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 28.05.2024

Substance name: 2-(2*H*-benzotriazol-2-yl)-*p*-cresol
CAS number: 2440-22-4
EC number: 219-470-5
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2024	Belgium	Cefic - ELiSANA	Industry or trade association	1
Comment received				
The members of the European Light Stabilisers and Antioxidants Association (ELiSANA), a Sector Group of Cefic, are pleased to provide scientific comments on the CLH proposals for 2-(2H benzotriazol-2-yl)-p-cresol (UV-P) on the hazard classes skin sensitisation and hazardous to the aquatic environment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2024 05 15_Comments on UV-P_final_rev.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2024	Germany	BASF SE	Company-Manufacturer	2
Comment received				
BASF SE as lead registrant support the comments submitted by Elisana. In support of these comments, BASF SE as lead registrant would like to submit the following confidential attachments: - Study report for OECD 406 (Guinea pig maximization test, 1992) - Study report for Hill Top Research Institute (1960) - Study report for OECD 201 (Alga, Growth Inhibition Test with Pseudokirchneriella subcapitata, 72 hours, 2018) - Study report for OECD 211 (Daphnia magna Reproduction Test, 2011) BASF SE would like to ask the dossier submitter, rapporteur and the members of RAC to take the comments brought forward by Elisana as well as the additional information submitted in the attachments into account prior to taking a decision on the classification and labelling of 2-(2H-benzotriazol-2-yl)-p-cresol. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2440-22-4_submission data_2024-05-02.pdf				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
30.04.2024	France		MemberState	3
Comment received				
FR agrees with the proposed classification as Skin Sens. 1 (without sub-categorisation) and a GCL of 1% on the basis of: - a guinea pig maximisation test that showed a positivity rate of 80% and 90% at 24h and 48h resp. at 5% intradermal induction but with some positive reactions in negative controls (10% and 20% at 24h and 48h resp.); - positive reactions from human data but with no information on the exposure.				

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2024	Belgium	Cefic - ELiSANA	Industry or trade association	4
Comment received				
Conclusion: • The Dossier Submitter (DS) proposes a harmonized classification for Skin Sensitization as Category 1 based on the data available since "2-(2H-benzotriazol-2-yl)-p-cresol acts as a skin sensitiser as shown by human data. There are no OECD TG-conform and reliable animal data available to conclude on the potency of 2-(2H-benzotriazol-2-yl)-p-cresol and therefore, available data do not allow for sub-categorisation." • The registrants disagree with this conclusion and will provide evidence on the possibility of sub-categorization for skin sensitization in this document. • According to Regulation (EC) 1272/2008 (CLP), Annex I, section 3.4.2.2.1.1, "Skin sensitizers shall be classified in Category 1 where data are not sufficient for sub-classification." Annex I, section 3.4.2.2.1.2 specifies that "Where data are sufficient a refined evaluation […] allows the allocation of skin sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other skin sensitisers." • The registrants have classified the substance under evaluation as Skin Sens 1B based on a weight-of-evidence approach, laying down the criteria specified in CLP and ECHA's Guidance on the Application of the CLP criteria, taking into consideration all available and reliable data. In the following sections, the weight-of-evidence approach will be presented in detail. • Overall, both animal data and human data available support the criteria in CLP laid down for Skin Sens 1B. Thus, sub-classification as requested under CLP can be performed and should be applied to result in classification of 2-(2H-benzotriazol-2-yl)-p-cresol as Skin Sensitiser, Category 1B. For these reasons, ELiSANA believes that the proposed classification of Skin Sens. 1; H317 is not warranted. Please refer to the attachment for details. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2024 05 15_Comments on UV-P_final_rev.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2024	Belgium		MemberState	5
Comment received				
Based on the available data, BE CA agrees with BAuA to classify 2-(2H-benzotriazol-2-yl)-p-cresol for skin sensitization in category 1 (Skin Sens. 1, H317) without sub-categorisation.				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
30.04.2024	France		MemberState	6

Comment received

1/ In section 11.1.1, rapid biodegradability of 2-(2H-benzotriazol-2-yl)-p-cresol was evaluated using results from two standardized tests according to OECD guideline 301 B (from the registration dossier) and OECD Guideline 301 C (from the Japanese J-CHECK database). Both tests presented in the CLH dossier show that the substance does not meet the criterion of ready degradability. Based on these results and according to the CLP guidance, 2-(2H-benzotriazol-2-yl)-p-cresol is considered to be not rapidly degradable. These two OECD tests were performed by exposing an inoculum to one or more concentrations of the tested substance. The results presented in the CLH dossier were obtained using high concentrations of 2-(2H-benzotriazol-2-yl)-p-cresol, which exceeded the water solubility value of the substance. No information is available on inoculum adaptation and/or the occurrence of inhibition of microorganisms under these high concentrations. In some cases, when using high concentrations, a toxic effect could be observed on the inoculum, resulting in a low degradation of the substance. This information is of great importance in a CLH dossier (especially when using results from MITI (I) test "OECD TG 301C") in order to ensure proper classification of the substance. However, taking into account (in a WOE approach) the results from the QSAR estimations (using BIOWIN (v4.11) as well as two studies from literature (Lai et al., 2014 a, b), the absence of rapid degradation of 2-(2H-benzotriazol-2-yl)-p-cresol is supported. Hence, FR agrees that the substance is not rapidly degradable.

