Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

(5-chloro-2-methoxy-4-methyl-3-pyridyl)(4,5,6-trimethoxy-*o*-tolyl)methanone; pyriofenone

EC Number: 692-456-8
CAS Number: 688046-61-9

CLH-O-0000001412-86-287/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (5-CHLORO-2-METHOXY-4-METHYL-3-PYRIDYL)(4,5,6-TRIMETHOXY-*O*-TOLYL)METHANONE; PYRIOFENONE

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.

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Substance name: (5-chloro-2-methoxy-4-methyl-3-pyridyl)(4,5,6-trimethoxy-*o*-tolyl)methanone; pyriofenone
EC number: 692-456-8
CAS number: 688046-61-9
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Belgium		MemberState	1
Comment received				
BECA thanks UKCA for the CLH proposal				
Dossier Submitter's Response				
Noted, thank you for your support.				
RAC's response				
Noted, thank you for the support.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2018	Belgium	ISK Biosciences Europe NV	Company-Manufacturer	2
Comment received				
The Proposal for Harmonised Classification and Labelling for pyriofenone includes a proposal for classification as Carc. 2 - H351 as stated in table 2.1 of the CLH report for pyriofenone. ISK Biosciences Europe doesn't agree with this proposal. A comprehensive review of the data concludes that it is considered that the hepatocellular neoplastic lesions, found in the male rat, are unlikely to be related to treatment and not relevant to humans. To support its view ISK Biosciences Europe have summarized their argumentation in a summary document with reference n° RSA/ISK005_4160_001 (including references)and which is uploaded as attachment to this comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment ISK_comments_public consultation_pyriofenone.rar				

Dossier Submitter's Response
Thank you for your comments and the provision of a review of the carcinogenic effects of pyriofenone. The conclusions raised in your report were: A rat carcinogenicity study with pyriofenone showed low incidences of hepatocellular adenomas and carcinomas in males only at above maximum tolerated dose levels that compromised the survival of the animals. The increased incidences of hepatic neoplastic lesions were not statistically significant when compared to concurrent controls and were within the incidence range observed in relevant historical control databases. After a comprehensive review of the data it is considered that the hepatocellular neoplastic lesions, found in the male rat, are unlikely to be related to treatment since they are within the HCD for this tumour type in this sex/strain of rat and the fact that they were only seen at excessive dose levels is highly suggestive that they will not be relevant to humans since it is highly improbable that humans would be exposed to these extreme doses for such a prolonged period of time. As noted in the CLH dossier, increased mortality was seen among top dose male rats during the last 3 weeks of this study when compared to all the other dose groups. In week 101, cumulative mortality was 14 %; in the final week 104, cumulative mortality was 17 %. Strictly, this top dose was therefore above the MTD recommended for a carcinogenicity study. However, on the basis of the individual animal data, there was no link seen between increased mortality and the incidence of liver tumours. In the animals found dead before the end of the study, 3/17 (18 %) were found to have liver adenoma and 1/17 (6 %) had carcinoma of the liver. In those surviving to the end of the study, 3/33 (9 %) had adenoma of the liver and 1/33 (3 %) had liver carcinoma. Historical control data (HCD) were provided from the laboratory where the carcinogenicity study in rats was carried out. This included the incidences of hepatocellular adenoma and carcinoma in control male F344 rats in studies carried out from 1978 – 2011. The incidence ranges of adenoma and carcinoma during this period were 0 – 12 % and 0 – 4 %, respectively. The findings in the concurrent study are within these ranges, however according to CLP, HCD should be contemporary to the study being evaluated (e.g. within a period of up to 5 years of the study) and data older than this should be used with caution and acknowledgement of its lower relevance and reliability. Further, closer analysis of the HCD showed that the majority of the higher incidences of adenoma and carcinoma occurred between the years 1980 and 1986, which indicates that tumour incidences in control animals may have changed with time. Taking this into account, and utilising only the studies within a 5 year time period of the concurrent study, the incidence of adenoma ranged from 0 – 4 % and carcinoma incidence was 0. Thus the finding of adenoma (12 %) at the top dose of 5000 ppm was above the HCD data range. It is noted that the control incidence of 8 % in this study was also above the HCD. The findings of carcinoma in the low, mid and top dose group (2, 2 and 4 %) were also all above the HCD range. Whilst it might be improbable that humans would be exposed to extreme doses for a prolongued period of time, the purpose of classification and labelling is to assess the intrinsic hazard of a substance and not the risk. Therefore, the DS stands by their view that there is limited evidence of carcinogenicity following treatment of pyriofenone in male rats.

