Committee for Risk Assessment

RAC

Opinion

Proposing harmonised classification and labelling
at EU level of

chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol

EC Number: 200-431-6
CAS Number: 59-50-7

CLH-O-0000001412-86-103/F

Adopted

10 March 2016

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CLH-O-0000001412-86-103/F

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: **chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol**

EC Number: **200-431-6**

CAS Number: **59-50-7**

The proposal was submitted by **France** and received by RAC on **13 May 2015.**

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

PROCESS FOR ADOPTION OF THE OPINION

France 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 **16 June 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **31 July 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Andrew Smith**

Co-Rapporteur, appointed by RAC: **José Luis Tadeo**

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 **10 March 2016** by **consensus.**

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

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	604-014-00-3	chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol	200-431-6	59-50-7	Acute Tox. 4 * Acute Tox. 4 * Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1	H302 H312 H318 H317 H400	GHS05 GHS07 GHS09 Dgr	H302 H312 H318 H317 H400			
Dossier submitters proposal	604-014-00-3	chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol	200-431-6	59-50-7	**Retain** Eye Dam. 1 Aquatic Acute 1 **Add** Skin Irrit. 2 STOT SE 3 Aquatic Chronic 3 **Modify** Acute Tox. 4 Skin Sens. 1B **Remove** Acute Tox. 4 *	**Retain** H318 H400 **Add** H315 H335 H412 **Modify** H302 H317 **Remove** H312	**Retain** GHS05 GHS07 GHS09 Dgr	**Retain** H302 H317 H318 **Add** H315 H335 H410 **Remove** H312 H400		**Add** M(acute)=1	
RAC opinion	604-014-00-3	chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol	200-431-6	59-50-7	**Retain** Aquatic Acute 1 **Add** Skin Corr. 1C STOT SE 3 Aquatic Chronic 3 **Modify** Acute Tox. 4 Skin Sens. 1B **Remove** Acute Tox. 4 * Eye Dam. 1	**Retain** H400 **Add** H314 H335 H412 **Modify** H302 H317 **Remove** H312 H318	**Retain** GHS05 GHS07 GHS09 Dgr	**Retain** H302 **Add** H314 H335 H410 **Remove** H312 H400 H318		**Add** M(acute)=1	
Resulting Annex VI entry if agreed by COM	604-014-00-3	chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol	200-431-6	59-50-7	Acute Tox. 4 Skin Sens. 1B Skin Corr. 1C STOT SE 3 Aquatic Acute 1 Aquatic Chronic 3	H302 H317 H314 H335 H400 H412	GHS05 GHS07 GHS09 Dgr	H302 H317 H314 H335 H410		M (acute) = 1	

GROUNDS FOR ADOPTION OF THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal

In tests, chlorocresol has been shown to not be highly flammable or to liberate gases in hazardous amounts in contact with water. It does not deliver indications of pyrophoric properties and does not undergo spontaneous combustion. The structure of chlorocresol does not have any oxidising groups or other chemically unstable functional groups and is incapable of rapid decomposition with evolution of gases or release of heat and will not react exothermically with a combustible metal. Therefore, chlorocresol does not meet the criteria for classification for physico-chemical properties.

Comments received during public consultation

There were no comments regarding the classification for physico-chemical hazards.

Assessment and comparison with the classification criteria

Chlorocresol does not meet the classification criteria for a flammable solid. Examination of the chemical structure did not indicate that chlorocresol would have any explosive or oxidising properties and so does not meet the criteria for classification as an explosive substance or an oxidising solid.

RAC opinion: **No classification** is warranted for physico-chemical hazards.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The acute toxicity of chlorocresol has been tested in a number of oral, inhalation and dermal studies in rats and rabbits.

Oral Exposure

There are three studies available for the assessment of acute oral toxicity in the rat.

In the first study (Bomhard, 1988a), males and females were treated to a single limit dose of 2000 mg/kg bw of chlorocresol. The LD_{50} was < 2000 mg/kg bw for both males and females.

