Committee for Risk Assessment

RAC

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

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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: **resorcinol; 1,3-benzenediol**

EC Number: **203-585-2**

CAS Number: **108-46-3**

The proposal was submitted by **Finland** and received by RAC on **6 November 2020.**

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

PROCESS FOR ADOPTION OF THE OPINION

Finland 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 **7 December 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5 February 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Ralf Stahlmann**

Co-Rapporteur, appointed by RAC: **Pietro Paris**

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 **16 September 2021** by **consensus**.

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

	Index No	Chemical name	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	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Aquatic Acute 1	H302 H315 H319 H400	GHS07 GHS09 Wng	H302 H315 H319 H400			
Dossier submitters proposal	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	**Modify** Acute Tox. 4 **Add** STOT SE 1 Skin Sens. 1A **Retain** Aquatic Acute 1	**Modify** H302 **Add** H370 (nervous system) H317 **Retain** H400	**Retain** GHS07 GHS09 Wng	**Modify** H302 **Add** H370 (nervous system) H317 **Retain** H400		**Remove** * **Add** Oral: ATE = 500 mg/kg bw **Add** M = 1	
RAC opinion	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	**Modify** Acute Tox. 4 **Add** STOT SE 1 Skin Sens. 1B **Retain** Aquatic Acute 1	**Modify** H302 **Add** H370 (nervous system) H317 **Retain** H400	**Modify** GHS08 Dgr **Retain** GHS07 GHS09	**Modify** H302 **Add** H370 (nervous system) H317 **Retain** H400		**Remove** * **Add** Oral: ATE = 500 mg/kg bw **Add** M = 1	
Resulting Annex VI entry if agreed by COM	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	Acute Tox. 4 STOT SE 1 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1B Aquatic Acute 1	H302 H370 (nervous system) H315 H319 H317 H400	GHS07 GHS08 GHS09 Dgr	H302 H370 (nervous system) H315 H319 H317 H400		Oral: ATE = 500 mg/kg bw M = 1	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Resorcinol is a chemical used in various industrial and consumer products, such as rubber products, wood adhesives, flame retardants, dyes, anti-acne ointments, and hair colours.

Toxicokinetic studies suggest rapid absorption of orally administered resorcinol. The main metabolite is a monoglucuronide conjugate. After oral or subcutaneous administration in rats, the most of the substance was excreted via urine within 24 hours. Dermal absorption in human skin is low (between 0.32 and 5 % of the applied dose) and depends on concentration, vehicle and metabolic activity. Higher absorption rates (up to 74 %) were observed in frozen, thus not metabolically active, human skin explants using low doses (< 100 µg/cm^2) with phosphate buffered saline (PBS) as vehicle.

The substance had a harmonised classification under the Dangerous Substances Directive (DSD) which was transposed to a harmonised classification under the CLP Regulation. A minimum classification was applied to the acute oral toxicity endpoint and for aquatic toxicity no M-factor at that time was introduced. Thus, the current Annex VI entry for resorcinol is Acute Tox 4* H302, Skin Irrit. 2 H315, Eye Irrit. 2 H319, and Aquatic Acute 1 H400. The dossier submitter (DS) proposed to remove the minimum classification for acute oral toxicity, and to add Skin Sens. 1A H317 and STOT SE 1 H370 (nervous system) classifications. Acute Aquatic 1 classification is proposed to be retained, and an M-factor of 1 added. Other hazard classes were not assessed in the dossier and were not open for discussion at the consultation phase.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral

The DS summarised two human case reports and four oral toxicity studies in rats.

In both human cases, patients received resorcinol in lieu of glucose during a glucose challenge test. One adult female, who came to treatment with signs of intoxication approximately two hours after ingestion of 75 g of resorcinol and subsequently died of cardiopulmonary arrest six hours later. The other adult female, who was pregnant and was treated already half an hour after ingestion of 50 g of resorcinol, survived but lost her child 24 hours after an emergency caesarean section. Clinical signs in both cases included unconsciousness, respiratory failure, convulsions, tonic-clonic seizures, and severe metabolic acidosis. In the woman who died, methaemoglobinaemia and hyperaemia in all organs were observed at autopsy.

The available animal data comprised one OECD TG 401 (1981) acute oral toxicity study which was comparable to studies using the fixed dose method similar to OECD TG 420 (1992) performed according to good laboratory practice (GLP) in 26 laboratories, one OECD TG 420 (2001) GLP compliant study, and one non-GLP acute oral toxicity study performed according to the U.S. Federal Hazardous Substances Labeling Act (FHSLA, 1961) in 1962.

In the oldest study, the LD_{50} was between 795 mg/kg bw and 1580 mg/kg bw. For the OECD TG 401 study, which the DS deemed the key study, the available publication states that mean LD_{50} values are 533 mg/kg bw for males and 489 mg/kg bw for females. The publication does not

specify vehicle, purity, dose levels or number of animals used per dose level. In the fixed dose studies used for comparison, a total of 370 rats were dosed by gavage with 5 to 2000 mg/kg bw (5 rats/sex/dose, vehicle and purity of the test substance not specified). No LD_{50} values were stated in the publication but according to the DS results suggest the same dose range as for the OECD TG 401 study.

