Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Lenacil (ISO)

EC number: 218-499-0
CAS number: 2164-08-1

CLH-O-0000002461-82-02/A2

Adopted

5 December 2013

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LENACIL (ISO); 3-CYCLOHEXYL-6,7-DIHYDRO-1H-CYCLOPENTA[D]PYRIMIDINE-2,4(3H,5H)-DIONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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

Substance name: lenacil (ISO); 3-cyclohexyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione
EC number: 218-499-0
CAS number: 2164-08-1

Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	France		MemberState	1
Comment received				
France agrees with the classification proposal.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany		MemberState	2
Comment received				
The German CA supports the proposed classification as Aquatic acute 1, H400 and Aquatic chronic. 1, H410.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	United States	E.I. DuPont de Nemours	Company-Manufacturer	3
Comment received				
(ECHA note: The commenter has provided only attachment which is copied below.)				

Comments on Proposed Classification of Lenacil (2164-08-1)

We kindly submit for consideration by the Risk Assessment Committee (RAC) our reply to a Proposal for Harmonized Classification and Labelling for Lenacil.

Proposed classification based on CLP and Directive 67/548/EEC criteria:

Current proposal for consideration by RAC	• Aquatic Acute category 1, H400, M-factor = 10; • Aquatic Chronic category 1, H410, M-factor = 10	• N, R50/53 • SCL: concentration Cn in % • N, R50/53 Cn≥2.5 • N, R51/53 0.25≤Cn<2.5 • R52/53 0.025≤Cn<0.25
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	• Aquatic Acute category 1, H400, M-factor = 10; • Aquatic Chronic category 1, H410, M-factor = 10	• N, R50/53 • SCL: concentration Cn in % • N, R50/53 Cn≥2.5 • N, R51/53 0.25≤Cn<2.5 • R52/53 0.025≤Cn<0.25

Proposed labelling:

Directive 67/548/EEC:

Indication of danger: N
R-phrases: R50-53
S-phrases: S35 and S57

CLP Regulation:

Signal word: Warning
Hazard statements: H410: Very toxic to aquatic life with long lasting effects
Precautionary statements:
Prevention – P273: Avoid release to the environment
Response – P391: Collect spillage
Disposal – P501: Dispose of contents/container in accordance with local regulations

Introduction and Background

The rapporteur has prepared a CLH proposal based mainly on the information presented in the assessment of lenacil under Directive 91/414/EEC. Industry agrees fully with the proposal as presented by the rapporteur as summarized in the CLH report, extracted below:

"None of the physico-chemical properties displayed by Lenacil require classification according to the criteria applied under the Dangerous Substances Directive (DSD) or the Classification, Labelling and Packaging Regulation (CLP).

In mammals, Lenacil is not acutely toxic via oral, dermal or inhalation routes; is not irritating to skin or eyes nor shows sensitising potential. In short-term toxicity studies rats and dogs were the most sensitive species, showing alterations in the liver and thyroid function: the relevant oral NOAELs are 40.6 mg/kg bw/d and 44 mg/kg bw/d (rats and dogs, respectively; 13-week studies), which do not result in classification. Based on results from a battery of mutagenicity investigations Lenacil is unlikely to be genotoxic. None of these results necessitated classification.

Increased incidences of malignant mammary adenocarcinomas were observed in rats and were initially considered to be of relevance for humans. In mice, increased incidences of single alveolar tumours (adenoma and carcinoma) were observed in the lungs and were considered of equivocal relevance for humans. Based on mammary gland and lung tumour incidence in rats and mice, the EFSA proposed classification under the DSD for Lenacil as Carc. cat.3 (R40) '*Limited evidence of a carcinogenic effect*'.

However, supplementary evidence submitted to the RMS after the EU review, in the form of a review of potential tumorigenicity, indicated that there are no substantive data to indicate any carcinogenic effects of Lenacil administration which are relevant for the human hazard assessment. The 'Carc. Cat. 3' (Xn, R40) classification (according to DSD criteria) was proposed by the EFSA in the conclusions to the DAR. The proposed classification is not supported in the proposed CLP classification on the basis of insufficient evidence of human carcinogenic hazard. The current proposal of no classification is supported by a position paper prepared by D Andrew, TSGE (Lenacil: Review of Carcinogenicity and Proposed R40 Classification. Report No. TSGE 19-10-05. Andrew, D. 2011) which reviews extensive historical background data relating to both tumour types, and which concludes an absence of hazard for human health assessments. The confidential document is added in chapter 13 of the IUCLID.