In the second study (Bomhard, 1978 and Löser, 1992), the LD_{50} of chlorocresol was determined in males only. The study results reveal moderate toxicity following acute oral exposure (LD_{50} = 1830 mg/kg bw in males).

The third study (Miles Inc, 1981), considered as invalid by the Dossier submitter (DS), gave an LD_{50} of 5129 mg/kg bw for males and 3636 mg/kg bw for females. The number of deaths at each tested dose was not recorded.

The lowest acute toxicity estimate value is 1830 mg/kg bw (oral LD_{50} for male rats). This value lies within the range (300-2000 mg/kg) for classification as Acute Oral Tox. 4 (H302; Harmful if swallowed).

Inhalation Exposure

In an acute inhalation study, rats were exposed nose-only to chlorocresol for 4 h. The resulting LC_{50} was > 2871 mg/m^3 (2.87 mg/L) (the maximal attainable concentration); therefore no classification is required.

Dermal Exposure

Three studies are available for the assessment of acute dermal toxicity, two in rats and one in rabbits.

In rats, the dermal LD_{50} was > 2000 mg/kg bw (in both studies). In rabbits, the dermal LD_{50} was > 5000 mg/kg bw. These values are both above the classification cut-off of 2000 mg/kg bw; therefore no classification is required.

Comments received during public consultation

One Member State Competent Authority (MSCA) supported the proposed classification for acute oral toxicity.

Assessment and comparison with the classification criteria

RAC is in agreement with the DS's assessment of the available data.

In the three available oral studies, the lowest LD_{50} obtained was 1830 mg/kg bw in male rats. A limit test in rats, with a single dose of 2000 mg/kg bw supported this value. The value is in accordance with the criteria for classification in Acute oral toxicity, category 4 ($300 < LD_{50} \leq 2000$ mg/kg).

In the acute inhalation study in rats, the LC_{50} was > 2.87 mg/L (the maximum attainable concentration). Therefore, chlorocresol does not meet the criteria for classification for Acute Inhalation Toxicity.

In the dermal studies in rats and rabbits, the LD_{50} were > 2000 and > 5000 mg/kg bw respectively. No classification for Acute dermal toxicity is warranted.

RAC considers that classification as **Acute Tox. 4; H302 (Harmful if swallowed)** is justified. No classification is warranted for acute dermal or inhalation toxicity.

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

Summary of the Dossier submitter's proposal

Chlorocresol was of low acute toxicity by the inhalation route in an acute rat toxicity study. However, although no mortalities occurred, oedema and necrosis in the nose, reddened nostrils with red encrustations, nasal discharge, and abundant secretions in the trachea were viewed as signs of upper respiratory irritation. Based on these results, chlorocresol was considered to be irritating to respiratory system.

The criteria for STOT SE 3 (respiratory irritation) state that "this evaluation is primarily based on human data" but that "useful information may be obtained from the single and repeated inhalation toxicity tests" in animals. Effects that are relevant to consider for respiratory irritation according to the CLP criteria are clinical signs such as dyspnoea and rhinitis, and histopathology findings such as hyperaemia, oedema, minimal inflammation and thickened mucous layer, which are reversible effects.

In the absence of relevant human data for chlorocresol, the acute inhalation study provides relevant evidence of respiratory irritation. The clinical signs observed were indicative of respiratory distress, and included subdued demeanour, decreased body weights, emaciation and hypothermia. No rats died during this study, but in some animals the clinical signs lasted until the end of the 2-week post-exposure period. However, most rats showed evidence of recovery during the study period (see table below). Necropsy findings consisted of a collapsed lung and secretions in the trachea. Therefore the evidence of respiratory irritation comes only from the observed clinical signs.

Target Concentration (mg/m^3 air)	**Maximum duration of clinical signs**
Males (n=5)	
0	-
2000 Analytical concentrations (mean values): 1337 mg/m^3	9 d
3000 Analytical concentrations (mean values): 2871 mg/m^3	12 d
Females (n=5)	
0	-
2000	8 d
3000	14 d

As the tested substance is a white solid, it cannot be excluded that the mechanical effect of solid particles contributed to the irritation observed at high concentrations. However, clinical signs indicating respiratory irritation were not only observed at the high dose of 2.87 mg/L, but also at 1.33 mg/L, and therefore mechanical irritation may not fully explain the observed clinical signs.