The newest study (2004) used one Sprague-Dawley rat each in a preliminary study with a dosing of 200, 500, and 2000 mg/kg bw of resorcinol (98.8 %) in purified water. The test substance was administered by gavage. Animals of the two higher dose groups died within 20 or 15 minutes after dosing, respectively. At 200 mg/kg bw piloerection and dyspnea were observed. The main study used four animals and the lowest dose from the preliminary study. No mortalities occurred and no LD_{50} could be derived.

Based on the mean LD_{50} of 489 mg/kg bw for female rats in the OECD TG 401 study, the DS proposed to remove the minimum classification leading to an **Acute Tox. 4, H302** classification. For ATE value, the category 4 converted acute toxicity point estimate of 500 mg/kg bw was proposed.

Dermal

The DS summarized two old (1962 and 1970) non-GLP acute dermal toxicity studies in rabbits. In both studies, LD_{50} values were above the cut-off for category 4 (2000 mg/kg bw).

The DS also listed several human case reports that all described cases of adverse reactions to repeated use of resorcinol containing ointments on broken skin resulting in goitre (hyperplasia of the thyroid). No clear conclusion on acute dermal toxicity of resorcinol in humans could be drawn from these reports.

No classification for acute dermal toxicity was proposed by the DS.

Inhalation

There is only one old (1976) non-guideline, non-GLP acute inhalation toxicity study in female Harlan-Wistar rats available. Resorcinol of unspecified purity was dissolved in distilled water and administered as aerosol in different concentrations. In some concentrations the solution turned milky and precipitation was noted. The achieved concentrations were therefore not clear. No LC_{50} could be determined in this study after an 1-hour- or 8-hour exposure up to a nominal concentration of 1732 ppm (7.8 mg/L). Clinical signs were not reported.

The DS concluded that no classification for acute inhalation toxicity was possible due to inconclusive data.

Comments received during consultation

Two member state competent authorities (MSCA) commented, both supported the proposed acute toxicity classification. However, one MSCA requested clarification why the proposed ATE for oral toxicity was not based on the LD_{50} for female rats (489 mg/kg bw). The DS responded that this value could be used but that they proposed the value of 500 mg/kg bw due to deficiencies in the study used to derive the LD_{50}.

Assessment and comparison with the classification criteria

Oral

Acute oral toxicity was assessed in several studies. The most recent test guideline and GLP-compliant study failed to establish an LD_{50} due to a low dose (200 mg/kg bw) in the main study.

In the preliminary dose range finding study, animals died at a dose of 500 or 2000 mg/kg bw resorcinol. At 200 mg/kg bw piloerection and dyspnea were observed within 2 hours after treatment. 200 mg/kg bw dose was also chosen for the main study and none of the four treated animals died. Clinical signs comprised hypoactivity, piloerection, dyspnea and tremors, which all resolved by day 2 after treatment. No conclusions can be drawn from this study regarding acute toxicity classification.

In the oldest reported study from 1962, resorcinol of unspecified purity (reported as flaked grade and industrial grade) was administered via gavage to ten (low dose) or five male albino rats per dose at doses of 398, 795, 1580, and 3160 mg/kg bw. All animals died in the two highest dose groups, 3 and 2 hours after exposure, respectively. At 795 mg/kg bw one animal died 3 hours after exposure. At necropsy, all animals that died showed hyperaemia and distention of the stomach and intestines. The LD_{50} was between 795 mg/kg bw and 1580 mg/kg bw and therefore within the ATE boundaries for category 4 (300 to 2000 mg/kg bw).

In the key study, as noted by the DS, as performed according to OECD TG 401 (1981), neither dose levels, vehicle or purity of the test substance were specified. The LD_{50} values were between 425 and 723 mg/kg bw for males (mean 533 mg/kg bw) and between 397 and 650 mg/kg bw for females (mean 489 mg/kg bw). These results support assignment to category 4. For comparison, 26 laboratories performed an acute toxicity study according to the fixed dose method. No details on the test substance and number of animals that died at each dose level were given, and no LD_{50} values were reported. According to the DS, the results support assignment to category 4.

Two human case reports were also summarised. In both cases, women received resorcinol by accident. Upon review of the publications, RAC estimated the doses. The dose of 769 mg/kg bw was not lethal. However, the patient's baby died within 24 hours after emergency caesarean section. The dose of 833 mg/kg bw proved to be lethal in the other case. Both doses are in the range of observed lethal doses in the animal studies.

In conclusion, RAC supports the DS proposal to remove the minimum classification and to classify resorcinol as **Acute Tox. 4, H302**. As for **ATE**, RAC considers the converted acute toxicity point estimate of **500 mg/kg** bw appropriate given the reporting gaps in the study that derived an LD_{50} of 489 mg/kg bw for female rats.

Dermal

The LD_{50} values in the two available non-GLP, non-guideline studies were 3360 mg/kg bw for the flaked grade resorcinol, 2830 mg/kg bw for industrial grade resorcinol, and 3830 mg/kg bw for resorcinol without grade specification. Although the determination of the LD_{50} of 3360 mg/kg bw is not clear to RAC because 2 out of 4 animals died at 3980 mg/kg bw in this study, all of the LD_{50} values are above the cut-off for classification.

