classification of eugenol as skin sensitiser 1A, while a classification 1B seems adequate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment <confidential> CLP Consultation Response eugenol – cas 97-53-0– August 2023.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2023	Belgium	Pranarom International S.A.	Company-Manufacturer	11
Comment received				
Given the elements presented in the attached document, we conclude, based on overall weight of evidence and the data available, that a Skin Sens. 1B classification would be the most appropriate. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Pranarom SA - comments CLH REPORT EUGENOL.docx				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	France	Laboratoire Puressentiel	Company-Manufacturer	12
Comment received				
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o In addition, data from Frosch et al. predates the publication in 1995 (patch test dates unknown) and are the oldest and probably least relevant data in this category.
o A more relevant and reliable meta-analysis of all data (excluding the 2 above-mentioned studies) shows a total of 168/24184 (0.69%) positive patch test results to eugenol in unselected dermatitis patients in data covering 2003 until 2016. This analysis supports a low/moderate frequency (<1%) of sensitization in unselected dermatitis patients (Cf. Table above).

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Exposure data is reported as "low" weighting and assigned a score of 0 in the CLH report. This is based on expected exposure <1% in consumer products only and does not take into account potential for induction of sensitization coming from all sources.

o However, workplace exposure would be expected to have the potential to be "high" and the maximum concentrations in the IFRA standard limit for eugenol can be ≥1% in several consumer products such as fine fragrances, leave-on products applied to the face/hair/body or household care products with mostly hand contact (Cf. Table 10 of the CLH report).
o In addition, data use of oils, for example clove oil (which contains high levels of eugenol) as an antimicrobial and as a pain reliever for conditions such as toothache and muscle pain, would lead to the potential for "high" exposure.
o A compromise for the exposure concentration/dose between a low exposure (score 0) and high exposure (score 2) would be more relevant, as the concentration/dose of Eugenol cannot be reliably determined. A score of 1 would therefore be more appropriate (Cf. Table below).

Additional information
o Eugenol is considered as a weak sensitizer based on robust collective consideration of human, animal, in chemico, in vitro and in silico data (RIFM, 2022) with a weight-of-evidence-based Non-Expected Sensitisation Induction Level of 5900 µg/cm2 (NESIL) (RIFM, 2016) .

o The sub-categorisation of category 1B (moderate sensitizer) for eugenol is supported by new approach methods (NAMs), such as the in vitro tests GARDpotency (OECD 442E) and SENS-IS1, to predict the hazard and potency of potential skin sensitizers as part of the weight of evidence.

o Evaluation of human data must be carried out with caution because human data are not normally generated in controlled experiments with volunteers for the purpose of hazard classification but are usually derived from case-control or other, less defined studies.
As an example, a recent retrospective analysis (Dittmar et al., 2018) over 20 years shows that 30 to 40% of weakly positive patch test reactions were not reproduced on retesting (Dittmar et al, 2019; Bennike et al, 2019) , .

o Some of the human skin test results may be false positives, occurring due to the irritation potential of eugenol applied for several days under occlusion (Lefevre et al, 2021) .

Conclusion on sub-categorisation for skin sensitisation

o The animal data convincingly place Eugenol as Skin Sens. 1B.
o Human data present some issues on interpretation but the largest and most recent studies confirm a low frequency of reactions. A high frequency of cases is reported in highly targeted dermatitis patients who have tested positive using Fragrance Mix (FM) which contains Eugenol or previous testing using fragrance. It is therefore expected that positive patch test reactions.
o Exposure data indicate repeated and frequent exposures where concentration and dose

from all sources of exposition cannot be reliably determined.
The rationale for a Skin Sens. 1B for Eugenol is done according to table 3.4 in the guidance on the application of the CLP criteria and summarized in the table below:

Animal data: Animal data (LLNA and GPMT) are consistent with SS1B classification (EC3 >2%; GPMT Moderate potency) --> conclusion Skin Sens. 1B

Human data: Patch tests, general population data (0.19% = low frequency)), Patch tests, unselected dermatitis patients (0,69% = low frequency), Patch test, selected dermatitis patients (difficult to clearly interpret = NA), Workplace studies (0,66% = low frequency), Number of published cases (>100 cases = high frequency))

Exposure data: Concentration/dose (Consumer product exposure expected to be low. Worker/other exposure can be high --> score 1), Repeated exposure (≥ once daily --> score 2), Number of exposures (irrespective of concentration of sensitiser) (≥ 100 exposures --> score 2)
Human Exposure classification: Relatively high exposure, Relatively low frequency of occurrence of skin sensitisation --> conclusion: Skin Sens. 1B

To conclude, based on overall weight of evidence and the data available a Skin Sens. 1B classification would be the most appropriate.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Puressentiel-CONSORTIUM HE- CLH REPORT EUGENOL.docx

Dossier Submitter's Response

RAC's response

PUBLIC ATTACHMENTS
1. <confidential> IVDK comment on CLH report Eugenol 05-03-2023.pdf [Please refer to comment No. 8]
2. IFRA Position on proposed classification Skin Sensitization 1A for Eugenol Final August 16 2023.pdf [Please refer to comment No. 9]
3. <confidential> CLP Consultation Response eugenol – cas 97-53-0– August 2023.pdf [Please refer to comment No. 3, 10]
4. Puressentiel-CONSORTIUM HE- CLH REPORT EUGENOL.docx [Please refer to comment No. 2, 12]
5. CONSORTIUM HE- comments CLH REPORT EUGENOL.pdf [Please refer to comment No. 1, 7]
6. DSMFirmenich Comments to Public Consultation on CLH Proposal of Eugenol.pdf [Please refer to comment No. 4, 6]

CONFIDENTIAL ATTACHMENTS
1. Pranarom SA - comments CLH REPORT EUGENOL.docx [Please refer to comment No. 11]