Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2′,4′-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide

EC Number: -
CAS Number: 83164-33-4

CLH-O-0000001412-86-285/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIFLUFENICAN (ISO); N-(2,4-DIFLUOROPHENYL)-2-[3-(TRIFLUOROMETHYL)PHENOXY]-3-PYRIDINECARBOXAMIDE; 2',4'-DIFLUORO-2-(α,α,α-TRIFLUORO-M-TOLYLOXY) NICOTINANILIDE

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: diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2',4'-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide
EC number: -
CAS number: 83164-33-4
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	Germany	Bayer AG	Company-Manufacturer	1
Comment received				
We would like to provide our comments on the environmental fate topic. Please find the corresponding document in the zip. archive attached. Thank you. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Diflufenican - Comments for ECHA.zip				
Dossier Submitter's Response				
Thank you. Please find a response in comment 7.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2018	Germany		MemberState	2
Comment received				
DE-CA supports the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and the acute/chronic M-factor of 1000/100. Nevertheless in our view a classification as Repr. 2 (H361f) might be justified.				
Dossier Submitter's Response				
Thank you. Support for proposal of classification for environmental hazards is noted. Please see a response to your comment regarding classification for reproductive toxicity (comment number 4).				

RAC's response
As regards classification for reproductive toxicity, see response to comment 4.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2018	France		MemberState	3
Comment received				
FR agrees that no classification is warranted for reproductive or developmental toxicity.				
Dossier Submitter's Response				
Noted, thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2018	Germany		MemberState	4
Comment received				
In the 2-generation study with rats dystocia was observed in the high-dose group in both generations. Dystocia is listed in the CLP guidance as an effect that might lead to a classification for sexual function and fertility, since it is an adverse effect on pregnancy outcomes. The reasoning for non-classification is not comprehensible: 1. A low incidence of dystocia (5.1%) was observed, but clearly above the historical control data (0.2-0.5%). 2. According to DS, dystocia occurred only at a dose that exceeds the limit dose, but the exceedance is low (F0: 1042 mg/kg bw/d, F1: 1168 mg/kg bw/d). It should be rather discussed the significance of these effects at limit dose. 3. According to the dossier submitter maternal toxicity was evident at this dose, which means reduced body weights of the dams up to 17 % compared to the control group. However, the decrease in body weight was possibly due to the unpalatable nature of diflufenican as indicated by a decrease in food consumption (up to 20%). Furthermore, it is not known that a reduced body weight of the dams causes dystocia. 4. No evidence from the reproductive toxicity or repeated dose toxicity studies that diflufenican acted through a specific mode-of-action that might result in dystocia is no justification for for non-classification (see also RAC opinion for 2-methylimidazole). 5. Since effects were observed predominantly after second mating, the relevance of bioaccumulation of diflufenican in fat, gonads and uteri should be additionally assessed. In summary, a classification in category 2 (H361f) should be considered by RAC.				
Dossier Submitter's Response				
Thank you for your comment.				

There are a number of reasons why dystocia might occur in animals. These include (but are not limited to) disturbances in endocrinological control of gestation and parturition, physical malformations of the reproductive tract or large or malformed foetuses and the general health status of the dam.

Examination of the reproductive tracts both in the 2-generation study and in other repeat-dose studies conducted with diflufenican showed no macroscopic or microscopic abnormalities which would indicate an alteration in either endocrine function or in overall reproductive function.

Body weight and body weight gain were sharply impacted by diflufenican administration during the 2-generation study. In general, body weight was reduced in a dose-dependant manner from 2500 ppm. In the F0 adults, this decrease was evident from week 3 of the pre-mating phase, while in subsequent generations body weight was reduced from the first week of treatment. There were no studies available to show that this reduction in body weight was specifically due to unpalatability of the test substance. Without these studies it is hard to say if the rats were not gaining weight because the food was unpalatable or if they were not eating due to the general toxic effects of the test substance.

As mentioned in the CLH, toxicokinetic studies indicated slower excretion of diflufenican from fat, gonads and uteri. However, tissue accumulation of radioactive material in general was reported to be low, with < 0.67 % of the dose retained in tissues after 168 h. Therefore, the relevance of these findings is unclear.

Overall, the DS believes that the incidences of dystocia observed in top-dose animals only were likely to be secondary to the non-specific general toxicity observed. The effect was only observed in dams that received a dose of diflufenican exceeding the limit dose of 1000 mg/kg bw/day. No other signs of disruption to the reproductive system were observed. Therefore, we conclude that the effects observed do not provide clear evidence of an effect on sexual function or fertility and no classification is warrented.

RAC's response

RAC is of the opinion that the findings of dystocia provide some evidence of an effect on sexual function or fertility. However, other toxic effects observed and the fact that the effects is mainly observed at a dose level exceeding the limit dose decrease the concern. Therefore, RAC is of the opinion that no classification is justified for adverse effects on sexual function and fertility.