The human case reports summarised by the DS all describe symptoms observed after repeated application of resorcinol containing ointment. They are therefore not suitable to draw conclusions on acute dermal toxicity in humans. On the contrary, these reports could have been used in an assessment on STOT RE, but this endpoint was not evaluated in the dossier.

RAC concurs with the DS that **no classification** for acute dermal toxicity is warranted.

Inhalation

Since no reliable study on toxicity via inhalation is available (deficiencies in reporting and realisation and no LC_{50} established), RAC concurs with the DS that **no classification** is possible due to inconclusive data.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Animal Data

The DS summarised clinical signs observed in the acute toxicity studies (four oral, two dermal, and one inhalation studies) and in a non-guideline, non-GLP toxicokinetic study with exposure via subcutaneous injection in male rats. Furthermore, they provided data from several repeated dose toxicity studies in rats and mice within the U.S. National Toxicology Program (NTP 1992), and from one GLP-compliant OECD TG 408 study in rats (Anon. 2004a).

Clear signs of neurotoxicity (dyspnea, hypoactivity, ataxia, tremors, and convulsions) were seen in rats after single exposure to resorcinol at non-lethal doses 200 mg/kg bw and above. Tremors and convulsions were also observed in rabbits after a single dermal exposure but at doses associated with lethality. In rats, at doses of 140 mg/kg bw and above via subcutaneous injection, slight tremors progressing to tonic-clonic convulsions occurred within ten minutes of dosing. Although this route of exposure is less relevant, these results underpin the neurotoxic properties of resorcinol. Clinical signs were not specified in the acute inhalation toxicity study available.

In repeated dose toxicity studies in rats and mice, neurotoxic effects (tremors, tachypnea, prostration, ataxia, and intermittent convulsive movements) were observed after bolus doses 100 mg/kg bw and above. At these doses no treatment-related lethality occurred. The effects were observed shortly after dosing and subsided within one hour.

Human Data

Human data included the two case reports already described in the acute toxicity section, and WHO reviewed case reports of patients repeatedly using ointments and peeling agents with resorcinol concentrations of up to 50 %. Symptoms in humans comprised green-coloured urine, sore throat, burning sensation, tachycardia, hypotension, shortness of breath, respiratory failure, pulmonary oedema, dyspnea, shivering and tremors, dizziness, drowsiness, vertigo, confusion, disorientation, amnesia, unconsciousness, coma, tonic-clonic seizures, convulsions, and hypothermia.

Laboratory examinations showed increase in liver enzyme activity, severe metabolic acidosis, oliguria, haemoglobinuria, methaemoglobinaemia, leucocytosis, high bilirubin levels, haemolytic anaemia, cyanosis and hypothyroidism.

Some of these intoxications were fatal.

Respiratory tract irritation and narcotic effects

Although resorcinol has a harmonised classification as skin and eye irritant, no signs of respiratory tract irritation were observed in the acute inhalation toxicity study and no human data are available that would show respiratory tract irritation in humans. A throat spray test in guinea pigs and rats (Flickinger 1976) showed transient irritation in the throats of the animals, but this was not considered sufficient for classification.

The DS concluded that the observed neurotoxic effects do not fulfil criteria for narcotic effects.

Conclusion on classification

Neurotoxicity was observed in several animal studies at doses relevant for classification in category 1 (< 300 mg/kg). Human data affirm neurotoxic effects of the substance.

The DS proposed classification as **STOT SE 1, H370 (nervous system)**.

Since the quality of inhalation toxicity study is poor, neurotoxic effects cannot be ruled out after inhalation exposure. Therefore, no specification of the route of exposure was proposed.

Comments received during consultation

Two MSCAs commented on this endpoint. Both supported the proposed classification.

Assessment and comparison with the classification criteria

Animal data

The DS summarised several studies in rats, mice, rabbits, and guinea pigs with oral, inhalation, dermal, and subcutaneous routes of exposure. Where reported, clinical signs after single exposure (or occurring in repeated dose toxicity studies but shortly after dosing and resolving within hours) at non-lethal doses relevant for classification were the following:

- piloerection and dyspnea in a preliminary study by gavage in rats at 200 mg/kg bw (Anon 2004b),
- hypoactivity, dyspnea, and tremors in rats at 200 mg/kg bw in the main OECD TG 420 study resolving after 2 days (Anon 2004b),
- slight tremors progressing to moderate to marked tonic clonic convulsions in rats after subcutaneous injection occurring within 10 minutes and resolving within 1 to 1.5 hours after dosing in a toxicokinetic study,
- hyperexcitability and tachypnea at oral doses from 55 mg/kg bw in female rats and at doses from 225 mg/kg bw in male rats appearing within 30 minutes and resolving within 2 hours after dosing in a 17-d range finding study (NTP 1991, 1992),
- ataxia, prostration, salivation, and tremors at oral doses of 100 mg/kg bw in female rats and at 112 mg/kg bw in male rats in a 104-week study (NTP),
- prostration and tremors at oral doses of 300 mg/kg bw in female mice and at 150 mg/kg bw in male mice in a 17-d range finding study (NTP),
- ataxia, recumbency, and tremors in mice at oral doses from 112 mg/kg bw in a 104-week study (NTP),
- for ptosis, posture, respiratory effects, diarrhoea and diuresis, lethargy, ataxia, abnormal gait, tremors, convulsions, prostrate coma, salivation, lacrimation and exophthalmus in rats after oral exposure in the validation study for the fixed dose method (similar to OECD TG 420) performed in 26 laboratories no dose levels were reported,
- irritation of the throat was observed in rats and guinea pigs in a throat spray test with 1 % resorcinol in water with three daily sprayings over two weeks without histopathological correspondence.