Based on the observed irritation in the respiratory system, classification as STOT SE 3; H335 (May cause respiratory irritation) was proposed.

Comments received during public consultation

One MSCA supported the proposed classification as STOT SE 3; H335.

Assessment and comparison with the classification criteria

In the available acute toxicity studies, carried out by the oral, inhalation and dermal routes, there were no clinical signs, significant functional changes or organ damage occurring in the absence of mortality or at doses relevant for classification for Specific target organ toxicity categories 1 or 2.

Following inhalation exposure to chlorocresol, signs of upper respiratory irritation were apparent in rats exposed to 1337 mg/m^3 and 2871 mg/m^3. These included oedema and necrosis of the nasal passages and signs of respiratory distress – subdued demeanour, decreased body weights, emaciation and hypothermia. In some rats these clinical signs lasted until the end of the 2-week observation period. However most showed recovery during this time.

According to RAC, Classification as **STOT SE 3; H335 (May cause respiratory irritation**) is warranted.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

In a skin irritation study, the average dermal irritation score, following exposure for 4 hours, was equivalent to 1.9 for erythema. This is below the classification threshold of 2.3; however, the study duration was only 96 h and observations were only carried out at 24 and 48 h post removal of the dressing. Local effects were also observed in an acute dermal study in rabbits.

No data was available on the reversibility of the observed effects. The erythema was still present at 96 h (last examination time) and it can therefore be viewed that no reversibility was observed at the end of the study and that inflammation persisted until the end of the observation period. Normally, this should be seen in at least 2 animals after 14 days, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling. In absence of any further details, the DS considered the findings relevant for classification for Skin Irritation category 2; H315 (Causes skin irritation).

Comments received during public consultation

No comments were received on this endpoint.

Assessment and comparison with the classification criteria

A single study of skin irritation in rabbits was described in the CLH report (1976; non-OECD/non-GLP). Six animals were exposed to chlorocresol for a period of 4 h and skin reactions were noted at 4, 24 and 48 h. There was no 72 h observation. The study duration was 96 h, i.e. considerably shorter than the OECD TG recommendation of 14 days.

	Rabbit											
Observation Time (h)	**1**		**2**		**3**		**4**		**5**		**6**	
	E	O	E	O	E	O	E	O	E	O	E	O
4	0	4	0	3	0	1	0	1	0	1	0	2
24	2	2	2	1	2	1	2	0	2	0	2	1
48	2	1	2	0	2	0	2	0	2	0	1.5	0.5
Mean (24 + 48 h)	**2**	**1.5**	**2**	**0.5**	**2**	**0.5**	**2**	**0**	**2**	**0**	**1.5**	**0.5**

E – Erythema, O – Oedema

From the information available, it is not possible to apply the guidance criteria for classification directly as there is no 72 h timepoint. In 6/6 rabbits the scoring for erythema worsened from 4 – 24 h, up to a score of 2, and there was only very limited evidence (from 1 animal) of reversibility at the 48 h time point.

Further information on the skin irritancy of chlorocresol can be found in an acute dermal study in rabbits. In this study rabbits were exposed to various doses of chlorocresol for the longer time period of 24 h. Severe effects were observed at the site of contact. Marked epidermal and dermal necrosis was observed in all rabbits of the treated groups at the end of the observation period. Additionally, obliteration of adnexal structures, marked pleocellular inflammatory infiltrate and acanthosis were noted. There was no appreciable difference in severity between the abraded and intact application sites or between rabbits receiving the various doses of the test material. It is unclear whether the corrosive effect was a function of the extended exposure time.

The DS commented very briefly in the section of the CLH report on Skin Sensitisation that "superficial skin burns" had been noted in personnel at a chlorocresol manufacturing facility after skin contact with spilt chlorocresol-containing liquids. However, no further details were provided by the DS and as such this information is considered too brief in detail to contribute to this assessment.

