Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

fenpyroximate (ISO); tert-butyl 4-[({[(E)-(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate

EC number: -

CAS number: 134098-61-6

CLH-O-0000002368-70-02/F

Adopted

5 December 2013

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: fenpyroximate (ISO); tert-butyl 4-[({[(E)-(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate
EC number: -
CAS number: 134098-61-6
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.06.2013	United Kingdom	Nichino Europe Co., Ltd., Cambridge, UK	Company-Manufacturer	1
Comment received				
Chapter 1.1 and 1.2 (tables 5 and 6) IUPAC name: The IUPAC name in CLH report differs from the IUPAC name used in EFSA Scientific Report (2008) 197, 1-104, Conclusion on the peer review of fenpyroximate, and Commission Directive 2008/107/EC of 25 November 2008. Therefore we ask for harmonisation to the ISO common name (IUPAC): tert-butyl (E)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneaminooxy)-p-toluate . Please take care "tert" and "E" are in italics. With same reason CAS name should be the same as the latest CAS name in ISO: (E)-1,1-dimethylethyl 4-[[[[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino]oxy]methyl]benzoate Please take care "E" and "H" are in italics.				
Dossier Submitter's Response				
Thank you for your comment. The IUPAC and CAS name was submitted by ECHA during the accordance check. Therefore no changes have been made.				
RAC's response				
ECHA prefers to use IUPAC names based on the default IUPAC rules used by the ECHA substance identity team (who provided the IUPAC name used in the CLH report). The Commission must decide which version is preferred. The CAS name is not relevant for the entry in Annex VI of the CLP Regulation.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Spain		MemberState	2
Comment received				
p. 23 Summary and discussion of acute toxicity Acute oral toxicity The Spanish CA supports the proposed classification of fenpyroximate as Xn, R22: "Harmful if swallowed", according to Directive 67/548/EC (criteria: 200<LD50 ≤ 2000 mg/kg bw)				

and as Acute Tox 3 (oral), H301: "Toxic if swallowed", according to Regulation EC 1272/2008 (criteria: 50< LD50 ≤300mg/kg bw). This classification is due to the LD50 value in female rats (LD50 = 245 mg/kg bw) obtained in the oral toxicity study in rats (Blaszcak, 1989).

Acute inhalation toxicity
The Spanish CA supports the proposed classification of fenpyroximate as T+; R26 "Very toxic by inhalation" according to Directive 67/548/EC (criteria aerosols or particulates: LC50 ≤ 0.25 mg/l/4h) and as Acute Tox. 2 (inhalation) H330: "Fatal if inhaled" according to Regulation EC 1272/2008 (criteria dusts and mists: 0.05 < LC50 < 0.5 mg/l/4h). This classification is based on the LC50 value in male rats (LC50 = 0.21 mg/l/4h) in an inhalation toxicity study in rat (Hoffman, G.M. 1991).

Dossier Submitter's Response
Thank you for your comment.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	3

Comment received

p 25-26 : France disagrees with the proposal of classification R36 irritating to eyes based on the results of a study performed with a fenpyroximate 5% SC formulation of unknown composition.

Dossier Submitter's Response

Agreement with comments number 3, 4 and 5. Classification of fenpyroximate as Xi, R36 is no more proposed by the Dossier submitter.

Proposed classification before public consultation		Proposed classification after public consultation	
CLP Regulation	DSD Direktive	CLP Regulation	DSD Direktive
Acute Tox 3; H301 Acute Tox 2; H330 Eye Irrit. 2; H319 Skin Sens. 1B; H317 Aquatic acute 1; H400 Aquatic chronic 1; H410 M_{acute} = 100 $M_{chronic}$ = 1000	Xn; R22 T+; R26 Xi; R36 R43 N; R50/53	Acute Tox 3; H301 Acute Tox 2; H330 Skin Sens. 1B; H317 Aquatic acute 1; H400 Aquatic chronic 1; H410 M_{acute} = 100 $M_{chronic}$ = 1000	Xn; R22 T+; R26 R43 N; R50/53

Justification:
The proposal of classification R36 – Irritating to eyes was based on results in animal studies with the preparation and on findings in humans. This proposal agreed with the proposed classification and labelling of fenpyroximate in the EFSA Scientific Report (2008) 197. This conclusion was based on the discussion of the DAR by the EU member states.