A panel reviewed the central nervous system symptoms reported in the NTP studies and concluded they were acute responses occurring shortly after dosing and resolving within two hours, in a time frame corresponding with the rapid clearance of the test substance.

Human Data

Human data are already described in detail in the acute oral toxicity section. Overall symptoms observed in humans after accidental ingestion of resorcinol match clinical signs seen in the animal studies. No data on respiratory tract irritation in humans are available.

Conclusion on classification

Neurotoxic effects in laboratory animals were consistently seen at doses below the cut-off 300 mg/kg bw for category 1 in oral toxicity studies in rats and mice.

Such effects were also reported in studies with dermal exposure but at doses also inducing mortality. Clinical signs were not specified in the acute inhalation toxicity study report. RAC concurs with the DS that it cannot be excluded with certainty that exposure to resorcinol via these routes will not lead to neurotoxic effects. Therefore, RAC concurs not to specify the route of exposure in the classification.

Clinical signs in animals and symptoms in humans that did not lead to death were transient in nature, but they included tonic clonic convulsions, tremors, and severe respiratory symptoms which go beyond effects considered for a STOT SE 3 - narcotic effects classification.

In conclusion, RAC concurs with the DS that data from experimental animals and humans warrant classification of resorcinol as **STOT SE 1, H370 (nervous system)** without specification of the route of exposure.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Animal Data

The DS presented data from one OECD TG 429 and GLP-compliant Local Lymph Node Assay (LLNA), data from three LLNAs compiled in a publication, and one OECD TG 406 and GLP-compliant Guinea Pig Maximisation Test (GPMT).

The first LLNA that used dimethylformamide (DMF) as a vehicle and 25 % hexyl cinnamic aldehyde (HCA) as a positive control. This was deemed the key study by the DS. Two tests were run in this study. In the first test, all tested (non-irritating) concentrations (2.5 to 50 %) gave positive results with stimulation index (SI) values > 3. Since no dose-response was observed, a second test was performed with concentrations 0.1, 0.5, 1, 5 and 25 % (producing SI values 1.58, 2.87, 1.97, 3.51 and 5.74, respectively). As the SI value measured at 1 % departed from the otherwise observed dose-response, it was excluded from the calculation of the EC3. This yielded an EC3 value of 1.4 %.

Basketter et al. (2007) reported results from three different LLNAs, the latest of which was compliant with GLP and OECD TG 429. In the two older datasets no positive controls were used and both tests were negative. The oldest data was considered unreliable by the authors since vehicle controls gave higher SI values than treated samples. The second test yielded SI values of 1.0, 2.2, 2.2, 2.7 at 0, 5, 10, and 25 % resorcinol in DMF, respectively. Since no positive control was included, reliability of these results was deemed questionable. The most recent LLNA was performed with 1, 5, 10, 25, and 50 % resorcinol in acetone: olive oil (4:1). There was a clear dose response and an EC3 value of 6.3 % was calculated.

In the GPMT, 7 out of 10 animals showed very slight to clearly circumscribed erythema at the 24-h-observation after topical challenge with 25 % resorcinol in 0.9 % sodium chloride (intradermal induction: 2 %). At the second reading at 48 h after challenge, 5 animals showed erythema.

Human Data

The DS presented data from 17 patch test series in dermatitis patients, one epidemiological worker study in a tyre factory, and several case reports. The number of published cases exceeded 100, but frequencies in unselected and selected dermatitis patients as well as workers (including hairdressers) were low with median values of 0.75, 1.45, and 0.6 %, respectively. Highest frequencies were generally observed in older patch test series from the 1960s and 70s.

Based on the results from the key LLNA, the DS proposed classification of resorcinol as Skin Sens. 1A, H317. Since there is no scientific information showing concern for a potential high sensitising potency of resorcinol, no specific concentration limit (SCL) was proposed.

Comments received during consultation

Two MSCAs and one industry association (IND) submitted comments in the consultation. Both MSCAs supported the proposed classification. One of them pointed out, that systemic toxicity was observed in the key LLNA concentrations from 5 % onwards but as these effects occurred above the EC3, the classification proposal was accepted.

Industry noted in their comment that the Scientific Committee on Consumer Safety (SCCS October 2020) and others have re-evaluated the first LLNA study (Anon. 2005) since the initial submission of the REACH registration dossier and used the previously excluded SI value (1.97) from 1 % test concentration as point of departure for EC3 value calculation. By linear extrapolation the corrected EC3 value was 3.67. Industry queried the interpretation of human data provided by the DS, noting that negative results from 42 workers at a tyre factory were not included in the overall number of workplace cases, thus skewing the median positive rate. Moreover, positive data from sensitised hairdressers may have been compromised by positive responses to other substances usually present in hair dye formulations and therefore, these should have been excluded from the number of reported cases.

