Committee for Risk Assessment

RAC

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: not allocated
CAS number: 134098-61-6

CLH-O-0000002368-70-02/F

Adopted

5 December 2013

5 December 2013

CLH-O-0000002368-70-02/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

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

EC number: not allocated

CAS number: 134098-61-6

The proposal was submitted by **Germany** and received by the RAC on **19 March 2013.** In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **30 April 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14 June 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Peter Hammer Sørensen**

Co-rapporteur, appointed by the RAC: **Stephen Dungey**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **5 December 2013** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion on **fenpyroximate (ISO)** that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	No current Annex VI entry									
Dossier submitters proposal	607-713-00-1	fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	Acute Tox. 3 Acute Tox. 2 Skin Sens. 1B Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H301 H330 H317 H319 H400 H410	GHS06 GHS09 Dgr	H301 H330 H319 H317 H400 H410		M=100 (acute) M=1000 (chronic)
RAC opinion		fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	Acute Tox. 3 Acute Tox. 2 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H301 H330 H317 H400 H410	GHS06 GHS09 Dgr	H301 H330 H317 H410		M=100 (acute) M=1000 (chronic)
Resulting Annex VI entry if agreed by COM		fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	Acute Tox. 3 Acute Tox. 2 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H301 H330 H317 H400 H410	GHS06 GHS09 Dgr	H301 H330 H317 H410		M=100 M=1000

Classification and labelling in accordance with DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits
Current Annex VI entry	No current Annex VI entry						
Dossier submitters proposal	607-713-00-1	fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	T+; R26 Xn; R22 Xi; R36 R43 N; R50/53	T+; N R: 22-26-36-43-50/53 S: (1/2-)26-28-36/37-38-45-60-61	
RAC opinion		fenpyroximate (ISO); tert-butyl4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	T+; R26 Xn; R22 R43 N; R50/53	T+; N R: 22-26-43-50/53 S: (1/2-)28-36/37-45-60-61-63	N; R50-53: C ≥ 0,25 % N; R51-53: 0,025 % ≤ C < 0,25 % R52-53: 0,0025 % ≤ C < 0,025 %
Resulting Annex VI entry if agreed by COM		fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate	-	134098-61-6	T+; R26 Xn; R22 R43 N; R50-53	T+; N R: 22-26-43-50/53 S: (1/2-)28-36/37-45-60-61-63	N; R50-53: C ≥ 0,25 % N; R51-53: 0,025 % ≤ C < 0,25 % R52-53: 0,0025 % ≤ C < 0,025 %

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

Fenpyroximate is an active substance used as a Plant Protection Product. Therefore, RAC has evaluated all hazard classes for which the Dossier Submitter (BAuA, Germany) has provided appropriate information.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal

No classification for physical hazards is proposed by the Dossier Submitter.

Comments received during public consultation

None.

Assessment and comparison with the classification criteria

The submitted studies include information for the following physical hazard classes:
Explosives, flammable solids, self-heating substances and mixtures and oxidising liquids. None of the enclosed studies indicates a need for the classification of physical hazards.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The Dossier Submitter proposed to classify fenpyroximate as Acute Tox. 3; H301 (Xn; R22) and Acute Tox. 2; H330 (T+; R26) in accordance with the CLP Regulation and Directive 67/548/EEC (DSD), respectively.

The oral LD_{50} of fenpyroximate was between 350 mg/kg bw in rats (245 mg/kg bw in females and 480 mg/kg bw in males) and 500 mg/kg bw in mice.

The acute dermal toxicity was low (LD_{50}>2000 mg/kg bw). Therefore, no classification for acute dermal toxicity is required.

The acute inhalation toxicity was tested in two studies. In the first study, the LC_{50} of fenpyroximate as active ingredient was 0.33 mg/L in males and 0.36 mg/L in females (0.36 mg/L for both sexes combined). In the second study, the LC_{50} was calculated to be 0.31 mg/L for the combined sexes, 0.21 mg/L for males and 0.33 mg/L for females. Although fenpyroximate was formulated with 10% dioxosilane (silicon dioxide) in this study, the observed mortality was considered to be due to the active substance and not to the dioxosilane.

