Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

pyriproxyfen (ISO); 2-(1-methyl-2-(4-phenoxyphenoxy)ethoxy)pyridine; 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy) propyl ether

EC Number: 429-800-1
CAS Number: 95737-68-1

CLH-O-0000007433-76-01/F

Adopted

14 March 2024

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PYRIPROXYFEN (ISO); 2-(1-METHYL-2-(4-PHENOXYPHENOXY)ETHOXY)PYRIDINE; 4-PHENOXYPHENYL (*RS*)-2-(2-PYRIDYLOXY) PROPYL ETHER

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: pyriproxyfen (ISO); 2-(1-methyl-2-(4-phenoxyphenoxy)ethoxy)pyridine; 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy) propyl ether
EC number: 429-800-1
CAS number: 95737-68-1
Dossier submitter: The Netherlands

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Belgium		MemberState	1
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (invertebrates: Mysidopsis Bahia with 96h LC50 = 0.065 mg/L, invertebrates: Daphnia magna with 21d NOEC = 0.0000088 mg/L), the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of regulation 1272/2008, as Aquatic acute 1, H400 and Aquatic Chronic 1, H410. In view of the proposed classification and toxicity band for acute toxicity between 0.01mg/l and 0.1 mg/l, an M-factor for acute toxicity of 10 can be assigned and an M-factor for chronic toxicity of 10 000 (not rapidly degradable substance and 0.000001 mg/L <NOEC ≤0.00001 mg/L) The proposed environmental classification is supported.				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2023	United Kingdom	Health and Safety Executive	National Authority	2

Comment received
Pyriproxyfen (ISO) (EC: 429-800-1; CAS: 95737-68-1). The key study for aquatic chronic classification is the Daphnia magna reproduction study by Blakemore et al 1992 (with additional statistical analysis by Lewis et al, 2016). The GLP study is well reported following US EPA Pesticide Assessment Guidelines, 72-4(b) and broadly follows OECD TG 211. However, details of DMF solvent concentrations are not included in the CLH report and the RAR indicates that solvent concentrations in treatments may have exceeded the solvent control concentration…'The concentration of DMF in the vehicle control was a factor of 17 lower than in the 20 ng/L test concentration' While this comment appears to relate to Test 2, please can the DS provide details of solvent concentrations in controls and treatments for both Test 1 and 2. This information is important to consider the potential impact of the solvent and aid interpretation of the statistically significant Test 2 NOEC of 0.00002 mg/L (mm) when comparing treatments to the solvent control only. The CLH report considers that the study 21-day NOEC is 0.000015 mg/L (mm) from Test 1. We are unclear of the basis of this endpoint given no statistically significant effects were observed in Test 1 when treatments were compared to pooled or solvent controls. The RAR states that '… while not significant, young / adult reproduction days was slightly reduced at the mean measured concentration of 0.000031 mg a.s./L' indicating this is the basis of the NOEC at the 0.000015 mg/L (mm) treatment below it. On this basis, we would consider a statistically significant NOEC should take precedence – this would result in a 21-day NOEC ≥0.000031 mg/L (mm) from Test 1. The quoted 21-day EC10(reproduction) of 0.0000088 mg/L (mm) is derived from effects observed at all treatments in Test 2. It is below the lowest treatment (0.00002 mg/L mm) and therefore outside of the model. OECD and ECHA guidance (ECHA, 2010) recognise that estimated ECx values outside the concentration-response modelling are subject to great deal of uncertainty. In addition, the 95% CIs of 0.0000026 to 0.000016 mg/L span 2 hazard classification bands. While preference is to use an EC10 in place of a NOEC if available, we recognise the uncertainty with the extrapolated EC10 and consider a NOEC may be more statistically reliable in this instance. Alternatively, we note a 21-day EC20(reproduction) of 0.000018 mg/L is also available – this is just below the lowest Test 2 treatment of 0.00002 mg/L which represents the Test 2 NOEC if comparing to the solvent control. Considering the long-term NOEC, EC10 and EC20 endpoints from the Blakemore et al 1992 study, the Test 2 EC10(reproduction) is the most stringent (resulting in a chronic M-factor of 10000) and is the only endpoint in the 0.000001<NOEC/ECx≤0.00001 mg/L range. However, it is the endpoint with the highest degree of uncertainty. We note the DS calculated a Test 2 EC10(reproduction) of 0.0000123 mg/L which would result in an M-factor of 1000. Given the Test 1 NOEC, the ECx endpoint with less uncertainty (EC20), and potential Test 2 NOEC (when comparing to the solvent control) lie in the 0.00001<NOEC/ECx≤0.0001 mg/L range, it appears that a weight of evidence supports a chronic M-factor of 1000. ECHA (2010) Guidance on information requirements and chemical safety assessment Chapter R.10: Characterisation of dose [concentration]-response for environment
Dossier Submitter's Response
Thank you for your comment, DS is confident in RAC's response and confirmation by other MS. For reproduction, the solvent control was not statistically different from the blank control (t-test, t = 1.4156, df = 5.8985, p-value = 0.2075). Thus, the controls were

