COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 04.09.2023

Substance name: thymol; 5-methyl-2-(propan-2-yl)phenol
CAS number: 89-83-8
EC number: 201-944-8
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	1
Comment received				
No comment				

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2023	United Kingdom	IFRA UK	Industry or trade association	2
Comment received				
IFRA UK CLP Consultation Response – thymol – CAS 89-83-8 - September 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. IFRA UK has some comments about this which we would like to set out. About IFRA UK. As a respected trade association, IFRA UK strives to support the development and advancement of the British fragrance industry and highlight the benefits of fragrance to health and well-being. IFRA UK 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. Conclusion on classification IFRA UK does not support the Skin Corr. 1, H314, Skin Sens. 1, H317 or STOT SE 3, H336 classification. Thank you for taking note of our feedback, we hope it is helpful and will aid constructive dialogue on the classification of thymol.				

Date	Country	Organisation	Type of Organisation	Comment

				number
01.09.2023	Germany	Lanxess Deutschland GmbH	Company-Manufacturer	3
Comment received				
Comments were prepared and can be found in the attachment. Please refer to the comments in the attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment_Thymol_LXS_Symrise.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	4
Comment received				
We agree with all of the dossier submitter's proposed classifications. However, several aspects in the CLH report require further elaborations. 1. We are of the opinion that the evaluation of STOT RE requires additional consideration and attention. In particular, the 30-d repeated dose mouse neurotoxicity study by Baldissera et al. (2018) is missing as evidence for the STOT RE evaluation, and this study demonstrated significant effects in the central nervous system (CNS) from repeated exposure to thymol that would not be covered by the proposed STOT SE 3 (H336) classification and might warrant STOT RE classification. 2. It would be helpful if the dossier submitter could comment on the basis of proposing 500 mg/kg bw as the ATE for acute oral toxicity. This is not clearly described in the report. 3. Since Thymol is a crystalline solid the particle size distribution might be relevant. However, we noticed that no data on granulometry was provided. Is there a reason why this analysis was not carried out?				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	5
Comment received				
We agree that no classification on carcinogenicity can be made on thymol due to data lacking.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	6
Comment received				
Was no reviewed.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	7
Comment received				
We agree with the dossier submitter's proposal of not classifying thymol for germ cell mutagenicity. There was no indication of gene mutation in vitro. Even though there were some positive in vitro results of chromosomal aberrations in human lymphocytes, two in vivo bone marrow chromosomal aberration studies (one in mouse and one in rat), both				

considered acceptable for evaluation, showed negative results with proof of bone marrow exposure. Therefore, thymol is of no genotoxic concern given the available data.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	8
Comment received				
Was no reviewed.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	9
Comment received				
We agree with the dossier submitter's assessment that the existing dataset on reproductive toxicity of thymol (primarily one GLP-compliant 43-day combined repeated dose and reproductive/developmental toxicity screening test in rats) is insufficient to propose any classification for reproductive toxicity. As mentioned by the dossier submitter, there are, however, some concerns regarding developmental effects in rats (e.g., decreased pup weight and weight gain without clear indication of maternal toxicity) that might warrant further investigation.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	10
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	11
Comment received				
We support the dossier submitter's proposal of keeping the existing acute (oral) Tox., category 4 (H302) classification. However, more justification is required on the proposed ATE value of 500 mg/kg bw for this classification. First of all, the genotoxicity studies by Shibuya et al. (1996; B.6.4.2.1-01) in mice and by <confidential> (2009; B.6.4.2.1-03) in rats could be considered as evidence for the acute oral toxicity evaluation. Even though no definite LD50 was determined in these studies, they provide some indication of doses, at which mortality was observed, and the data reporting of these studies is better than the studies presented in Table 18. Nearly all of the acute toxicity animal data are supporting information with major data reporting deficits, and the reported LD50 values (except for cats in one study) from this dataset exceeded 500 mg/kg bw. While we agree that it is not appropriate to select the lowest LD50 (250 mg/kg bw reported in cats) as the ATE, it is not clear to us the justification of selecting 500 mg/kg bw as the proposed ATE.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	12