2/ In section 11.3.2, two standardized studies (OECD 305-I and OECD 305C) from the registration dossier evaluating the bioaccumulation potential of the substance are described by the DS. In the first and most reliable study (OECD 305-I), a waterborne exposure of juvenile rainbow trout was conducted at a nominal concentration of 0.5 µg/L of 2-(2H-benzotriazol-2-yl)-p-cresol. In accordance with the OECD 305 guideline, for highly hydrophobic substances the dietary test is recommended. However, in this study, the aqueous exposure was conducted under flow-through conditions, and the test concentration seems to be controlled all along the uptake phase (measured concentration: 0.477 ± 0.036 µg/L), which justify the waterborne exposure instead of dietary exposure. The uptake phase duration was 35 days and according to the registrant, "The data illustrate that steady state was quickly reached during the uptake period, after the sampling on day 2" (information provided on ECHA disseminated website). These two informations are contradictory, because according to OECD 305 guideline, the uptake phase should be run for 28 days unless it can be demonstrated that steady-state has been reached earlier (paragraph 38 of the guideline). It is not understandable why the registrant performed a 35-days uptake phase while it was reported that a steady state was observed on day 2. No information was given in the CLH report, nor on the ECHA website on the concentrations measured in fish during the uptake period. However, based on the evaluation provided by the DS that noted a rapid decrease in the measured concentrations between day 21 and day 35, with a variation of more than 20% between the last three points of analysis, FR agrees to conclude that the steady-state has not been reached in this study. Hence, the estimation of bioconcentration of 2-(2H-benzotriazol-2-yl)-p-cresol in juvenile rainbow trout should be performed using the kinetic approach (BCFk), instead of using BCFss calculation. FR agrees with the new calculated value of BCF using estimated k2 value (BCF > 500 L/kg).
The first study seems to be more compliant than the second one, despite the shortcomings noted by the DS. Hence FR agrees with the DS to use results of the OECD 305-I study to calculate BCF value of 2-(2H-benzotriazol-2-yl)-p-cresol. The BCF value was > 500. Nevertheless, based on this value, we suggest that the conclusion should be "… has a potential for bioaccumulation in the aquatic environment" instead of "High potential for bioaccumulation in the aquatic environment" to meet the scheme classification proposed by

the CLP guidance (Annex III, section III.5), and CLP regulation text: "A BCF in fish of ≥ 500 is indicative of the potential to bioconcentrate for classification purposes." (section 4.1.2.8.1 of CLP regulation Annex I).

3/ In section 11.4, acute aquatic hazard was assessed by the DS based on 4 standardized studies (Table 15). Two of them were conducted on fish (Oncorhynchus mykiss and Danio rerio, using OECD 203 test), and the two other studies were performed on Daphnia magna (crustacean, OECD 202) and Raphidocelis subcatpitata (algae, OECD 201).
OECD 203 test on Oncorhynchus mykiss was the key study used to address the acute toxicity of 2-(2H-benzotriazol-2-yl)-p-cresol on fish (section 11.4.1). No information was given in the CLH dossier regarding the presence of a control solvent group, nor on the concentration of DMF which was used to solubilize the substance. No mortality was observed during the exposure period, and the measured concentrations were below the solubility value of 2-(2H-benzotriazol-2-yl)-p-cresol (i.e. 0.173 mg/L). However, it seems that the deviation from the nominal concentrations was above 20%. Hence, the 96h LC50 should be calculated based on the measured concentration (96 h-LC50 > 0.075 mg/L). Indeed, according to paragraph 31 of the OECD 203 guideline "It is recommended that results should be calculated using the measured concentrations of the test chemical. If the deviation from the nominal concentrations is smaller than 20%, results may also be based on the nominal concentrations". The same recommendation is reported in paragraph 177 of the Guidance Document No. 23, on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, 2019).
When addressing toxic effects of 2-(2H-benzotriazol-2-yl)-p-cresol on invertebrates, only one study (CIBA-GEIGY Ltd., 1988c) was reported in the CLH dossier. The study was conducted according to an old test guideline that follows the OECD 202 with some important shortcomings that should invalidate the use of the corresponding results. Indeed, in addition to the reduced exposure time (24h instead of 48h recommended to assess the acute toxic effect on invertebrates), the concentrations used in this study were 300 to 5000-fold higher than the substance's water solubility value, which explains the deposit observed in all test concentrations. Based on the CLH dossier, it appears that no measurement were made during exposure, even though chemical analysis is very important for the validity of the test, particularly in the case of poorly soluble substances. Based on these elements, we think that this study should have a Klimisch 3 assessment instead of Klimisch 2 as reported in the CLH dossier.
Based on the available data on fish and algae studies, FR agrees with the DS that no acute aquatic classification is required for 2-(2H-benzotriazol-2-yl)-p-cresol.