In contrast to the assumption in comment number 5 necessary information on the coformulants of the preparation Kiron have been submitted by the notifier for the EU pesticide risk assessment and are well known to the dossier submitter. No coformulant in the preparation Kiron would require the classification R36 of the product. Eye irritation was also observed in 2 workers engaged in manufacturing technical grade substance fenpyroximate and in workers and farmers who produced or used the product. Furthermore, the product Kiron was eye irritating in the primary eye irritation study in rabbits. However, the most relevant primary eye irritation study with the active substance fenpyroximate in rabbits was negative. Based on this study classification R36 and Eye Irrit. 2, H319 is not necessary.
RAC's response
According to the CLP regulation, substances may be classified in Category 2 (irritating to eyes) if there is adequate existing human experience which provides evidence that the substance is irritating to eyes. However, as there have only been two incidents reported in workers engaged in manufacturing technical grade of fenpyroximate and these more than 20 years ago, together with the knowledge that the most relevant primary eye irritation study with the active substance fenpyroximate in rabbits was negative, RAC considers that classification as Eye Irrit. 2, H319 (CLP) and Xi; R36 (DSD) is not appropriate.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2013	United Kingdom		MemberState	4
Comment received				
The active substance, fenpyroximate, tested negative in a standard rabbit eye irritation study. Although some very minor conjunctival redness and chemosis was observed the scores were insufficient to support classification. In contrast, a 5% formulation is reported to have caused eye irritation in humans when used in a spray application. Additional information in the DAR indicates that this formulation causes eye irritation in experimental animals also. As the only information showing eye irritation relates to a 5% formulation, we suggest that classification is not appropriate for the active substance itself.				
Dossier Submitter's Response				
See response on comment number 3.				
RAC's response				
See response to comment number 3.				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Spain		MemberState	5
Comment received				
p. 24 Summary and discussion of irritation Eye irritation The Spanish CA doesn´t support a classification of fenpyroximate as Xi, R36: "Irritating to eyes" according to Directive 67/548/EC and as Eye Irrit. 2, H319: "Causes serious eye irritation" according to Regulation EC 1272/2008. In a standard eye irritation study in rabbit (Kosaka, 1988) the results obtained were negative. In contrast a 5% formulation is reported to have caused eye irritation in humans when used in a spray application.				

However, the coformulants contained in this formulation are unknown. As the only information showing eye irritation related to a 5% formulation, Spanish CA considers that classification of fenpyroximate as irritating to eyes is not justified.
Dossier Submitter's Response
See response on comment number 3.
RAC's response
See response to comment number 3.

OTHER HAZARDS AND ENDPOINTS – Skin Senzitation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Spain		MemberState	6
Comment received				
p. 27 Summary and discussion of sensitisation The Spanish CA supports the proposed classification of fenpyroximate as skin sensitizer; R43: "May cause sensitisation by skin contact", according to Directive 67/548/EC and as Skin Sens. 1B, H317: "May cause an allergic skin reaction" according to Regulation (EC) 1272/2008. This classification is based on the results of the Guinea Pig Maximisation Test (Kosaka,T., 1998) with fenpyroximate (purity 98.4%) in which a positive response in 36% of the tested animals was observed after an intradermal induction dose of 5%.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Spain		MemberState	7
Comment received				
p. 24 Summary and discussion of irritation Respiratory tract irritation The Spanish CA proposes to classify fenpyroximate as Xi; R37: "Irritating to respiratory system" under DSD criteria. Similarly, according to CLP criteria, fenpyroximate can be classified for specific target organ toxicity after single exposure as STOT SE 3, H335; "May cause respiratory irritation". Findings observed in acute inhalation studies (Hoffman1989 and 1991) and subacute inhalation study (Hoffman, 1991) in rats are considered signs of reversible respiratory tract irritation: laboured breathing, gasping, rales and the histopathological data from the respiratory system (oedema, reddening and firm lugs, frothy fluid in the trachea and atrophy, desquamation and squamous metaplasia of nasal passage mucosa).				
Dossier Submitter's Response				
For fenpyroximate classification T+, R26 – very toxic by inhalation is already proposed. Therefore, an additional classification R37 would not contribute much additional safety. In 2 acute inhalation studies the mentioned findings have mainly been observed in the lethal dose range. Therefore, it is questionable to base the classification/labelling of specific				

target organ toxicity on the results of these extreme doses.

For the decision on the classification the results of the short term inhalation toxicity study (4-week study in rats) are considered to be also relevant. According to the protocol of this study 6 samples of the lungs (from each lobe) and from mainstem bronchi of all animals have been examined histopathologically. No effects of the test substance have been observed in these comprehensive investigations. Therefore, the cause of the increased lung weight is questionable. Furthermore, in comment 7 squamous metaplasia of respiratory mucosa is mentioned. However, the incidence of this finding was not increased after 14 days recovery period. Squamous metaplasia is a serious change of the organ structure. It is highly questionable if such fundamental transformation can be reversible within 14 days. Furthermore, the incidence of this finding in male animals of the highest dose group was 2. The incidence of this finding in the recovery control group was also 2. Therefore the incidences of the highest dose group are considered to be within the range of control animals.
All in all, the described effects in the inhalation studies do not sufficiently evidence a specific target organ toxicity on the respiratory system. Therefore, classification R37 and STOT SE 3, H335 is not proposed.