Comment received
Was no reviewed.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	13
Comment received				
We agree with the dossier submitter's proposal of classifying thymol as Eye Dam. 1 based on the skin corrosive properties (i. e. Skin Corr. 1) of thymol. As the dossier submitter already mentioned in Section 2.6.2.5.2 of the CLP report, "hazard statement H318 is already included in the hazard statement H314 for skin corrosion" and H318 is not included in the End Points for labelling purposes to avoid duplication.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	14
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	15
Comment received				
Skin sensitization We agree with the dossier submitter's proposal of classifying thymol as Skin Sensitiser, Cat. 1 (H317). The existing human and animal data collectively demonstrated that thymol is a weak skin sensitiser, but the reporting is not sufficient for subcategorisation of this hazard class. The available human data presented in the CLH report showed at least 44 subjects with positive reactions to thymol. Looking at the concentrations in the patch tests, at 1 % thymol, people who already have dermatitis showed positive reaction (Berova, 1990; Fisher, 1989), but at 5 % thymol, the positive rate rose significantly to 13 % (Djerassi and Berowa, 1966). Similarly, weak sensitisation effects were observed with 20 % thymol in animals (via guinea pig maximisation test/GPMT) but not at 10 % (using 4 different skin sensitisation tests). In addition, there is a published case study not mentioned here in the report (Lorenzi et al. (1995), Allergic contact dermatitis due to thymol. https://doi.org/10.1111/j.1600-0536.1995.tb02092.x) that also demonstrated skin sensitising reaction from thymol. Skin corrosion/irritation: We agree with the dossier submitter's proposal of classifying thymol as Skin corrosion, Cat. 1 (H314) without subcategorisation within this category due to insufficient data.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	16
Comment received				
Was no reviewed.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	Germany	Information Network of Departments of Dermatology (IVDK)	Academic institution	17

Comment received

Ladies and Gentlemen,

in the Combined Draft Assessment Report to (EC) No 1107/2009 (renewal) and the CLH report, Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation): Thymol, 5-methyl-2-(propan-2-yl) phenol, Volume 1 of February 2023, it is proposed to categorize thymol as skin sensitizer category 1.

The Information Network of Departments of Dermatology (IVDK) holds the world's largest contact allergy database including data of about 900 patients patch tested with thymol. In single studies published as well as temporarily in the IVDK, thymol was partly patch tested in problematic test concentrations and vehicles. A thorough analysis reveals that thymol elicits allergic reactions in single cases only if patch tested in an adequate preparation.

Based on our and published data, which we present and discuss in the attached document, we do not support the above-mentioned proposal.

Category 1 should be used if data are not sufficient for sub-categorization, which is not the case for thymol. We present agglomerate data pointing out that thymol is a weak sensitizer. We kindly ask to take our data into consideration and plead for marking thymol as skin sensitizer sub-category 1B.

Kind regards,
<confidential>

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment on classification proposal for Thymol IVDK.pdf

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2023	Germany	Lanxess Deutschland GmbH	Company-Manufacturer	18

Comment received

Comments were prepared and can be found in the attachment. Please refer to the comments in the attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment_Thymol_LXS_Symrise.pdf

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2023	United Kingdom	Health and Safety Executive	National Authority	19

Comment received

Thymol

Hazard category: Skin sensitisation

It is debateable whether the criteria for classification as a skin sensitiser are met.

According to table 3.4.2 of Annex I of CLP "Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test (see specific criteria in paragraph 3.4.2.2.4.1)."

The animal data come from two published papers which summarise the results of various guinea pig studies; the original study reports have not been seen/reviewed by the DS, and the animal data are considered to be supportive only. Results from studies (various methods) testing concentrations of up to 10% thymol were all negative. A 'weak positive' was reported in a single study which tested a concentration of 20% thymol (the CLH report states: "Weak sensitization effects with 20% thymol were observed (mean response was 0.4 using 20% thymol)"). Individual scores for the animals are not available. We question whether an overall mean score of less than 1 can really be considered a "positive result".

The human data are difficult to interpret, as no information is available on exposure (the types of products the substance is found in, the typical concentrations, frequency of use, etc). Furthermore, only a small number of positive cases have been reported overall – it is debateable whether this constitutes a 'substantial number of persons'.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	20
Comment received				
We agree with the dossier submitter's proposal of classifying thymol as STOT SE 3 (H336) for the transient narcotic effects observed in several animal studies. However, studies with i.p. injections and i.v. perfusion of the substance should not be considered for the STOT SE assessment because they are not common routes of exposure in humans (in the CLP Guidance, Annex I: 3.8.1.5. "Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation."). It should be pointed out that a number of studies from the acute oral toxicity dataset showed narcotic effects at doses near LD50, and thymol is already classified as acute oral Tox., Cat. 4 (H302). As the data reporting is also limited, the studies with narcotic effects near LD50 would not be sufficient to support STOT SE 3 (H336) classification. In our opinion, the basis of classifying thymol as STOT SE 3 (H336) could be provided by the two bone marrow genotoxicity tests (one in mice and one in rats) and the repeated dose toxicity study in rats, which showed transient narcotic effects at doses below mortality. We support also the additional labelling of EUH071 "corrosive to the respiratory tract" as specified in CLP Guidance, Section 3.2.4.2, Annex II: 1.2.6 (EUH071 is applied for "substances and mixtures in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled"). Thymol is corrosive to the skin, and no acute inhalation toxicity data were available for evaluation.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	21