4/ In section 11.5, the long-term aquatic hazard of 2-(2H-benzotriazol-2-yl)-p-cresol was assessed based on two standardized studies available in the CLH dossier. Both studies were conducted respectively on Daphnia magna (crustacean, OECD TG 211) and Raphidocelis subcapitata (algae, OECD TG 201). Based on Daphnia magna results, the lowest NOEC reported was 0.0083 mg/L (21-d NOEC; OECD TG 211). Based on this value, the DS proposed to classify the substance as Aquatic Chronic 1 with a multiplication factor of 10, and FR agrees with this conclusion.

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2024	Belgium	Cefic - ELiSANA	Industry or trade association	7
Comment received				
Conclusion: • As reliable, relevant, and valid experimental data on the degradability of the substance are available, the estimated data (calculated with BIOWIN v4.11) provided by the Dossier				

Submitter should not be used for the assessment and should be removed from the CLH report.
• Experimental as well as QSAR bioconcentration data demonstrate that the BCF is < 2000 L/kg and thus not bioaccumulative.
• The BCF for UV-P alone is likely to be < 500 L/kg as indicated by comparison of the three bioconcentration studies with different analytical methods: determination of total radioactivity (no distinction between parent, metabolites, and assimilated carbon) vs. substance-specific chemical analysis.
• Metabolism in organism is supported by studies with oral uptake by rats and humans, which show a rapid uptake with a subsequent rapid metabolization in the liver and rapid excretion via the kidney.
• For the assessment of long-term aquatic hazard, the critical value is the 21-d NOEC derived in the Daphnia magna reproduction test according to OECD TG 211 (BASF SE, 2020). In contrast to the value considered by the Dossier Submitter (21-d NOEC = 0.0083 mg/L, measured), the Registrant demonstrated that UV-P remained stable in the exposure system and was not lost due to degradation, volatilization or significant adsorption to the test vessel.
• The Registrant is therefore of the opinion that it is justified to consider the nominal effect value of the study: 21-d NOEC = 0.013 mg/L.
• Based on the 21-d NOEC of 0.013 mg/L, the substance is to be classified as Aquatic Chronic 2. An M-factor of 1 is applicable.
For these reasons, ELiSANA believes that the proposed classification of Aquatic Chronic 1; H410, Aquatic Chronic1, M-factor=10 is not warranted.
Please refer to the attachment for details.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2024 05 15_Comments on UV-P_final_rev.pdf

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2024	Belgium		MemberState	8

Comment received

Acute aquatic toxicity:
We agree with no classification for acute aquatic toxicity based on the lowest EC50 for algae (Raphidocelis subcatpitata): 72h EC50 > 0.0822 mg/L (meas). It is however noted that there is some uncertainty, as it is unknown whether effects would occur at concentrations between 0.0822 mg/L and the WS of 0.173 mg/L.

Chronic aquatic toxicity
Based on the lowest chronic aquatic toxicity for invertebrates (Daphnia magna with 21d NOEC = 0.0083 mg/L) and the fact that the substance is considered as not rapidly degradable it is justified to classify the substance as Aquatic chronic 1, H410 with M-factor of 10 (0.001 mg/L <NOEC ≤ 0.01 mg/L).
As no data are available for all trophic levels (no data on fish) also the surrogate approach should be used. Based on the fish 96h LC50 > 0.17 mg/L and thus no chronic toxicity seen up to the water solubility (0.173 mg/L) 'no classification' is warranted.
In such case classification should be according to the most stringent outcome and therefore we support classification as Aquatic chronic 1, H410 with M-factor of 10.

PUBLIC ATTACHMENTS
1. 2024 05 15_Comments on UV-P_final_rev.pdf [Please refer to comment No. 1, 4, 7]

CONFIDENTIAL ATTACHMENTS

1. 2440-22-4_submission data_2024-05-02.pdf [Please refer to comment No. 2]