Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

resorcinol; 1,3-benzenediol

EC Number: 203-585-2
CAS Number: 108-46-3

CLH-O-0000007036-78-01/F

Adopted

16 September 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON RESORCINOL; 1,3-BENZENEDIOL

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: resorcinol; 1,3-benzenediol
EC number: 203-585-2
CAS number: 108-46-3
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.02.2021	Sweden	ChemSec	International NGO	1
Comment received				
We strongly support the proposed classification which should be implemented without delay. However in our opinion one additional property is missing in this suggested classification, Resorcinols well known endocrine disrupting properties. It should be complemented in this CLH proposal.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Comment noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2021	France		MemberState	2
Comment received				
Thank you for the detailed assessment of data on resorcinol. Our comments on the different hazard classes in discussion are detailed below.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	United Kingdom	Resorcinol Task Force (representing resorcinol manufacturers)	Industry or trade association	3
Comment received				
N/A ECHA note – An attachment was submitted with the comment above. Refer to public attachment Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2021	France		MemberState	4
Comment received				
Based on available data, ANSES support the conclusion that a classification Acute Tox 4 is warranted by oral route and no classification by dermal route and inhalation.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	United Kingdom	Resorcinol Task Force (representing resorcinol manufacturers)	Industry or trade association	5
Comment received				
No comments submitted ECHA note – An attachment was submitted with the comment above. Refer to public attachment Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	Germany		MemberState	6
Comment received				
The German CA generally agrees with the classification of resorcinol as Acute Toxic substance. Even if the available oral route studies have deficiencies (regarding purity and vehicle specification), the clear case reports suggest an acute toxic effect. Therefore, The German CA supports the classifica-tion as Acute Tox. Category 4, H302 according to the data of the animal study. An ATE value of 500 mg/kg bw is proposed in the report with reference to table 3.1.2 of Annex I to the CLP Regulation. This is the procedure when only acute toxicity range values are available. How-ever, an LD50 of 489 mg/kg bw was determined in female rats, which is recommended for classifica-tion by the DS. It should be explained why the ATE is not based on the LD50, which would imply an ATE of 489 mg/kg bw (see notes to table 3.1.1 of Annex I). Furthermore, the dermal and inhalation route studies demonstrate that classification is not possible or necessary (according to CLP criteria), as has been adequately argued.				
Dossier Submitter's Response				
Thank you for your support. Regarding an ATE value, we agree that the ATE of 486 mg/kg bw could be used. The ATE value of 500 mg/kg bw was proposed following a prudence principle, because there was some deficiencies in the study, but we agree that the ATE of 489 mg/kg bw could be more correct.				
RAC's response				
Given the reporting gaps in the study that derived the LD50 of 489 mg/kg bw and the fact that this value is close to the default value of 500 mg/kg bw, RAC supports the dossier submitter's proposal.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2021	France		MemberState	7
Comment received				
ANSES supports the proposed classification Skin Sens 1A. The skin sensitising potential of resorcinol is evidenced by human data and experimental data, the negative results in some experiments being observed in studies with limitations (deficiencies in controls and/or lower doses tested). The sub-categorisation 1A is supported by a reliable LLNA study and is in accordance with CLP guidance. Documentation of the expected level of exposure through hairdressing mixtures (and possible changes over time) would help the interpretation of available human data.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	United Kingdom	Resorcinol Task Force (representing resorcinol manufacturers)	Industry or trade association	8

Comment received
RTF's comments relate to pages 21 to 30 in the CLH Report and are contained in the attached document "Resorcinol Task Force Response to CLH Report on Resorcinol - Final". ECHA note – An attachment was submitted with the comment above. Refer to public attachment Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf
Dossier Submitter's Response
Thank you for your comments. Regarding animal data: We consider that it is justified that the study author has used the departure point 0.5 % in calculating the EC3 value resulting in the final EC3=1.4. You have stated: *"It appears that the study author did not use the correct departure point in calculating the EC3 value resulting in the discrepancy of the final EC3 that is presented in the study 1.4 verse 3.67."* You have not argued your interpretation more closely and the reason why you have excluded the concentration of 0.5 %. Regarding human data: *"The findings undoubtably indicate that although there is a small incidence of irritation/skin sensitisation which is not necessarily associated with resorcinol itself but as part of use as in hair dye application (or other formulations) in which resorcinol is present at a very low percentage (up to 1.25% in oxidative dyes for hair and eyelashes) and in which other known and documented sensitisers are present such as e.g. Hydroxyethyl-3,4-Methylenedioxyaniline HCl and m-Aminophenol. As a result, relying on data in which resorcinol is present in a formulation or mixture in which other sensitisers may be present or in which a population is routinely exposed to other sensitisers is erroneous as it provides a misperception that any positive effects are solely related to resorcinol."* The results rely on data from patch-tests where resorcinol has elicited positive skin reactions in a number of patch tests carried out on patients with dermatitis (Table 14. in CLH report). There are also a few case reports describing dermal sensitisation caused by resorcinol where Castellani paint, a skin cream containing 2% resorcinol and hair dye (positive patch test to resorcinol: ++ (day 2), +++ (day 4)) were used. Hence, we are not relying on data regarding formulations or mixtures. *"It appears that most studies were conducted on patients that had abraded skin in some manner, i.e., dermatitis, eczema, paint formulation, ulcers, psoriasis, inflammatory acne. These data cannot therefore be used to evaluate the sensitisation potential of resorcinol."*