RAC's response

RAC agrees with the response from Dossier Submitter.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Spain		MemberState	8

Comment received

p. 29 Summary and discussion of repeated dose toxicity

Repeated dose toxicity oral

Based on the comparison of repeated dose toxicity data with DSD and CLP classification criteria, the Spanish CA suggests that classification as R48/22: "Harmful: danger of serious damage to health by prolonged exposure if swallowed" and STOT RE 2, H373: "May cause damage to organs through prolonged or repeated exposure" could be considered. This suggestion is based on the high mortality (50%) observed in females in a 13-day study in dog at 50 mg/kg bw/d, which occurred within the cut-off value (50 and 100 mg/kg bw/d for DSD and CLP classification criteria, respectively). Besides, at this same dose, in this study lethargy, emesis and bradycardia in both sexes were observed and these could indicate a possible effect in the Central Nervous System. In females, depleted hepatocytic glycogen and fine cytoplasmic vacuolacion in the cells of the renal medullary rays were also observed. Althought this increase on mortality was not repeated at the 52-weeks study in dog, the highest evaluated dose in this study was 15 mg/kg bw/d. Therefore is not possible to know the incidence of the active substance at higher doses.

Dossier Submitter's Response

A 13-week and a 52-week study with fenpyroximate in dogs have been submitted. No spontaneous mortality was observed in both studies. In the 13-week study 2 female animals of the highest dose group have been killed during the study after a period of inappetence and body weight loss.
Bradycardia and lethargy can be caused by emaciation, diarrhoea, dehydration and starvation. Such effects have been observed in this study. There are no evidences of

neurotoxic effects of fenpyroximate. The proposal of classification R48/22 and STOT RE 2, H373 is not supported.
RAC's response
RAC agrees with the response by the Dossier Submitter.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.06.2013	Netherlands		MemberState	9
Comment received				
NL-CA agrees that fenpyroximate is not readily biodegradable and is toxic to aquatic organisms. p.42 Findings of the long term toxicity study of fenpyroximate to fish. In the CLH report, details of an early life stage study with fathead minnow are provided. We have a question with regard to the description of the analytical results of the test concentrations. It is stated that the analytical method resulted in measured concentrations in the high concentration ranged from 53 to 89% of nominal and indicated that the parent compound accounted for 100% of the radioactivity present in the solution. It is not totally clear which concentration is the high concentration. Is it the highest concentration of nominal 0.20 µg/L? The measured range of 53 – 89% of nominal is below the accepted one of 80 – 120% of nominal. Can the DE-CA give more explanation, a clear description, about these analytical results? p.47 The chronic M factor. In our view, the chronic M factor should be 100 instead of 1000, based on the lowest chronic toxicity data for the fish, fathead minnow (NOEC value of 0.00011 mg/L (0.11 µg/L). The DE-CA has rounded off this NOEC value to 0.1 µg/L. However, in the table on page 43 a mean measured NOEC of 0.11 µg/L is given. You may consider not rounding off the toxicity values for consistency sake.				
Dossier Submitter's Response				
Thank you for your comments. p. 42 Findings of the long term toxicity study of fenpyroximate to fish. You are right, that there is confusion about analytical results in the study summary. Because three different analytical measurements were made in the study (Liquid Scintillation Counting (LSC) of each treatment, control, quality control and stock solution; HPLC/RAM only at the highest test concentration (0.2 µg/L nominal) and HPLC/UV only of the stock solution. Additionally the stock solution of the diluter in this flow through study with 23 µg/mL consists of 17.25 µg/mL (75%) non radiolabeled fenpyroximate and 5.75 µg/mL (25%) [14C]fenpyroximate. The results of the HPLC/RAM measurement of the highest test concentration of 0.2 µg/L (nominal) were 53-89% (mean 75%) with 100% distribution as [14C] fenpyroximate. In contrast the concentrations of total [14C] measured by LSC in all exposure solutions during exposure phase (from day 0 until day 34) were 110% of the nominal concentrations. The results of quality controls ranged from 94.7 to 143% of the nominal fortified levels (0.0106 to 0.254 µg/L. Diluter stock (23 µg/mL) analyses with HPLC/UV ranged from 116 to 125% of the nominal value. Because of all these different results **we consider the nominal concentration of 0.0001 mg/L relevant for determination of NOEC**. The mean measured value of 0.00011 mg/L (LSC) which has only a precision of 90%(it was determined at the study that at the 90% confidence level all water samples of net 48 cpm (instrument detection limit) with background subtract of 39.40 cpm had an associated counting error of 10%. This				

percentage was the maximum acceptable error and was associated with the minimum net counts per minute (cpm) of that sample.