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	Germany	Bayer AG	Company-Manufacturer	5

Comment received

We would like to provide a Position Paper on the reproductive toxicity topic. Please find the corresponding document in the zip. archive attached. Thank you.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Diflufenican - Comments for ECHA.zip

Dossier Submitter's Response

Thank you for the clarification regarding the treatment period of P0 and F1 animals. As you mention in your position paper, dietary administration of diflufenican was continuous from the start of the pre-mating period to sacrifice of the respective adult animals after

the weaning of the F2 pups. There was no cessation of treatment prior to mating to produce the second litter of pups in the F1 and F2 generations, respectively. We apologise for any lack of clarity regarding the description of mortalities in Table 2 of the CLH dossier. As mentioned in your position paper, the female dosed with 500 ppm diflufenican died on day 18 of the mating period and was not pregnant. We believe that Table 6 of the CLH dossier clearly shows the incidence of perinatal mortality and deaths occurring to potential dystocia. We note your support for the position of no classification for this endpoint.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2018	France		MemberState	6
Comment received				
FR agrees with the classification and M factors (acute and chronic) proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	Germany	Bayer AG	Company-Manufacturer	7
Comment received				
We would like to provide our view on the bioaccumulation topic. Please find the corresponding document in the zip. archive attached. Thank you. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Diflufenican - Comments for ECHA.zip				
Dossier Submitter's Response				
Thank you for your comments. 1. **Sections 11.1.4.3 "Water and water-sediment degradation data (including simulation studies) - Water/sediment studies" (p. 46/47) & 11.2.1 "Summary of data/information on environmental transformation" (p. 47)** You will note in the CLH that the DT_{50} values were not normalised to 12 °C as it was agreed that correction of degredation rates to more environmentally realistic temperatures would not change the overall rapid degradability determination. 2. **Section 11.3 "Environmental fate and other relevant information" – "Soil adsorption" (p.48)** 2.1 Range of KFOC values, calculation of geometric mean KFOC and arithmetic mean 1/n				

The DS agrees that the study (Anon 2012a) contains several deviations from the OECD 106 guideline (as noted in your comments) and it is acknowledged that the endpoint calculated from these soils should be treated with caution. However, overall, we consider the study to be acceptable. It is noted that, ultimately, the interpretation of this study does not impact on the overall classification of the substance.

We note that, the statistical fit of the Freundlich isotherms were less than 0.975 for four out of six soils. The DS considered that the R^2 was low for some soils because of large variability in the replicate samples. The OECD 106 checklist highlights that 0.975 is not a definitive cut-off and that supporting information regarding the goodness of fit obtained from the plot of residuals can also be used. These plots were acceptable and therefore the soils with lower R^2 values could not be excluded for this reason alone. Were this study to be excluded from the assessment, the overall geomean Koc would increase from 2115 to 3400 ml/g and the overall arithmetic mean 1/n value would increase from 0.866 to 0.927. The result of this would not change the conclusion that diflufenican appears to be strongly absorbed to soil.

As noted above, in any case, the interpretation of this study does not impact on the classification of the substance.

2.2 Proposed pH-dependent adsorption of diflufenican

In our opinion, the data provided do indicate that K_{FOC} is pH dependent. We have reservations about using a correlation test (Kendall test), as suggested in your comments, to imply directional causation. Kendall's Tau is a correlation test, therefore it doesn't indicate whether one variable controls the other or not. There can be no conclusion made regarding the *existence* or the *direction* of a cause-and-effect relationship only from the fact that variable A and B are correlated. Determining whether there is an actual cause-and-effect relationship requires further investigation, even when the relationship between *A* and *B* is statistically significant. For this you need a regression analysis - regression/correlation are not interchangeable with one another. A linear regression model, as used by the DS, indicates that pH is a good and significant indicator of K_{FOC} ($r = 0.6732$, $p < 0.05$ for Simmonds and Brett, 2006) and therefore the DS considers K_{FOC} to be pH-dependent. That said, as with comment 2.1, the pH dependence does not impact on the proposed classification of the substance.

Thank you for the information regarding aquatic toxicity, provided in the document "Diflufenican: comments on the CLH dossier – Ecotoxicology Aquatic". Regarding the comments relating to discrepencies in lipid analysis (study Anon 2008), an amendment to the original study report by the performing CRO has not yet been made available to the UK. However, we have had sight of a statement provided by the Company.

In this statement, the Company concludes that the lipid content of the study by Anon 2008 is exceptionally low and the fish used for lipid determination were not representative of the fish used for a.s. analysis as requested b OECD test guidelines 305 (2012). The Company conclude that the lipid values obtained in this study should have been corrected based on the $factor_{nonedible/edible}$ derived from fish used for a.s. analysis. This would bring the BCF value more inline with the second study available (Anon. 1998a).

The details provided by the Company indicate that the normalised BCF value included in the CLH report for the Anon 2008 study may indeed be unreliable. However, this point does not impact on the conclusions in the CLH report, including the assessment of bioaccumulation potential and the proposed classification. All relevant data should be made available to RAC for due consideration and taken into account for the final classification.
RAC's response
RAC agrees that 20 °C or higher are not environmental realistic temperatures for European surface water bodies and that DT_{50} values should always be normalised to 12 °C as it was agreed to be more environmentally realistic temperatures. In the case of diflufenican, it clearly does not affect the conclusion on degradability since diflufenican is very persistent in the environment. RAC notes the comment that the normalised BCF value for the Anonymous (2008) study may indeed be unreliable. RAC has not assessed this further, because this does not impact the conclusion that diflufenican has a high potential to bioaccumulate.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Finland		MemberState	8
Comment received				
FI CA supports the conclusion that diflufenican is not rapidly degradable but potentially bioaccumulative. The lowest acute toxicity was 72 h EC50 value of 0.0006 mg/L and the lowest chronic toxicity was 72 h EC10 value of 0.000157 mg/L for alga R. subcapitata. We support the use of EC10 value over NOEC to determine the chronic classification in this case. Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 1000 and Aquatic Chronic 1, H411 with M-factor of 100 for diflufenican.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Diflufenican - Comments for ECHA.zip [Please refer to comment No. 1, 5, 7]