In the patch tests allergens are affixed to intact skin on the patient's back. Another area that can be used is the upper arms and upper thighs if a patient had acne etc. on his back.

"It should be noted that dose/concentration levels that are exhibiting sensitisation are typically greater than 2-5%, which is the greater than the concentration of resorcinol present in consumer and medicinal products."

Many strong sensitisers cause sensitisation on much lower concentrations than 2-5 %. Sensitisers which are classified to category 1A have to be taken into account when a concentration is 0,1 % or more. The lower concentration that causes the sensitisation the stronger sensitiser a substance is. Concentrations tested in the patch tests vary from 0,5 % to 5 %. In the patch tests with 0.5 % resorcinol positive reactions vary from 0.2 % to 1.9 % and with 5 % resorcinol from 0.5 % to 7.9 %. It is also worth to mention that in the study Barbaud et al, 1996 one patient had a positive reaction (++) to 0.01 % resorcinol.

"The most relevant and telling findings were noted in Abbate et al, 1989, in which skin test were negative in all subjects at a motorcycle tyre plant."

There are many deficiencies in the reporting and for example the concentration of resorcinol used in the skin test is not specified so it is not justified to state that these study findings are the most relevant. Although the skin test results were negative in all subjects it was possible to draw the following conclusions: All the subjects affected developed dermatitis coincidentally with the increase of resorcinol in the compound and in all cases it affected the skin that had the most contact with resorcinol.

"We disagree with the total number of positive patch test and positive cases identified in the Summary of Human Data as 117 patch-test positive cases for a variety of reasons. For instance, they are not necessarily associated with resorcinol itself but with hair dye application or other formulations in which other known sensitisers are present."

Firstly, we have not included any studies where hair dye application or formulations have been investigated. All studies are patch-tests to resorcinol and there are 117 positive cases. Secondly, case studies have been observed from formulations, but patch test performed in the case studies are done to resorcinol.
In the studies, where strength of symptoms is specified, positive reactions were mostly extreme positive reaction (+++) or strong positive reactions (++).

The workplace study of 42 workers at the motorcycle tyre (Abbate et al, 1989) with negative skin test to resorcinol was not included in the total number of workplace studies which would increase the number of total workers evaluated thus substantially altering the median positive % rate"

All studies in the table are patch tests. The epidemiological study (Abbate et al, 1989) and case studies are excluded from the table. However, if we add the study Abbate et al, 1989 to the results median 0.6% would be 0.5 % instead. It would still be under < 1 % and indicate low or moderate frequency. We would like to still highlight that there are many deficiencies in the reporting of the study and the concentration of resorcinol used in the skin test is not specified.

To conclude, the overall weight of evidence from human and animal data indicates that