The relevant NOAEL from the long-term toxicity and carcinogenicity studies is 12 mg/kg bw/d (rat study). No specific effect on reproductive parameters was found in multi-generation studies with rats: the relevant parental NOAEL is 81.9 mg/kg bw/d, the offspring NOAEL is 1727 mg/kg bw/d and the reproductive toxicity NOAEL is 4300 mg/kg bw/d. When tested in developmental toxicity studies, Lenacil did not cause malformations in the rat and rabbits: the relevant maternal NOAEL in both species is 1000 mg/kg bw/d; the relevant developmental NOAELs are 1000 and 4000 mg/kg bw/d in rat and rabbits respectively (highest dose level tested). None of the reproductive or

developmental toxicity investigations resulted in any classification requirements for Lenacil.

Several studies (both acute and long-term) were available on aquatic organisms (fish, daphnia, algae and higher plants) for technical Lenacil, formulation product and the metabolites IN-KE 121 and IN-KF 313. Algae and aquatic plants were the most sensitive organisms. Regarding the degradability, Lenacil can not be considered rapidly degradable.

The endpoint driving the environmental classification was observed in a laboratory study with Lenacil and the unicellular green alga *Pseudokirchneriella subcapitata* (72h E_rC_{50} = 0.016 mg/L).

New data have been requested following the outcome of the EU review. These will not change the proposed classification and are therefore not discussed here."

Conclusion

The rapporteur has presented a clear and accurate classification proposal according to the CLP criteria based on a careful review of all the data and industry concurs with the CLH proposal.

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Dossier Submitter's Response
Noted. No further comment needed.
RAC's response
Noted. Detailed consideration of tumours incidences and historical control data shows that in particular the incidence of mammary adenocarcinomas in the female rats is elevated significantly and above the expected spontaneous incidence and RAC considers that a classification Carc 2 – H351 is appropriate for lenacil on this basis.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany		MemberState	3
Comment received				
The RMS (Begium, Addendum, February 2009) and the EFSA (EFSA Journal 2009; 7(10):1326) proposed the classification with R40 (DSD) or H351 (CLP), as a carcinogen due to a significant incidence of mammary adenocarcinoma in rats. However, the range of an updated database of historical control data, provided in April 2011, covers the experimental results of mammary adenocarcinoma which are within these updated historical control data. In agreement with the CLH Report for LENACIL (Belgium, Version number: 3; April 2013) no classification with R40 (DSD) or H351 (CLP), as a carcinogen is required for Lenacil.				

Dossier Submitter's Response
Noted.
RAC's response
Noted. Detailed consideration of tumours incidences and historical control data shows that in particular the incidence of mammary adenocarcinomas in the female rats is elevated significantly and above the expected spontaneous incidence and RAC considers that a classification Carc 2 – H351 is appropriate for lenacil on this basis.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	France		MemberState	5
Comment received				
We are in agreement with the DSD and the CLP proposals of classification for environmental hazards.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.06.2013	Sweden		MemberState	6
Comment received				
SE supports the environmental classification of Lenacil (CAS No 2164-08-1) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Denmark		MemberState	7
Comment received				
Agree with the proposed classification for acute and chronic toxicity. And agreed to the aplied M-factor.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number

26.06.2013	France		MemberState	8
Comment received				
Please RMS adds the minimum purity and max content of impurities in confidential part of IUCLID.				
Dossier Submitter's Response				
The minimum purity = 975 g/kg. From this value the maximum content of impurities = 25 g/kg is inferred.				
RAC's response				
Noted.				

ATTACHMENTS RECEIVED:

1. **Comments on Proposed Classification of Lenacil (2164-08-1)** (filename: Industry Response to CLH proposal for Lenacil.pdf), submitted on 28.06.2013 by United States (*ECHA note: This attachment has been copied under the section GENERAL COMMENTS)*