Comments received during public consultation

One MSCA expressed agreement with the proposal.

Assessment and comparison with the classification criteria

***Oral toxicity**:*
According to the CLP Regulation a substance should be classified as Acute Tox. 3 if the oral LD_{50} is derived in the following range: $50<LD_{50}\leq300$ mg/kg bw. The LD_{50} in female rats was 245 mg/kg bw. Therefore, classification as Acute Tox. 3 and the Hazard Statement H301: "Toxic if swallowed" is warranted.

According to DSD substances shall be classified as R22 "Harmful if swallowed" and assigned the symbol "Xn" if the LD_{50} per oral, rat is $200 < LD_{50} \leq 2\,000$ mg/kg. Therefore, classification as harmful (Xn), and the risk phrase R22 "Harmful if swallowed" is warranted for fenpyroximate.

Inhalation toxicity:
According to the CLP regulation, substances can be classified as Acute Tox. 2 by inhalation route if the following criteria are fulfilled for dusts and mists: 0.05 mg/L < LC_{50} < 0.5 mg/L. In the submitted studies, fenpyroximate dusts have been tested, and the LC_{50} values fall within that range. The experimental exposure period was 4 h. Therefore, no correction factor is necessary. Consequently, classification as Acute Tox. 2, H330 "Fatal if inhaled" is needed.

According to DSD substances shall be classified as R26 "Very toxic by inhalation" and assigned the symbol "T+" if the LC_{50} inhalation, rat, for aerosols and particulates is ≤ 0,25 mg/litre/4h.
Consequently, classification as very toxic (T+), and the risk phrase R26 "very toxic by inhalation" is appropriate for fenpyroximate.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal

The dossier submitter provided no data but noted that "the available studies on fenpyroximate are valid according to the data requirements. However, they are considered to provide insufficient information for STOT-SE."

Comments received during public consultation

One MSCA proposed classification as Xi; R37 "Irritation to respiratory system" under DSD and STOT SE 3; H335 "May cause respiratory irritation", based on the findings observed in acute inhalation studies (Hoffman, 1989 and 1991) and in a subacute inhalation study (Hoffman, 1991) in rats, in which the following signs of reversible respiratory tract irritation were observed: 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).

Assessment and comparison with the classification criteria

For fenpyroximate, classification as Acute Tox. 2; H330 (Fatal if inhaled) / T+, R26 (very toxic by inhalation) has already been proposed by the DS. Therefore, an additional classification as STOT SE 3, H335 / R37 would not provide significant additional hazard information.

In two acute inhalation studies, the findings reported were mainly observed in the lethal dose range. Therefore, it is questionable to base the classification for specific target organ toxicity on the results of studies at these extreme doses.

However, the results of the 4-week, short term inhalation toxicity study in rats are also considered to be relevant. According to the protocol of this study, 6 samples of the lungs (from each lobe) and from mainstem bronchi of all animals were examined histopathologically. No effects of the test substance were observed in these comprehensive investigations. Therefore, the cause of the increased lung weight is questionable. Furthermore, in one comment received during public consultation, squamous metaplasia of respiratory mucosa is mentioned. However, the incidence of this finding was not increased after a 14-day recovery period. Squamous metaplasia is a serious change in the organ structure. It is questionable whether such fundamental transformations 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 those in the control animals.

All in all, RAC considered that the effects described in the inhalation studies did not constitute sufficient evidence to support classification for specific target organ toxicity on the respiratory system.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

No evidence for skin irritating potential of fenpyroximate was observed in an OECD TG 404 -compliant study conducted with rabbits (New Zealand White (NZW), 6 males). Therefore, no classification is required.

Comments received during public consultation

None.

Assessment and comparison with the classification criteria

All average scores in the submitted study were 0, therefore no classification for skin corrosion/irritation is warranted.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

Slight eye irritation was observed in an OECD TG 405 –compliant study conducted in rabbits (NZW, 6 males). On the basis of this study, classification would not be warranted.