resorcinol is a skin sensitiser. Resorcinol shows a high potency in mice based on the results of the key LLNA and can therefore be presumed to have the potential to produce significant sensitisation in humans. The results meet the criteria for subcategorization and Category 1A is justified.
RAC's response
RAC evaluated the submitted comments and used a weight of evidence approach to derive a classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	Germany		MemberState	9
Comment received				
The human patch test data show that resorcinol has at least a skin sensitising potential. The well-conducted LLNA key study emphasises a SI > 3 and an EC3 of 1.4 %. This study underlines the classi-fication as skin sensitisation in Category 1A, H317. However, it must be taken into account that the first systemic toxicity effects were observed in the 5 % group in the key study. As these effects are above EC3, the classification can be accepted.				
Dossier Submitter's Response				
Thank you for your comments and support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2021	France		MemberState	10
Comment received				
ANSES supports the proposed classification STOT SE 1 (nervous system). Neurotoxic clinical signs are reported in acute toxicity studies. They are present below 300 mg/kg and at non-lethal doses in several studies (by oral route in Anonymous 2004b, by subcutaneous route in Merker 1982). They are also supported by neurotoxic clinical signs observed after repeated exposure in gavage studies in rats and mice. The time of onset of these clinical signs shall be further discussed to attribute it to acute effects but this conclusion is supported by the fact that they began shortly after chemical administration and lasted from 30 minutes to an hour, which is consistent with rapid metabolisation of resorcinol. They became more pronounced at the end of each 5-day dosing period. In the 90-day study by gavage (Anonymous, 2004a), an increase in landing footsplay was observed in females from 80 mg/kg/d in a test performed after week 10. This effect is statistically significant and provides an indication of a sensorimotor dysfunction that shall not be considered as fortuitous. In contrast, no clinical signs of neurotoxicity are reported in a two-generation study performed through dietary exposure (Welsch 2008). It is however likely that in contrast to dietary exposure, gavage exposure result in peak exposure and acute toxicity is observed only by gavage.				

Finally, for comprehensiveness, other data are available for resorcinol and some of them focus on the investigation of thyroid function so that general toxicity is not reported. However, tremors are observed during the hour after subcutaneous injection of 50 mg/kg resorcinol in Cheymol (1951).
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	United Kingdom	Resorcinol Task Force (representing resorcinol manufacturers)	Industry or trade association	11
Comment received				
No comments submitted. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	Germany		MemberState	12
Comment received				
The German CA follows the reasoning and supports the classification as STOT SE 1, H370 (nervous system). Neurotoxicity was detected in humans and the available animal studies show clear effects on the nervous system and the single-dose exposures of < 300 mg/kg bw also suggest this classifi-cation. As also conclusively shown, other organ effects (such as respiratory tract irritation) cannot be classified unequivocally on the available data and should be taken into account if there is an indi-cation of such effects in human.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2021	Belgium		MemberState	13
Comment received				
BE CA supports the proposal to add an M-factor of 1 for aquatic acute toxicity.				

Dossier Submitter's Response
Thank you for your support
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	The Netherlands		MemberState	14

Comment received
Based on the available data, we agree with the proposed classification Aquatic Acute 1 M=1 (H400). Long-term toxicity aquatic hazard – fish (Oncorhynchus mykiss) The dossier submitter classifies the 60d study with Oncorhynchus mykiss as key study and a reliability score of 2. We question the reliability score of this study as information is missing for us to conclude the same score. Initial test concentrations are missing and analytical monitoring was not performed. As the substance is rapidly biodegradable, it is likely that concentrations changed over time during the test. Note that this study will not affect the classification of resorcinol as Daphnia magna are the most sensitive species for chronic toxicity and will determine the classification of the substance (see below). Long-term toxicity aquatic hazard – aquatic invertebrates (Daphnia magna) The lowest NOEC is observed for daphnia magna: 21d NOEC ≥ 0.172 mg/L. Although none of the test concentrations in this test showed an effect (including 0.172 mg/L), and the NOEC could have been higher when higher concentrations were tested, the NOEC implies that the substance potentially classifies as Aquatic Chronic 3 (H412) according to criteria set in table 4.1.0 (b) (ii). The substance can be considered rapidly degradable and the NOEC is currently lower than the threshold value for category Aquatic Chronic 3 (Chronic NOEC or ECx (for crustacea) ≤1 mg/l). The classification is supported by the fact that the 48h EC50 for Daphnia magna (same species) is 1.0 mg/L and chronic toxicity occurs generally at lower concentrations. Based on the above and the fact that the substance is rapidly degradable, a classification with Aquatic Chronic 3, H412 seems more appropriate.
Dossier Submitter's Response
Thank you for your comments. The reliability scores reflect the Klimisch scores in the registration dossier. We agree that this study has shortcomings due to lack of analytical monitoring of the test substance. However, the test media was renewed three times a week. No information about initial test concentrations are available in the study report, but it can be estimated from the study report that the lowest test concentrations used for the resorcinol were probably at least at the range of 1-10 mg/L and no adverse effects were observed at those concentrations. Based on this study the eMSCA consider that it can be conluded that the fish are not the most sensitive species for chronic toxicity. We agree that the lowest available NOEC value of ≥0.172 mg/L could imply that the