The DS in their response insisted that using the 0.5 % test concentration SI value as point of departure in calculating the EC3 was justified. They noted deficiencies in the reporting of the tyre factory data as to the concentration of resorcinol used in the patch test. Including these 42 workers into the overall workplace cases would alter the median positive rate from 0.6 to 0.5 %. The DS clarified that reports of positive reactions to hair dye formulations were excluded from the evaluation, and that the patch tests included in the evaluation use defined substances, not formulations. The DS concluded that category 1A was warranted based on human and animal data applying a weight of evidence approach. Severe reactions to low resorcinol concentrations were observed in some cases and based on the reliable LLNA data with an EC3 value of 1.4 %.

Assessment and comparison with the classification criteria

Animal Data

According to the guidance, criteria for category 1A are:

- for LLNA test results; EC3 value ≤ 2%,
- for GPMT test results; ≥ 30 % tested animals are responding at ≤ 0,1 % intradermal induction dose or ≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose.

and criteria for category 1B are:

- for LLNA test results; EC3 value > 2 %,
- for GMPT test results; ≥ 30 % to < 60 % responding animals at > 0,1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose.

The LLNA (Anon. 2005), which the DS considered the key study, yielded an EC3 value of 1.4 % or 3.67 %, depending on which data point was used as point of departure for the calculation. For the second LLNA performed in the Basketter working group (2007), an EC3 value of 6.3 % was calculated. RAC notes that the newest experiments of this publication were performed according to OECD TG 429 and GLP standards and that Basketter made a significant contribution to the validation of the LLNA-method and has solid experience in conducting this assay. The results reported by this working group can be considered reliable. The two other LLNAs summarised in the same publication predated the recommendation to include a positive control and results are therefore less reliable. Basketter et al. performed a re-evaluation of the results of the first test that yielded SI values < 1 because of unusually high vehicle SI values. They used historical SI values for this vehicle (acetone-olive oil) from their lab to re-calculate values for treatment groups. When combined with data from the latest LLNA, a clear dose-response was observed over a wide concentration range (0.1 % to 50 %, for graphical analysis see supplemental information). The combined EC3 value was 5.5 % which is similar to the re-calculated EC3 value for the LLNA reported in Anon. 2005.

Depending on the calculation method, there are reliable LLNA data that point to category 1A in one case and category 1B in one case, or category 1B in two cases.

In the GPMT, > 30 % of the tested animals reacted to an intradermal induction concentration of > 1 % pointing to category 1B. However, lower induction concentrations were not tested in this study. Thus, category 1A cannot be excluded and no sub-categorisation is possible based on these results alone.

Human Data

When considering human data, frequencies of sensitisation to the substance in general population, unselected dermatitis patients, selected dermatitis patients, unselected workers, and workers with known exposure have to be considered as well as overall exposure levels. The DS presented a whole series of patch test data from unselected and selected dermatitis patients as well as workers with known exposure to resorcinol (mostly hairdressers). In these populations a low median frequency of occurrence of sensitisation towards resorcinol was generally observed. Resorcinol concentration used in patch tests was mostly 1-2 %. In two series, a 5 % concentration was used yielding a high positive rate of 7.9 % in one of them (Baer et al. 1973), and a 0.5 % concentration in another two series in unselected, consecutive patients with positive rates between 0.2 to 1.9 % (Storck and Baumann 1975; Jarisch and Sandor 1978). Other high positive rates of 4.5 % and 2.7 % were reported in patch test series using 2 % resorcinol in petrolatum (Blondeel et al. 1978; Fräki et al. 1979). Selected patients with known exposure to resorcinol containing ointments/creams all reacted positively to 1 or 2 % resorcinol (8 each, Keil 1962; Barbaud et al. 1996). The highest positive rates were seen in the oldest patch test series. More recent series in selected patients reported positive rates of 1.9 % to 0.1 % using resorcinol concentrations of 1-2 %.

In summary, median frequencies for all tested populations were in the range of a low to moderate frequency according to CLP guidance. These are less than 1 % in unselected, consecutive dermatitis patients (median 0.75 %), less than 2 % in selected patients (median 1.45 %), and less than 1 % in selected workers with known exposure (median 0.6 %).

More than 100 cases were reported which is regarded as high frequency according to CLP guidance. RAC notes that these 117 positive patch test cases were reported over a time span of 54 years (1962 to 2016), amounting to an average of 2 cases per year. For comparison, positive patch tests for cinnamaldehyde which RAC recently proposed to classify as Skin Sens. 1A based *inter alia* based on a high frequency of sensitisation in dermatitis patients, comprised more than 2300 cases in 38 years (~ 60 cases/year).

As to exposure, the DS stated that data is insufficient to draw a conclusion on its extent and no data were presented in the CLH report.

Conclusion on classification

RAC follows the re-calculation of the LLNA data (Anon. 2005) published by the SCCS (see also supplemental information) yielding an EC3 value of 3.67 % that is above the cut-off of 2 % for category 1A classification. Similar values (6.3 % with the newest data alone, and 5.5 % using historical control data to re-calculate SI values for a second dataset) were obtained in a second reliable LLNA dataset (Basketter et al. 2007). The GMPT results fall within the guidance values for category 1B but category 1A cannot be excluded based on concentrations tested.