Comment received
Was no reviewed.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	22
Comment received				
The 30-d repeated dose mouse neurotoxicity study by Baldissera et al. (2018) should be included as evidence for the STOT RE evaluation. This study demonstrated multiple effects in the CNS, which might warrant STOT RE classification. We acknowledge and support the STOT SE 3 (H336) classification based on the transient narcotic effects, e.g., observed in female rats after 1 day of exposure to 200 mg/kg bw/d thymol (<confidential>, 1996). On the other hand, the Baldissera et al. (2018) study demonstrated that Swiss male mice exposed to 20 or 40 mg/kg bw/d thymol for 30 days exhibited toxicologically relevant and potentially significant morphological changes (increased blood-brain barrier permeability) and functional disturbance (memory loss as indicated by decreased latency time to the inhibitory avoidance task compared to control). In addition, biochemical effects in the CNS, such as increased acetylcholinesterase activity and reactive oxygen species as well as decreased Na+, K+-ATPase activity, were reported at the same doses. The effect dose of 20 mg/kg bw/d from this 30-day mouse study would, in theory, be equivalent to 6.7 mg/kg bw/d for a 90-day exposure (using the Haber's rule for rats), which would fall under STOT RE 1. As the CNS effects between the single exposure and repeated exposure studies are not directly comparable (e.g., memory loss was not assessed in the acute exposure studies), we do not find it suitable to conclude that the STOT SE 3 (H336) covers the neurological effects observed from the repeated exposure study of Baldissera et al. (2018). Unfortunately, the tabular results of the behavioural and biochemical tests of the Baldissera et al. (2018) study are not presented in the CLH report to determine the severity of these effects. Therefore, no conclusion can be made at the moment regarding the STOT RE classification, but this hazard class deserves further elaboration and discussion.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	23
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	24
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany		MemberState	25
Comment received				

We agree that thymol is readily and rapidly degradable. However, two different acceptable OECD 301F studies are given in Vol. 1 in Table 70 (Summary of relevant information on rapid degradability), but only one of them is described in Vol. 3 B.8.2.2. According to 2.8.2.1.1 in Vol.1, one study is a study from REACH Registration dossier. However, in our opinion all information given in Volume 1 should also be described in Volume 3.

Table 79 and 80 list multiple studies on the same organism group as key studies. According to the guidance on the application of CLP criteria, normally only the study showing the highest toxicity for an organism group should be chosen as key study. We suggest to change the information in the tables accordingly. However, tables 81 and 82 only list the actual key studies, so our remark has no influence on the overall classification.
We would appreciate if the reference columns in tables 79 and 80 could also state the data point number or another clear identifier. Especially when the author names are anonymized, this would allow easier cross-check with e.g. CA Vol. 3 B9.
It is not clear why the endpoint EC50 = 4.46 mg/L from the study by MITI (2005) was used as relevant endpoint for acute toxicity to Daphnia magna in table 81. In table 79, the study by Grade & Wydra (2008) (EC50 = 4.9 mg/L) is listed as key study. The endpoint EC50 = 4.9 mg/L is also given in the list of endpoints as the relevant endpoint for Daphnia magna. Additionally, the study by MITI (2005) does not seem to be further described in Vol. 3 B9. We ask the RMS to check the data. If necessary, please adjust tables 79 and 81 accordingly, or give further explanation why the study by MITI (2005) was used. Since the endpoints from both studies are in a comparable concentration range, this does not influence the overall classification.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	26
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	27
Comment received				
Was no reviewed.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	28
Comment received				
Was no reviewed.				

PUBLIC ATTACHMENTS
1. Comment_Thymol_LXS_Symrise.pdf [Please refer to comment No. 3, 18]
2. Comment on classification proposal for Thymol IVDK.pdf [Please refer to comment No. 17]