As summarised in the section (see box in the background document), RAC was also presented with relevant information from ECHA's public database of registered substances. The entry for chlorocresol includes a skin irritation study different to the one presented by the Dossier Submitter. In this study, "necrotic lesions" were observed at the site of application on the skin of a single rabbit exposed to chlorocresol for 4 hours. A complete layer of necrotic tissue was removed after one week. Although the reporting of the study is limited, the registrant assigned it a Klimisch score of 2 and concluded that chlorocresol should be classified as a corrosive substance.

As the skin irritation study reported by the DS had significant shortcomings, it is considered appropriate to add weight to the alternative study that was summarised in the registration database. RAC therefore agrees with the position given in that database about the corrosive nature of chlorocresol.

Sub-category 1C is supported by the observation of a corrosive reaction in the skin following a 4-hour exposure period. No information is available to inform about the possible effect of shorter exposure periods, but additionally the lack of a corrosive effect after 4 hour in the skin irritation study summarised by the DS is informative. It would appear that chlorocresol may be corrosive after 4 hours exposure, but the evidence for this exposure period is not overwhelmingly positive. It therefore seems unlikely that exposure periods of 1 hour or less would lead to corrosive responses and a more stringent classification seems inappropriate.

In the opinion of RAC, **Skin Corr. 1C; H314 (Causes severe skin burns and eye damage)** is warranted.

RAC evaluation of serious eye damage /irritation

Summary of the Dossier submitter's proposal

Chlorocresol is currently classified for Eye Damage Category 1 (H318). The DS indicated that there was an eye irritation study performed in rabbits but did not present it as the results do not change the current classification.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

As this endpoint was not addressed explicitly in the CLH report, RAC has not assessed this endpoint. However, as RAC concluded that chlorocresol is to be classified as a corrosive substance, additional and specific classification for effects on the eyes is not required.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

Two studies in animals and a number of case studies and clinical tests in humans are available to assess the potential of chlorocresol to cause skin sensitisation.

In a Guinea Pig Maximisation Test (GPMT), chlorocresol caused sensitisation in 47 % of animals at 24 h and 87 % at 48 h following an intradermal dose of 25 %. It thus fulfils the criteria to be classified as Skin Sens. 1B (H317). The proposed classification is supported by a weak positive result in a modified Local Lymph Node Assay (LLNA) in mice.

Patch tests had been performed on a "large number" of dermatology clinic patients, with less than a 0.5% rate of positive results. The DS noted also that some cases of skin sensitisation had been reported to be due to contact with chlorocresol-containing steroid creams used for treatment of dermatitis, chlorocresol-containing disinfectants and other substances. However, no information was provided on the level of chlorocresol in these products. Overall, the human data appeared to indicate chlorocresol to be a low potency skin sensitiser and thus were consistent with the animal study results.

Comments received during public consultation

One MSCA queried whether the data were sufficient to justify classification in sub-category 1B. The protocol of the LLNA was not a standard one, and the classification criteria could not be applied to it. The induction dose used in the GPMT may have been too low as it did not cause mild-to-moderate skin irritation. It was unclear whether sodium lauryl sulphate had been used to create a local irritation. The DS indicated that they also had reservations about the value of the LLNA, and had only taken it into account to the extent that it had yielded a "positive" result. The DS, however, had concluded the GPMT to be a valid indicator of both skin sensitisation potential and potency.

One stakeholder organisation agreed with the classification proposal. They noted that the GPMT had shown a weak positive response (<30% responding) with intradermal induction at a concentration of 1% and a clear positive response (>30% responding) at a concentration of 25%. This justified a classification in Category 1B. This stakeholder further referred to literature supporting the use of the modified LLNA and how it was possible to apply the results taking a "cell count index" of 1.25 to be equivalent to an SI of 3 in the standard method. With a response of 1.28 at the 50% induction concentration, the result in this test could be viewed as weakly positive. Further supporting evidence for low potency was provided by 2 further reports of repeated patch tests in a total of 283 human volunteers: induction concentrations up to 20% had not produced any sensitising reactions in these people on challenge with 5% chlorocresol.