In contrast to the DS conclusion on the weight of evidence, in RAC's view human as well as most animal data clearly meet criteria for category 1B and thus classification of resorcinol as **Skin Sens. 1B**, **H317** is warranted.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Summary

For the environmental hazard, the DS provided studies from the REACH registration dossier. The DS proposed to keep the classification as Aquatic Acute 1 (H400), adding an M-factor of 1 based on the results in the relevant ecotoxicological studies on *Daphnia magna*, as described below. From the available information, no classification for chronic aquatic hazards was warranted.

Degradation

Hydrolysis is not expected to occur since resorcinol has no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions (Harris, 1990).

A study related to the effect of pH on the decomposition of hydrophenols in aqueous solutions by ultraviolet direct photolysis and the ultraviolet hydrogen peroxide process (Shen *et al*., 2003) indicated that the light absorbance and photolytic properties of resorcinol are highly dependent on pH and can be adequately described with a three-species distribution model. For the UV-H_2O_2 process, the individual contribution to the decomposition of pollutants by direct photolysis and indirect hydroxyl radical destruction was differentiated by studying the linear addition of UV light absorbance of various reactant species. The contribution to the decomposition of resorcinol by hydroxyl radical destruction was more than 95 % in acidic and neutral solutions for treatment with the UV-H_2O_2 process.

Several biodegradation studies are available from the registration dossier. The ready biodegradability was investigated by a modified MITI test (following OECD TG 301C). Resorcinol was added to non-adapted activated sludge at a concentration of 100 mg/L. The degree of biodegradation was 66.7 % (BOD) after 14 days at 25 °C and pH 7 and 100 % TOC removal after 14 days (Kitano, 1978). Based on the results of the study, resorcinol can be considered as readily biodegradable under aerobic conditions. Only limited information is available for this study, but the DS considered it valid and reliable for classification purposes.

BOD5/COD was determined for resorcinol with the value of ca. 1.74 demonstrating the rapid degradation of resorcinol (Pitter, 1976).

No simulation studies are available.

Based on the result of ready biodegradability study supported by the BOD5/COD value, the DS considered resorcinol to be rapidly degradable.

Bioaccumulation

A study on the bioaccumulation behaviour of the substance is not available. Based on a measured log K_{ow} of 0.8 at 20 °C (REACH registration dossier) being below the CLP criterion of 4, the DS considered resorcinol to have a low potential for bioaccumulation.

Aquatic toxicity

Acute and chronic aquatic toxicity studies are available for three trophic levels.

Acute Aquatic Toxicity

The table below shows a summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish					
Methods for Acute Toxicity Tests (EPA-660/3/75-009) GLP compliance not specified 96 h flow-through test	*Pimephales promelas*	resorcinol No information on purity of the test material	96h LC_{50}: 26.8 – 29.5 mg/L (mean measured)	2 (reliable with restrictions) Key study	Anonymous (1981a)
Fish short term toxicity study (test guideline not specified) GLP compliance not specified	*Leuciscus idus*	resorcinol (99% purity)	96h LC_{50}: 34.7 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1981b)
In house method, similar to OECD TG 203 GLP compliance not specified 96h semi-static test	*Gambusia affinis*	resorcinol (analytical grade)	96h LC_{50}: 181 mg/L (nominal) 72h LC_{50}: 184 mg/L	2 (reliable with restrictions) Supporting study Rate of oxygen uptake was significantly decreased at higher concentrations.	Anonymous (2000)
Methods for Acute Toxicity Tests (EPA-660/3/75-009) No GLP compliance	*Pimephales promelas*	resorcinol (industrial grade)	96h LC_{50}: 49.5 mg/L (measured concentration)	2 (reliable with restrictions) Supporting study	Anonymous (1979)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Pimephales promelas*	resorcinol No information on purity of the test material	96h LC_{50}: 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Oncorhynchus mykiss*	resorcinol No information on purity of the test material	96h LC_{50}: >100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)

Method	Species	Test material	Results	Remarks	Reference
Aquatic invertebrates					
OECD TG 202 GLP compliant 48h semi-static	*Daphnia magna*	resorcinol (99,75%)	48h LC_{50}: 1.0 mg/L (geom. mean measured) 48h LC_{50}: 1.3 mg/L (nominal)	1 (reliable without restriction) Key study	Harlan (2010)
Non-guideline study GLP compliance not specified 48h flow-through test	*Daphnia pulicaria*	resorcinol No information on purity of the test material multi-test substance study	48h LC_{50}: > 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	DeGraeve (1980)
Non-guideline study GLP compliance not specified 48h static test	*Daphnia magna*	resorcinol No information on purity of the test material	48h LC_{50}: 1.28 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Herbes & Beauchamp (1977)
Methods for Acute Toxicity Tests (EPA 660/3-75-009) No GLP compliance 96h static test	Daggerblade grass shrimp *(Palaemonetes pugio)*	resorcinol No information on purity of the test material	96h LC_{50} (mortality): 42.2 mg/L (nominal) and 32.7 mg/L (direct photometric measurement of phenol concentration)	2 (reliable with restrictions) Supporting study Saltwater media	Curtis (1979)
Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	resorcinol No information on purity of the test material	72h EC_{50} (growth rate): > 97 mg/L (measured) 72h EC50 (biomass): > 97 mg/L	1 (reliable without restriction) Key study Limit test	Springborn (2006)
Non-guideline study GLP compliance not specified 72h static test (saltwater)	Diatom *(Nitzchia Closterium)*	resorcinol No information on purity of the test material	89 % inhibition compared to control based on growth rate (55.05 mg/L nominal)	2 (reliable with restrictions) Supporting study	Florence & Stauber (1986)

For **fish**, 1 key study and 5 supporting studies are available, all based on non-OECD protocols, but which are claimed similar to OECD TG 203. The DS considered them valid and reliable for the classification purposes.