correctly pooled for the statistical analysis and conclusion by DS.Furthermore, in *the RAR it was concluded that the slight but significant effects observed in the 2nd test are not due to the use of the solvent (DMF), as a downward trend over the entire concentration range tested was observed for both parent length and live young per adult."*

RAC's response

RAC agrees with the DS response concerning the vehicle control. There is no information available on the details of the DMF solvent concentrations.

RAC notes the NA comments on EC_{10} of 8.8 ng/L. However, the weight of evidence approach was not supported by RAC. RAC agrees with the DS to consider Test 1 and Test 2 separately. The DS reanalysis of the study results noted that the EC_{10} was derived from combined dataset from the 1st and the 2nd study and RAC agrees that it can not be considered relevant for classification. In addition the reproductive output in this study had been expressed as young per adult per reproductive day instead of total number of living offspring per parent animal as required in the OECD 211 (version 2012). The DS calculated an EC_{10} of 13.3 ng/L which is considered reliable by RAC. This is supported by the NOEC of 15 ng/L.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2023	France		MemberState	3

Comment received

Thank you for giving us the opportunity to comment this CLH proposal.
We had a look to the data in the CAR of pyriproxyfen (NL, 21 September 2012) and have the following comments:

In the CAR, there are mesocosm studies (R.P.A van Wijngaarden, 2004) which are considered key acute studies and from which a LOECcommunity of 5 µga.s./L was derived (Ri=2). This study was used to calculate a PNEC (acute) in the CAR dossier. We do not have access to the Doc IIIA to check if an EC50 is available for this study. As it is the lowest endpoint for acute studies, we ask ourselves whether this endpoint needs to be checked to determine if it should appear in section 11.5 of the CLH report. In this case, the acute M factor could be increased (100). Moreover, the BPR dossier contains an efficacy test on Aedes aegypti from which EC50 (6h) of 21.4 ng/L is derived. This endpoint was not used in the BPR dossier because it is a target species. But as this target species is not claimed in the PPPR dossier, we wonder if this endpoint on Aedes should be taken into account for the acute classification.

Please also note that Koc value in the CLH report is different from the BPR endpoint. In the frame of the one substance/one health assessment, a harmonization of the endpoint would be valuable.
Please also note that the BPR dossier seems to contain an additional fish bioaccumulation study. However it will not change the conclusion.

We also have typo comments:
In Table 69: replace "HC biphasic model" by "HS biphasic model".
In Table 72: the data from the first line of the table (acute toxicity to fish) does not appear.
In Table 73: there is the same problem with the amphibian data.