Assessment and comparison with the classification criteria

RAC agrees with the DS that sufficient evidence is available to support classification of chlorocresol as a skin sensitiser. The observation in a GPMT of 47% of animals responding at 24 h and 87% responding at 48 h following a challenge dose of 25% clearly meets the criteria for classification.

Although the DS provided only very limited details of the studies, case reports of sensitisation in humans caused by skin contact with chlorocresol-containing mixtures such steroid creams and disinfectants provide supporting evidence.

The percentage of positive patch test responses to chlorocresol in dermatitis patients is low, although it's unclear from the CLH report whether the concentrations of test substance were maximised. In one study, 0.8% of 651 patients in one region of the UK and 0.7% of 1029 patients from another region reacted positively to chlorocresol (test concentration not specified). Similar response levels, or no responses at all, were seen in other studies reporting on patch tests conducted on dermatitis patients. Being below 1%, these response rates in unselected dermatitis patients suggest the potency of chlorocresol as a skin sensitiser may be low and support sub-categorisation in Category 1B.

The results of the GPMT support this, and specifically meet the criteria for a Category 1B classification. Whereas significant response rates of 47% and 87% (or 80% accounting for the control response) were seen at 24 and 48 h following induction with 25% chlorocresol, the response rates were only 27% and 13% in animals induced with a 1% solution.

Dosing	**% chlorocresol**			
	Males		**Females**	
Intradermal Dose	25	0	1	0
Topical Dose	25	0	1	0
Challenge 1	12.5	12.5	25	25
Challenge 2	25	25	50	50
		Vehicle control		**Vehicle control**
No. Sensitised (24 h after challenge 2)	7/15 (47 %)	0/15	4/15 (27%)	0/15
No. Sensitised (48 h after challenge 2)	13/15 (87 %)	1/15 (7%)	2/15 (13 %)	0/15

According to the criteria, if ≥ 30 % of animals respond at > 1 % intradermal induction dose then classification in subcategory 1B is appropriate. This was observed.

In order to be classified in subcategory 1A, a response of ≥ 30 % at a ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1- ≤ 1 % is required. The number sensitised after receiving an intradermal dose of 1 % was 27 %, therefore classification in subcategory 1A cannot be justified.

In a modified LLNA in mice, the stimulation index (SI) was found to be ≤ 1.28. There is no agreed standard for this modified assay, which according to the DS included the following deviations from the guideline method:

- Sacrifice was 1 day after the last treatment, instead of 3 days
- SI was measured by "cell counts" instead of radioactive counting.
- Additional ear swelling measurements were made

If judged against the criteria for the standard method, this test result would be negative for skin sensitisation as an SI ≥ 3 is required for a positive result. However, the DS considered this to be a weak positive result and included it as supporting evidence for the sensitisation potential of chlorocresol. This was consistent with the conclusions made by the study authors and was supported by an industry stakeholder that commented during the public consultation. RAC notes the view taken by the DS, the study author and the industry stakeholder but, as the protocol for this modified LLNA has not been validated, a definitive interpretation of the result is not possible. RAC considers the result of this study equivocal.

On the basis of the GPMT, in which 47% of males responded to an intradermal dose of 25% chlorocresol, RAC considers that there is sufficient evidence to show that chlorocresol meets the criteria for Skin Sens. 1B; H317 (≥30% sensitised following intradermal induction concentration of >1%). The human data are considered to support this conclusion.

From the results of the GPMT, chlorocresol would be considered to be of moderate potency. The GCL of 1% would therefore be appropriate.

In the opinion of RAC, **Skin Sens. 1B; H317 (May cause an allergic skin reaction)** is warranted.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

In Annex VI of CLP, chlorocresol is currently classified as Aquatic Acute 1 (M=1). The DS proposes to amend the classification retaining Acute 1 (M=1) and adding Aquatic Chronic 3.