Method/ Guideline	Species, Strain, Sex, No/group	Average score 1, 24, 48, 72 h				Reversible yes/ no	Results	Remarks	Reference
		Cornea	Iris	Redness Conjunctiva	Chemosis				
OECD 405	Rabbit, KBL:NZW 6M	0-0-0-0	0-0-0-0	1-1-0.7-0	1-0-0-0	Yes	Not irritating	None	Kosaka, T. (1988), report no. T-4009

However, there human data showed that eye irritation was observed in workers and farmers. Information concerning eye irritation in farmers who used fenpyroximate 5 % SC was gathered by Nihon Nohyku (Sano *et al.*, 1992). Eye irritation was found in 23 cases in 1991 and in 3 cases in 1992 in farmers applying fenpyroximate 5 % SC in a citrus field but was not reported in farmers using the formulation in any other crop. The occurrence of eye irritation only during use in citrus fields was considered to be related to the planting conditions of this crop, resulting in a higher exposure to the pesticide spray, in contrast to other crops (e.g. apple). The irritation was primary and recovery occurred within a short time after application. The incidence of eye irritation in 1992 was lower than that in 1991 in spite of an increase of the amount of fenpyroximate 5 % SC sold, as there was greater attention to avoiding exposure to fenpyroximate 5 % SC among farmers and the use of glasses and goggles was recommended.

Comments received during public consultation

Three MSCA expressed disagreement with the proposal for eye irritation. The Dossier Submitter agreed with the comments received during public consultation, and therefore classification of fenpyroximate as Xi; R36 is no longer proposed by the Dossier Submitter.

Assessment and comparison with the classification criteria

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 considered that classification as Eye Irrit. 2, H319

(CLP) and Xi; R36 (DSD) is not appropriate.

RAC evaluation of respiratory sensitisation

Summary of the Dossier submitter's proposal

No indication of respiratory sensitization in the acute inhalation toxicity studies.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

In a Magnusson/Kligman test a sensitisation rate of 36% was obtained. The intra-dermal induction concentration was 5%. Therefore, classification as Skin Sens. 1B (CLP) and R43 "May cause sensitisation by skin contact" (DSD) is proposed. The negative result (0/60) in a second test (Buehler test) is not relevant because there was clear evidence for the sensitising activity of the test substance in the GPMT.

Comments received during public consultation

One MSCA expressed agreement with the proposal.

Assessment and comparison with the classification criteria

Based to the results in the maximization assay (Kosaka, 1988) and considering the classification criteria in the CLP regulation, the test compound fulfills the criteria to be classified as Skin sensitiser Category 1B (H317) (R43 under DSD) since the intradermal induction concentration was 5% and the sensitisation rate was 36%.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

In the repeated dose toxicity studies, mainly nonspecific effects were observed (decreased body weight gain and food consumption, changes in blood chemistry indicated by reduced leukocyte counts, diarrhoea and emaciation). No substance related mortality was observed. The observed effects are considered to be reversible. There was no clear evidence of marked organ dysfunction. According to the criteria for classification concerning specific target organ toxicity (STOT RE) the DS considered that no classification is required.

Comments received during public consultation

One MSCA expressed disagreement and proposed classification as STOT RE 2, H373 "May cause damage to organs through prolonged or repeated exposure" (CLP) and Xn; R48/22 "Harmful: danger of serious damage to health by prolonged exposure if swallowed" (DSD). This was based on the high mortality (50%) observed in females in a 13-week study in dogs at 50 mg/kg bw/day, which occurred within the cut-off value (50 and 100 mg/kg bw/day for DSD and CLP classification criteria, respectively).

Assessment and comparison with the classification criteria

A 13-week and a 52-week oral study with fenpyroximate in dogs were submitted. No spontaneous mortality was observed in either study. In the 13-week study, two female animals of the highest dose group were euthanised (for ethical reasons) during the study after a period of inappetence and body weight loss. There was no specific organ toxicity or evidence of organ dysfunction in the remaining dogs.

Bradycardia and lethargy can be caused by emaciation, diarrhoea, dehydration and starvationand such effects were observed in this study. There was no evidence for neurotoxic effects of fenpyroximate.