substance potentially classifies as Aquatic Chronic 3 (H412) according to criteria set in table 4.1.0 (b) (ii). However, no information is available whether the aquatic chronic toxicity is in the range of 0.172 – 1.0 mg/L. As resorcinol is rapidly degradable and non-bioaccumulative the eMSCA considers that the long-term aquatic hazard classification is not warranted for resorcinol based on the available information.
RAC's response
According to available information, in the long-term test no adverse effects were observed up to the highest mean measured concentration of 0.172 mg/L. RAC agreed with the DS response that the long-term aquatic hazard classification was not warranted in the range of 0.172 – 1.0 mg/L, being resorcinol rapidly degradable and non-bioaccumulative, and considered that no information is available for the aquatic chronic toxicity in the range of 0.172 – 1.0 mg/L.

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2021	France		MemberState	15
Comment received				
Based on available data, ANSES support the conclusion that a classification of Aquatic Acute 1, with an M factor of 1 is warranted and that no chronic data indicated the need to classify the substance for long term aquatic hazards. ANSES supports the proposed classification for environmental hazards.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2021	United Kingdom	Health and Safety Executive	National Authority	16
Comment received				
resorcinol; 1,3-benzenediol (EC 203-585-2, CAS 108-46-3) Aquatic Chronic classification The DS considers resorcinol is rapidly degradable based on a MITI study cited as Kitano, 1978 which is considered equivalent to an OECD TG 301 study. The DS notes that limited data is available for the study but considers the study to be Klimisch 2 meaning it is valid and reliable for classification. As the study appears to be conducted by the Japanese National Institute of Technology and Evaluation (NITE), is additional study information (e.g. to consider study test design and validity as described in OECD TG 301) available via the NITE database or potentially via historical chemical assessments under the WHO CIPAD or OECD HPV programmes? This would be useful to support the Klimisch 2 score. Overall, we recognise that the wider fate data in Table 22 of the CLH report appear to support the substance as rapidly degradable for hazard classification. Noting this, it might be useful to consider if QSAR predictions are available to support this weight of evidence position?				
Dossier Submitter's Response				
Thank you for your comments.				

The reliability scores reflect the Klimisch scores in the registration dossier. Only short summary is available for the key study Kitano (1978) and it is provided by the registrant and no further information has been found in the existing databases in addition to presented in the classification proposal. We agree that this study has shortcomings due to limited documentation but we consider that together with the supporting information in the classification proposal it can be concluded that resorcinol is rapidly degradable.

QSAR predictions according to Biowin V4.10 are done by DS.

Biowin1 (Linear Model Prediction) : Biodegrades Fast
Biowin2 (Non-Linear Model Prediction): Biodegrades Fast
Biowin3 (Ultimate Biodegradation Timeframe): Weeks
Biowin4 (Primary Biodegradation Timeframe): Days
Biowin5 (MITI Linear Model Prediction) : Readily Degradable
Biowin6 (MITI Non-Linear Model Prediction): Readily Degradable
Biowin7 (Anaerobic Model Prediction): Biodegrades Fast
Ready Biodegradability Prediction: YES

Biowin1 (Linear Biodeg Probability) | | 0.9267
Biowin2 (Non-Linear Biodeg Probability) | | 0.9631
Biowin3 (Survey Model - Ultimate Biodeg) | | 3.0686
Biowin4 (Survey Model - Primary Biodeg) | | 3.7683
Biowin5 (MITI Linear Biodeg Probability) | | 0.5459
Biowin6 (MITI Non-Linear Biodeg Probability)| | 0.6909
Biowin7 (Anaerobic Linear Biodeg Prob) | | 0.6158

Biowin V4.10 model predictions support the conclusion that resorcinol is rapidly degradable.

RAC's response

RAC agrees with the comment. DS reported Klimish score 2 for the key study Kitano, 1978 although limited information is available in particular regarding the test design and validity. However, RAC agrees that BOD5/COD value of 1.74, other biodegradation studies results, considered as inherent biodegradability tests and QSAR predictions support the conclusion that resorcinol is rapidly degradable.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2021	United Kingdom	Resorcinol Task Force (representing resorcinol manufacturers)	Industry or trade association	17

Comment received

No comments submitted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Noted.

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PUBLIC ATTACHMENTS
1. Resorcinol Task Force Response to CLH Report on Resorcinol - Final.pdf [Please refer to comment No. 3, 5, 8 (the comment relates to skin sensitisation), 11, 17]