According to the DS, fish are the most sensitive species for acute and chronic effects. The acute LC_{50} of 0.92 mg/L for *Oncorhynchus mykiss* is lower than 1 mg/L, thus the substance meets the criteria for classification as Aquatic Acute 1 according to CLP criteria. As this value is within the range of 0.1-1.0 mg/L, an M-factor of 1 is justified. In addition, the DS considered chlorocresol as rapidly degradable and non-bioaccumulative. This finding together with a chronic NOEC of 0.15 mg/L for *Oncorhynchus mykiss*, this being lower than 1 mg/L, led the DS to propose classification of chlorocresol as Aquatic Chronic 3.

Comments received during public consultation

One commenter agreed with the DS proposal for classification. However, they also noted a mistake in table 22 of the CLH Report, which did not contain information on the bioaccumulation potential of chlorocresol.

Assessment and comparison with the classification criteria

Degradation

Chlorocresol is completely stable to hydrolysis at acidic, neutral and basic pH conditions. Phototransformation in water is not a relevant elimination pathway, as the substance does not have UV absorbance above 290 nm.

There were several studies available on the degradation of chlorocresol. In the key study on ready biodegradability according to OECD TG 301D (Müller, 1992), 78% of degradation was observed after 15 days, thus chlorocresol was considered readily biodegradable. However in another study (Hanstveit and Pullens, 1993) with lower tested concentrations of CMK and two levels of inoculum, long lag phases were observed and thus the substance was judged to be non-readily biodegradable (32% and 52% degradation after 56 days in the diluted and concentrated inoculums, respectively). Criteria for inhibitory substances were not fulfilled but the validity of inoculums was questioned and the study was not considered reliable. Some other supportive studies were also included in the report following ready or inherent biodegradability protocols. However degradability data produced with adapted inoculums cannot be considered relevant in the context of CLP hazard classification because adapted microorganisms have a higher potential for biodegradation compared to natural environments.

A reliable simulation test on water/sediment degradation (Möndel, 2009) following OECD TG 308 resulted in a DT_{50} (whole-system) of 1.2-1.9 days at 20ºC (2.3-3.6 days at 12ºC). This means that criteria for rapid degradation (i.e. half-life < 16 days) are fulfilled. Mineralisation accounted for 24-37% of applied radioactivity (AR) after 35 days and non-extractable residues were around 50%. Several unknown metabolites were detected mainly in the water phase in a total amount higher than 10% AR. However the analytical method was not able to identify the unknown products. A second study (Möndel, 2010) was run with similar conditions to identify and quantify the degradation products in order to investigate the aerobic biodegradation pathway with a better analytical method. Only phenol was identified as a product of concern with a maximum of 9.9% AR. Nevertheless, phenol is considered a readily biodegradable substance, without degradation products of concern.

In addition to these key studies, several other additional literature studies, monitoring reports and bibliographical monitoring data were summarised in the CLH report to support the rapid degradability of chlorocresol. The data showed low (or undetected) levels of chlorocresol (in the order of micrograms per liter) in rivers receiving SPT effluents of industrial plants using disinfectants, in catchments in Germany, the UK and Portugal. Other studies not following standard protocols showed that chlorocresol may be rapidly degraded by bacteria in the field.

Three supportive literature studies on degradation of chlorocresol in soil, showed half-lives from 2.7 to 59.4 days at 12ºC. A moderate adsorption of the substance to soil particles (mean Koc 195.6 L/Kg), also observed in the water/sediment degradation study, together with the possible need for acclimatation of the microbial populations to rapid biodegradation, could justify higher half-lives found in soil.

Considering together the evidence for rapid degradation, RAC agrees with the DS's proposal to consider chlorocresol as rapidly degradable.

Bioaccumulation

The experimental log Kow of chlorocresol is 3.02, which is below the criterion to be considered as potentially bioaccumulative (i.e. BCF ≥ 4). The BCF_{fish} was calculated to be 73.6 L/Kg (QSAR estimation from the Kow).

The DS supported the lack of bioaccumulation potential observed in the earlier estimations in information from the literature. Experimental BCF values for fish (*C. carpio*) included in the Japaneese database on existing chemicals (MITI, 1992) were in the range of 5.5 to 13 L/Kg for chlorocresol. In a literature study (Jennings *et al.,* 1996) on the bioconcentration of phenolic substances in two marine species, BCF values for mussels (*M. edulis*) and fish (*Trachurus nozaezelandiae*) were reported to be 38 and 121 L/Kg, respectively.