RAC's response
RAC supports the DS in their comments. There is cause for concern regarding the liver tumours in F344 rats and the available mechanistic data is insufficient to dispel the uncertainties and data gaps that exist. A more robust mechanistic data package is needed before consideration of no classification can be proposed.

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2018	Germany		MemberState	3
Comment received				
The proposed classification as Carc. 2 is supported. However, the statistical analysis for hepatocellular carcinoma should be complemented by trend testing (Cochrane-Armitage, Peto or Poly3 as appropriate). There appears to be a dose dependent increase in HCC in both species. One minor comment relates to page 44 in chapter 10.9.5 (Comparison with CLP criteria): with respect to historical control data it reads "laboratory control data was not provided". In contrast on page 27 it is stated "Historical control data (HCD) were provided from the laboratory where the carcinogenicity study in rats was carried out." This should be harmonized.				
Dossier Submitter's Response				
Thank you for your comment. According to the Manufacturers review of the data (provided during the public consultation), a Peto test was carried out and showed no statistical significance. In relation to the laboratory control data: on page 44, paragraph 3, it should read "laboratory control data contemporary to the current study was not provided".				
RAC's response				
Noted and agreed.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Finland		MemberState	4
Comment received				
FI CA supports the conclusions that pyriofenone is considered neither as potentionally bioaccumulative nor as rapidly degradable for the classification purposes. Adequate acute and chronic toxicity data are available for all three trophic levels. The study which leads to the most stringent outcome is Daphnia magna reproduction test (OECD 211). According to the study, the chronic toxicity NOEC value is between 0.01-0.1 mg/L; therefore, resulting in M-factor of 1. Based on the available information and the classification criteria, FI CA supports the proposed classification of Aquatic Chronic 1, H410 with M-factor of 1 for pyriofenone.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

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Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Belgium		MemberState	5
Comment received				
Based on the data as presented in the CLH dossier, BE CA supports the proposed classification of pyriofenone : Aquatic Chronic 1, H410 and Mchronic=1 Aquatic Chronic 1, H410 is warranted : the substance is not rapidly degradable and the chronic NOEC for the most sensitive species of the 3 tested trophic levels is <0.1 mg/L (aquatic invertebrates -Daphnia magna with a 21dNOEC= 0.0899 mg/l). In view of the toxicity band for chronic toxicity between 0.01mg/l and 0.1mg/l, a chronicM-factor of 1 is to be assigned. Classification for aquatic acute toxicity is not warranted : all acute L(E)50>1mg/L.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2018	Germany		MemberState	6
Comment received				
Page 80 point 11.6.1 chronic toxicity to fish: Study 1- Anon.(2008a) = Burke, Manson and Scholey (2008): The study results with Pimephales promelas from the ELS toxicity test are not completely. The 28-day NOEC for wet weight of fish is 0.435 mg as/L and is below the given NOEC of 1.27 mg as/L for mortality, hatch and length of fish. Page 81ff point 11.7.2 comparison with CLP criteria for long-term aquatic hazard: The lowest NOEC for fish is therefore NOEC of 0.435 mg as/L from the ELS toxicity test with Pimephales promelas, instead of 1.27 mg as/L. However, invertebrates are the most chronically sensitive trophic level with a NOEC of 0.0899 mg as/L for Daphnia magna.				
Dossier Submitter's Response				
Noted. According to Volume 3, section B9 of the DAR and the list of endpoints in the EFSA conclusion, the NOEC for fish was agreed to be 1.27 mg a.s./l.				
RAC's response				
RAC does not have possibility to evaluate results completely of the study with *Pimephales promelas* from the ELS toxicity test however in the DAR and the list of endpoints of EFSA conclusion, the NOEC for fish was agreed to be 1.27 mgL. As well that does not change the proposed classification or M-factor as classification is based on results of most sensitive spieces *Daphnia magna*.				

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Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	France		MemberState	7
Comment received				
FR agrees with the proposed classification for environmental hazards and chronic M factor value.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. ISK_comments_public consultation_pyriofenone.rar [Please refer to comment No. 2]