The lowest value was obtained in a test following EPA-660/3/75-009 on fathead minnows (*Pimephales promelas*) under flow through conditions (96h LC_{50} = 26.8 mg/L, mean measured).

Four studies were provided for **aquatic invertebrates**, all of them were considered valid and reliable by the DS. The key study was a 48h semi-static study with *Daphnia magna*, conducted according the OECD TG 202 and GLP compliant (Harlan, 2010). The nominal test concentrations

were 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L. A 48h LC_{50} value of 1.3 mg/L was calculated based on nominal concentrations as analytically verified test concentrations ranged from 92 % to 104 % of initial test concentrations. An LC_{50} value of 1.0 mg/L (95 % confidence limit of 0.041 – 27 mg/L) based on the geometric mean measured concentrations was calculated.

For **algae** two studies were provided: an OECD TG 201 study, for *Pseudokirchneriella subcapitata* (Springborn, 2006) and a study on the marine diatom *Nitzschia closterium* (Florence & Stauber, 1986*).* The key study is Springborn (2006) during which algae were exposed for 72 hours to mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (nominal test concentrations = 3.1, 6.3, 13. 25. 50 and 100 mg/L from Registration Dossier). The 72h E_bC_{50} and E_rC_{50} values (biomass and growth rate) were both greater than the highest mean measured concentration tested (> 97 mg/L).

These acute toxicity studies with algae are considered valid and reliable for classification purposes.

Chronic Aquatic Toxicity

The table below shows a summary of relevant information on chronic aquatic toxicity.

Method	Species	Test material	Results	Remarks	Reference
Fish					
Similarities with OECD TG 210 (early draft) GLP compliance not specified 60d semi-static test	*Oncorhynchus mykiss*	resorcinol (≥99% purity)	60d LOEC: 320 mg/L (mortality, total embryotoxicity) 60d LOEC: 100 mg/L (length) 32 mg/L (weight) Based on nominal concentrations	2 (reliable with restrictions) Key study	Anonymous (1990) *
OECD TG 212 GLP compliance not specified 7d semi-static test	*Danio rerio*	resorcinol (≥ 99% purity)	7d LOEC (mortality): 320 mg/L 7d LOEC (total embryotoxicity): 100 mg/L Based on nominal concentrations	2 (reliable with restrictions) Supporting study	Anonymous (1990) *
Aquatic invertebrates					
OECD TG 211 GLP compliant 21d flow-through test	*Daphnia magna*	resorcinol (USP Grade Flake) 99.96 % purity	21 d NOEC (reproduction): > 0.172 mg/L (mean measured, highest test concentration) No adverse effects observed at the highest test concentration	1 (reliable without restriction) Key study	Springborn (2004)
Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	resorcinol No information on purity of the test material	72h NOEC (biomass): 47 mg/L (measured) 72h NOEC (growth rate): 97 mg/L (highest mean measured dose tested)	1 (reliable without restriction) Key study Limit test	Springborn (2006)

*The Registration dossier provided Van Leeuven *et al*. (1990) as Reference

For **fish**, the DS reported two results (for *Oncorhynchus mykiss* and *Danio rerio*) claimed valid and reliable with restrictions (K2). The lowest value is a 60-day LOEC (weight) value of 32 mg/L for *Oncorhynchus mykiss* indicated as key study (Anonymous, 1990).

It is noted that the actual toxicity values may have been lower as no analytical monitoring was performed in the study and Resorcinol is demonstrated to be susceptible to biodegradation during the aquatic long-term tests for *Daphnia magna* (Springborn, 2004).

For **aquatic invertebrates,** a 21-day flow-through study according to OECD TG 211 and GLP compliant was performed with *Daphnia magna*. The daphnids were exposed to mean measured concentrations of 11, 35, 53, 111 and 172 µg/L of resorcinol (nominal test concentrations were 25, 50, 100, 200 and 400 µg/L). No adverse effects were observed at the end of the study for the reproduction, mortality, total body length or dry weight endpoints and the DS considered the NOEC value as ≥ 172 µg/L (mean measured), that corresponds to the highest concentration tested.

For **algae,** the DS reported the outcomes of the OECD TG 201 study on *Pseudokirchneriella subcapitata* (Springborn, 2006) exposed for 72 hours (mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (nominal test concentrations = 3.1, 6.3, 13. 25. 50 and 100 mg/L according to Registration dossier). The mean measured NOEC value for growth inhibition (biomass) endpoint was 47 mg/L and 97 mg/L (highest mean measured dose tested) for the growth rate endpoint.