Given that estimated and experimental BCF values were all below 500, it can be concluded that chlorocresol does not fulfil the criteria for bioaccumulative substances. Therefore RAC agrees with the DS's proposal to consider it a non-bioaccumulative substance for classification purposes.

Aquatic toxicity

A summary of the relevant aquatic ecotoxicity results for chlorocresol is presented in the table below.

Summary of relevant aquatic ecotoxicity results for chlorocresol

Method	Species	Results	Remarks	Reference
Fish				
US EPA FIFRA 72-1	*Oncorhynchus mykiss*	LC_{50} (96 h) = 0.92 mg/L (mean meas.)	Semi-static RI = 2	Gagliano and Bowers, 1993a
OECD TG 204 and TG 215	*Oncorhynchus mykiss*	NOEC (28 d) = 0.15 mg/L (mean meas.)	Semi-static RI = 2	Schneider and Wydra, 2007
Comparable to OECD TG 204	*Brachydanio rerio*	NOEC (14 d) = 1 mg/L (nominal)	Flow-through RI = 1	Caspers and Müller, 1991; Weyers, 2006c
Aquatic invertebrates				
US EPA FIFRA 72-2	*Daphnia magna*	EC_{50} (48 h) = 2.29 mg/L (mean meas.)	Static RI = 2	Gagliano and Bowers, 1993b
OECD TG 211	*Daphnia magna*	NOEC (21 d) = 0.32 mg/L (nominal)	Semi-static RI = 2	Weyers, 2007
Algae and aquatic plants				
OECD TG 201	*Desmodesmus subspicatus*	E_rC_{50} (72 h) 30.62 mg/L NOE_rC (72 h) = 9.8 mg/L (nominal)	Static RI = 1	Vinken and Wydra, 2007

There are adequate acute and chronic toxicity studies available for the three trophic levels. Fish are the most sensitive organisms in both acute and chronic studies.

The lowest acute endpoint for fish is the 96 h LC_{50} of 0.92 mg/L for *O. Mykiss,* based on measured concentrations. Given that the LC_{50} is lower than 1 mg/L, chlorocresol meets the criterion for classification as **Aquatic Acute 1**. As the LC_{50} value is within the range of 0.1 - 1.0 mg/L, an **M-factor** of **1** is assigned.

The lowest chronic endpoint is the 28 d-NOEC of 0.15 mg/L for *O. mykiss* based on measured concentrations and growth rate. This value was derived in a study conducted according to a testing protocol comparable to OECD TG 204 and 215. OECD TG 204 is a short-term test and should not be considered for chronic hazard assessments. OECD TG 215 is a sub-chronic test that may be used for chronic effects extrapolation, given that sublethal concentrations are tested over a prolonged exposure period, covering sensitive life stages.

Considering that chlorocresol is rapidly degradable and that the 28 d NOEC of 0.15 mg/L is within the range of 0.1-1.0 mg/L, the substance meets the criteria for classification as **Aquatic Chronic 3** for environmental hazard.

In addition, if the sub-chronic tests on fish were not considered adequate for hazard classification, then classification should be based on the most stringent hazard class assigned with (inadequate) chronic data and with acute data (surrogate approach). The lowest chronic endpoint would be in that case the 21 d NOEC of 0.32 mg/L for *D. magna*. As the NOEC < 1 mg/L, then Chronic 3 class would be assigned for rapidly degradable substances. Considering the lowest acute endpoint of 96 h LC_{50} of 0.92 mg/L for *O. mykiss,* which is below 1 mg/L, and the lack of persistency and/or potential for bioaccumulation, the substance would not be classified for chronic hazard. Therefore, the most stringent outcome would be Chronic 3.

In conclusion, RAC is in agreement with the DS's assessment of the available data, that chlorocresol should be classified as **Aquatic Acute 1 (M = 1) and Aquatic Chronic 3**.

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 by RAC (excluding confidential information).