Now there is a new relevant Full life-cycle test with fathead minnow for [14C] Fenpyroximate available (York, 2010). It is validated already. The new study results delivers a **NOEC of 0.000063mg/L (mean measured)** based on length reduction over 30 d of the F0 Generation. This new study result will complete and support the result and conclusion for aquatic chronic classification as H410 with M factor of 1000.
A summary of this study York, 2010 is given in Annex 1 (confidential information)

p.47 The chronic M factor
By a mistake the NOEC value of 0.011 µg/L (mean measured) was given in table 7.1-3 instead of the correct NOEC value of 0.01 µg/L (nominal). This study result support the chronic M factor of 1000 (not rapidly degradable substance and 0.00001 mg/L < NOEC ≤ 0.0001 mg/L). For further details see response to page 42 comment

RAC's response

RAC notes the existence of a new fish toxicity study that supports the original proposal, and the clarifying remarks about the concentration measurements for the FELS test.

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	10

Comment received

We agree with the proposal of classification regarding environmental hazards.

Dossier Submitter's Response

Thank you for your comment.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Belgium		MemberState	11

Comment received

Based on the results of the aquatic toxicity test on the most sensitive species (Oncorhynchusmykiss with 96hEC50 = 0.00105 mg/l (mm), Pimephalespromelas with 34dNOEC= 0.0001 mg/l (nom)) the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic chronic 1,H410. Furthermore, the substance shows potential to bioaccumulate (BCF >100/500).

In view of the proposed classification and toxicity band for acute toxicity between 0.001 and 0.001 mg/l, an M-factor for acute toxicity of 100 could be assigned, and an M-factor for chronic toxicity of 1000 (not rapidly degradable substance and toxicity band ≤ 0.0001 mg/l).

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Fenpyroximate should be classified as N, R50/53. Proposed SCL :
N, R50/53 : C≥ 0.25%;
N; R51/53: 0.025% ≤C< 0.25%
R52/53: 0.002.5% ≤C< 0.025%

In conclusion : we agree with the proposed environmental classification by the DE MSCA. Editorial comment: SCLs ENV should be given in Table 2 and Table 4
Dossier Submitter's Response
Thank you for your comment.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2013	United Kingdom		MemberState	12
Comment received				
The proposed chronic classification and M-factor for fenpyroximate is based in the CLH report on a stated 35-d early life stage NOEC for fathead minnow of 0.1 µg/L. However, further investigation of this study (see p 41-43 of report) indicates the mean measured NOEC to be 0.00011 mg/L (0.11 µg/L). As this is slightly above 0.1 µg/L would this change the CLP chronic M-factor to 100 rather than 1000? Please clarify. This would not otherwise affect the proposed classification.				
Dossier Submitter's Response				
Thank you for your comment. For further details and explanation for the relevant ELS study (Sousa, 2001) see above our response to comment number 9 from the Netherlands.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	13
Comment received				
Page 10: The minimum degree of purity of the substance is not confidential. Please add min 960 g/kg in the table 6 as it is specified in the report on the finalisation of the reference specification (08/2009). The confidential data in IUCLID should be amended with these validated specifications. Pages 11 and12: It seems that the current template has not been used. In the chapter classification for physico-chemical properties there is no table 10 with the summary of the studies and no summary and discussion. Moreover in the summary of physico-chemical properties no data is provided on the methods used. In the CLH report, the water solubility at pH7 has not been reported and no data is reported on the purity and the temperature for the partition coefficient n-octanol/water whereas it is				

specified in the LOEP of the DAR (March 2012). Please add the information. The measure of viscosity is not relevant for a powder. Please replace "not determined" by "not relevant". Please explain the purity specified for the explosive properties. Is there a study? In the LOEP of the DAR (March 2012), it is specified that it is a theoretical assessment.
Dossier Submitter's Response
Thank you for your comment. The minimum degree of purity of the substance could be set to "not confidential". The purity of Fenpyroximate with 960 g/kg could be added. The water solubility at pH7 is 23.1 µg/L. "Not determined" should be changed to "Not relevant". Only the statement should be used for the explosive properties (The molecular structure does not contain any chemically unstable or highly energetic group that may lead to an explosion.).
RAC's response
RAC notes these clarifications, but they do not affect the opinion.