Comments received during consultation

Three Member States and a National Authority commented on the environmental classification proposals.

The National Authority asked for additional information about the key biodegradation study (Kitano, 1978) since limited data are available and the DS considers it to be Klimisch 2. However, the National Authority recognised that the wider fate data in the CLH report appear to support the substance being considered as rapidly degradable; moreover, they asked if there are useful QSAR predictions to support this weight of evidence position.

The DS agreed that the study had shortcomings due to limited documentation, but no further information was found in the existing databases. However, it can be concluded that resorcinol is rapidly degradable based on the Kitano (1978) study together with the supporting information in the classification proposal. In addition, the DS provided Biowin V4.10 model predictions supporting the conclusion that resorcinol is rapidly degradable.

The Member States supported the DS proposal of Aquatic Acute 1 with an M-factor of 1. However, one of them suggested adding the chronic classification as Aquatic Chronic 3 (H412) according to criteria set in table 4.1.0 (b) (ii) and an observed 21d NOEC for *Daphnia magna* of ≥ 172 µg/L. Although the NOEC value could have been higher than the highest concentration tested, as the Member State considered chronic toxicity values likely to be below the 48h EC_{50} for *Daphnia magna* (same species) of 1.0 mg/L, the Member State hypothesized that the NOEC value could be between 0.172 and 1.0 mg/L, triggering to a chronic classification as Aquatic Chronic 3.

The DS responded that the long-term aquatic hazard classification was not warranted in the range of 0.172 – 1.0 mg/L, considering that no information is available for the aquatic chronic toxicity for *Daphnia magna* in the range of 0.172 – 1.0 mg/L and resorcinol being rapidly degradable and non-bioaccumulative.

Assessment and comparison with the classification criteria

RAC noted that the DS provided relevant acute and chronic aquatic toxicity studies for three trophic levels. RAC agrees with the DS that invertebrate is the most sensitive trophic level.

Degradation

RAC agrees with the DS proposal to consider resorcinol as rapidly degradable. The substance can be considered readily biodegradable, even if the information about the study is limited regarding the test design and validity. BOD5/COD value of 1.74 (greater than 0.5) supports the conclusion that resorcinol is rapidly degradable.

Bioaccumulation

No BCF data is available for resorcinol but based on experimental data, resorcinol has a measured log K_{ow} of 0.8. Therefore, RAC agrees with the DS's proposal to consider that the bioaccumulation potential of resorcinol is low.

Aquatic toxicity

For the fish trophic level, RAC noted some critical issues that do not allow clear conclusions on the reliability. Indeed, the studies are not carried out according to standard test guidelines, although they are claimed similar to OECD TG. No information is provided on the validity criteria for the OECD protocols, as, for instance, demonstrating that the concentrations of the test substance in solution have been satisfactorily maintained within $\pm$ 20% of the mean measured values, in particular for the chronic tests for which only nominal concentrations are provided.

However, despite the above shortcomings, RAC agrees that fish is not the most sensitive trophic level for the aquatic toxicity.

Regarding the proposal of a commenting Member State to classify resorcinol as Aquatic Chronic 3, RAC agrees with the DS's response confirming that the long-term aquatic hazard classification is not warranted, considered that: a) no adverse effect was observed up to the highest test concentration of 0.172 mg/L for the most sensitive organism *Daphnia magna*; b) no information is available for aquatic chronic toxicity in the range 0.172 – 1.0 mg/L for *Daphnia magna,* and c) resorcinol is rapidly degradable and non-bioaccumulative. Furthermore, RAC notes that for all the tested organisms no chronic adverse effects are observed below the criteria of 1 mg/L set out in CLP Table 4.1.0(b)(ii) for rapidly degradable substances.

However, RAC considers that the classification might be revised in case new data becomes available demonstrating long-term effects.

Comparison with the criteria

For acute aquatic toxicity, relevant information is provided for fish, aquatic invertebrates, and algae, indicating that invertebrates are the most sensitive trophic level. Based on the key study on *Daphnia magna* (Harlan, 2010) the lowest 48h LC_{50} value for was 1.0 mg/L (mean measured).

Therefore, RAC agrees that, based on the 48h EC_{50} value being in the range 0.1 mg/l < $L(E)C_{50}$ ≤ 1 mg/l, for resorcinol, hazard classification as Aquatic Acute 1 (H400) with an M-factor of 1 is warranted.

For chronic aquatic toxicity, relevant information is provided for fish, aquatic invertebrates, and algae, all indicating no classification for chronic hazards.

No adverse effects are observed for resorcinol for any of the tested organisms below the criteria of 1 mg/L set out in CLP Table 4.1.0(b)(ii) for rapidly degradable substances. For the most

sensitive species (also under acute testing, invertebrate: *Daphnia magna*) no adverse effects were observed at the highest test concentration (NOEC > 0.172 mg/L).

In conclusion, RAC agrees that based on the available information, no long-term aquatic hazard classification is warranted for resorcinol.

Conclusion

RAC agrees with the DS that resorcinol warrants classification as **Aquatic Acute 1, M = 1.**

Additional references

SCCS (2021) *Opinion on Resorcinol.* SCCS/1619/20 (final opinion, adopted March 2021)

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).