Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CHLOROCRESOL; 4-CHLORO-M-CRESOL; 4-CHLORO-3-METHYLPHENOL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: chlorocresol; 4-chloro-m-cresol; 4-chloro-3-methylphenol
EC number: 200-431-6
CAS number: 59-50-7
Dossier submitter: France

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Finland		MemberState	1
Comment received				
The Finnish CA supports the proposed classification for the acute toxicity.				
Dossier Submitter's Response				
eCA (09/2015): Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Germany	Lanxess Deutschland GmbH	BehalfOfAnOrganisation	2
Comment received				
Regarding skin sensitization we agree with the classification 1B. As mentioned in the CLH dossier: The Guinea Pig Maximization test showed a weak positive response (<30% responding) with intradermal induction at a concentration of 1% and a clear positive response (> 30% responding) with intradermal induction at a concentration of 25 % which based on the criteria lead to a category 1B. In addition, the available modified LLNA showed a positive response with the 50% concentration only, whereas there was no respective response up to 10%. As a positive LLNA with test substance concentration of > 2% according to the criteria leads to a category 1B this study also confirms the respective categorization. (Remark: in the CLH				

dossier it is mentioned that this modified LLNA (IMDS) is not validated and that no harmonized criteria exist. We would like to point out that in the OECD guideline for the LLNA (TG 429 from July 2010) and the respective EU test method (B.42 from July 2012) it is stated that modified test methods under certain circumstances are functionally and mechanistically similar and it is also highlighted that other endpoints as the Stimulation Index (SI) using radioactive labelling can be used for the assessment. Publications on the validation of the modified method used for p-chloro-m-cresol are cited in the reference list of the guidelines. For modified LLNA methods the level for a positive response have to be adjusted; in the method used for the assessment of p-chloro-m-cresol a cell count index of 1.25 is defined as "positive level" in the study report, that would be equivalent to an SI of 3 in the standard method. With a response of 1.28 at the 50% test substance concentration the result with p-chloro-m-cresol was weakly positive.

The very weak skin sensitization potential is confirmed by the human experience. As mentioned in the CLH dossier the percentage of positive patch test responses in patients is low. In addition, early published human repeated patch tests in human volunteers revealed no positive response with a test concentration of 5% to 20 % in the induction phase and 5% in the challenge phase (Marzulli & Maibach, J.Soc. Cosmetic Chem 24, 399-421, 1973 and Marzulli & Maibach, Fd. Cosmet. Toxicol 12, 219-277, 1974).

Short description of the referenced tests:

Test Species	Method	Induction	Challenge	Response fraction	
Human	Repeated Patch test; experimental sensitization study with 31 male volunteers	5% Vehicle: Petrolatum	5%	0/31	Marzulli & Maibach, J.Soc. Cosmetic Chem 24, 399-421, 1973
Human	Repeated Patch test; experimental sensitization study in 252 volunteers (98, 88 and 66 per group)	5, 10 or 20% Vehicle: Petrolatum	5%	0/98 0/88 0/66	Marzulli & Maibach, Fd. Cosmet. Toxicol 12, 219-277, 1974

Dossier Submitter's Response

eCA (09/2015): Thank you for your support.

Concerning the submitted modified LLNA, instead of radioactive labelling, cell counts were measured. Indeed, this protocol is not validated yet. The non-radioactive LLNA already validated are OECD 442A: LLNA: DA and OECD 442B: LLNA:BrdU-ELISA.

Moreover, the publication of Basketter *et al.* "An evaluation of performance standards and non-radioactive endpoints for the LLNA" (2008) reporting the conclusions of the ECVAM workshop 65, mentions that the method of counting cell corresponds to a major variation from the initial LLNA.

Therefore, we accept the result of this test only because it is positive.

RAC's response

Noted. The available evidence is consistent and supports the proposal of the dossier submitter that this substance be viewed as a low potency skin sensitiser.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Finland		MemberState	3
Comment received				
A modified local lymph node assay (LLNA) in mice showed that CMK has a weak skin sensitising potential. However, there is no validated protocol available for this test and no classification criteria exist. The study in guinea pigs resulted in positive skin sensitising reactions which meet the criteria for classification Skin Sens. 1B; H317 according to the CLP regulation. However, we think that following shortcomings reduce validity of the study. It's stated in the CLH report that test substance concentrations used for the induction exposure did not cause mild-to-moderate skin irritation. Apparently a pre-test to determine appropriate test substance concentrations was not conducted and it seems that the selected concentration 25% was too low. Moreover, according to the guideline, in case the test substance is not a skin irritant, sodium lauryl sulphate should be used before topical induction application to create a local irritation. It is not reported whether sodium lauryl sulphate was used. The intradermal induction concentration 25% followed by 25% challenge concentration resulted in skin reactions in 13 out of 15 test animals. Thus, more information of the study is needed to warrant classification for sub-category 1B.				
Dossier Submitter's Response				
eCA (09/2015):The only deviation from the guideline OECD 406, noted in this M&K test, is that the concentration used for induction was not irritating. We consider that this deviation is not a reason to rule out the result of the test, especially because there is a clear positive response (> 30% responding) with intradermal induction at a concentration of 25 %. Indeed, this result permits to propose a classification in category 1B. Even if the induction concentration is not irritant, it already induces sensitizing effects. Therefore, we maintain our proposal for a classification H317 cat.1B.				
RAC's response				
RAC agrees with the response provided by the dossier submitter.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Germany	Lanxess Deutschland GmbH	BehalfOfAnOrganisation	4
Comment received				
Regarding the classification and labelling for environmental effects we agree with the proposal given in the CLH dossier: Aquatic Acute 1, H400 Aquatic Acute 1. M-factor = 1 Aquatic Chronic 3, H412 However, CLH dossier mentions on page 55, Chapter 5.3 Aquatic Bioaccumulation, in Table 22 two studies by *Chapleo et al.* (1992) and *Chabassol et al.* (1991) which are not related to p-Chloro-m-cresol but which are included in another CLH dossier submitted for Fipronil. We suggest to delete both wrong table entries in the CLH dossier of chlorocresol.				

Dossier Submitter's Response
eCA (09/2015): Agree.
RAC's response
Noted. In the second version of the CLH report the table was still included, however RAC has not taken the erroneous information into account for the assessment.