Dossier Submitter's Response

In the regulation no use for mesocosms is mentioned, it is about endpoints from fish, algae and/or invertebrates. Community endpoints are not used in CLH. At this point in the procedure DS cannot alter the report for typo's anymore.
RAC's response
RAC does not consider the plankton dominated microcosm experiment with the formulation Pyriproxyfen EC10 relevant or reliable for aquatic hazard classification purposes. There is no EC50 available in the study report. The CLH Report states: "The RAR also reports studies conducted with the formulation Pyriproxyfen 10EC (S-71639). According to the Safety Data Sheet included in the RAR (Volume 3 CP B4) the formulation also contains Hydrocarbons, C10, aromatics, <1% naphthalene (CAS not available) at an amount of ≥10% w/v; 2-ethylhexan-1-ol (CAS 104-76-7) at >1% w/v and calcium dodecylbenzenesulphonate (CAS 26264-06-2) at >1% w/v. As these substances can affect the outcome of the aquatic toxicity tests (i.e. the latter two substances have been self-classified as affecting the aquatic environment), no reliable effect concentrations can be derived for pyriproxyfen from the test performed with the formulation. Therefore, the aquatic toxicity tests conducted with formulation are not further discussed." Aedes aegypti study: The guideline for the study was WHO (1981) Instruction for determining the susceptibility or resistance of mosquito larvae to insect developmental inhibitors (WHO/UBC/91.812). The result mentioned is from a continuous exposure method (the larvae were exposed continuously to the test solution until emergence). Test concentrations were not measured and RAC is of the opinion that the results are not reliable for classification purposes. (Document IIIA Section 7 of the CAR, May 2012). RAC could not find an additional fish bioaccumulation study in addition to studies presented in the CLH Report (*Lepomis macrochirus* and *Cyprinus carpio*).

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2023	Germany		MemberState	4
Comment received				
11.1 Rapid degradability of organic substances We agree with the conclusion that pyriproxifen is not rapidly degradable based on the available data. However, with respect to the water sediment degradation study (Lewis, 2000a) the DT50 values reported in the CLH-report (Pond = 22.12 d, Lake = 27.8 d at 20°C) differ from those reported in the CAR of 2012 (Pond = 5.4 d, Lake = 7.8 d at 20°C). Could you please check and explain this difference? 11.4 Bioaccumulation: Please note that the study on fish bioconcentration in C. carpio was judged as "not reliable" during evaluation for the renewal assessment report for pyriproxyfen (e.g. no kinetic BCF calculated, not enough consecutive analyses within ±20 % to derive a steady state, only two fish analysed per concentration). It would therefore be more appropriate to classify this study as supportive information only, and not as key study. Furthermore, according to our data the study is dated from 1998 and not 1993. Please check and correct the date, if necessary. We agree with the overall conclusion that the substance pyriproxyfen is classified as bioaccumulative for CLH-purposes (BCF > 500), primarily based on the bioconcentration study on L. macrochirus.				

Classification: We agree with the classifications as aquatic acute 1, M = 10 based on the EC50 of 0.065 mg/L for A. bahia and aquatic chronic 1, M = 10000 based on the EC10 of 0.0000088 mg/L for D. magna.
Dossier Submitter's Response
In the CLH proposal it is explained how these values were obtained. In the RAR DT50 values of 4.8 and 5.7 d were reported obtained by DFOP and HS, respectively. These are overall DT50 values though that consider both the faster initial and the subsequent slower portions of the decline curve. These values do not correspond to SFO kinetics. Pseudo-SFO were derived from these biphasic models using the rules of FOCUS Degradation Kinetics, thereby using slow phase k2 to derive the reported DT50 valeus.
RAC's response
RAC agrees with the DS regarding the comment on the DT50 values. The explanation is included in the CLH Report. The fish bioconcentration study in *C. carpio* is classified as supportive in the CLH Report. RAC agrees to consider pyriproxyphen having a potential for bioaccumulation based on the *L. macrochirus* study.