In addition, a 13-week oral toxicity study, a 4-week inhalation toxicity study and a 21-day dermal toxicity study with fenpyroximate in rats were submitted. No mortality which could be related to the treatment was observed in these studies.

Two key effects, decreased bodyweight/bodyweight gain and leukocyte counts, which were seen in both dogs and rats, are considered in detail below.

The 13-weeks dog study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg	
	Males	Females
0	12.0 (2.9)	11.6 (3.1)
2	12.4 (3.5)	10.8 (2.3)
10	11.7 (2.6)	9.9 (1.7*)
50	10.8 (1.7*)	8.6 (0.3***)

Dose level (mg/kg bw/d)	0		2		10		50	
	Males	Females	Males	Females	Males	Females	Males	Females
Total leucocyte counts 1000/µL (week 6)	13.2	16.4	14.6	14.1*	14.0	15.0	12.6	10.8***
Neutrophil counts 1000/µl (week 6)	6.0	7.0	7.0	6.8	6.3	6.3	5.4	4.3
Total leucocyte counts 1000/µL (week 12)	15.2	19.6	15.3	15.5	15.3	15.5	15.4	12.8*
Neutrophil counts 1000/µL (week 12)	7.9	11.4	8.2	9.9	8.0	8.7	8.6	6.9
Platelets 1000/µL (week 12)	203	194	198	199	224	218	228	233*
PTTK[#] secs (week 6)	13.9	12.7	13.6	14.2	14.5	13.5	13.3	17.0**
PTTK[#] (week 12)	17.7	14.4	19.3	15.3	15.1	12.9	16.5	17.2

[#]Activated partial thromboplastin time

The 52-week dog study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg			
	Males (day 91)	Males (day 364)	Females (day 91)	Females (day 364)
0	12.4 (3.8)	14.7 (6.1)	11.3 (3.0)	12.8 (4.4)
0.5	12.2 (3.6)	14.0 (5.4)	12.0 (3.5)	13.6 (5.2)
1.5	12.5 (3.6)	14.2 (5.3)	11.5 (3.2)	12.9 (4.6)
5.0	12.9 (3.9)	15.1 (6.1)	11.0 (2.8)	11.8 (3.6)
15.0	10.7 (1.8*)	13.0 (4.0**)	10.5 (2.1)	12.3 (4.0)

There were no treatment-related haematological or ophthalmological findings in this study. A slight but significant lowering of total plasma protein level was observed in males at 15 mg/kg bw/d.

The 13-week rat oral study:

Dose level (ppm)	Bodyweight (bodyweight change) in g	
	Males	Females
0	512 (383)	287 (177)
20	509 (379)	288 (176)
100	459* (327*)	260* (151**)
500	253*** (125***)	177*** (66***)

* P < 0.05; ** P < 0.01; *** P< 0.001

The 4 week-rat inhalation study:

Dose level (mg/m^3)	Bodyweight in g					
	Males			Females		
	Day 1	Week 4	Week 6	Day 1	Week 4	Week 6
0	286.8	394.6	457.6	179.3	238.6	259.6
2	282.0	379.8	-	178.0	230.2	-
10	280.2	379.8	-	175.2	235.6	-
50	282.5	363.6*	443.6	175.7	224.3*	251.2

Dose level (mg/m^3)	0		2		10		50	
	Males	Females	Males	Females	Males	Females	Males	Females
RBC mil/μL (week 4)	8.06	7.73	8.29	7.75	8.51*	7.88	8.67**	7.91
Total leucocyte counts 1000/μl (week 4)	10.2	8.1	10.6	11.2	11.9	11.8	14.6	16.9**
MCV μ^3	55	54	54	54	52*	55	53	55
MCH μg	19.8	20.0	19.6	20.2	18.9*	20.4	19.1	20.2

The 21-day dermal rat study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg							
	Males				Females			
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22
0	275.5	314.3 (38.8)	346.6 (71.1)	336.9 (61.4)	240.4	257.3 (16.8)	270.6 (30.1)	251.0 (10.5)
100	277.4	308.9 (31.5)	344.5 (67.1)	332.5 (55.1)	237.5	249.6 (12.0)	265.1 (27.6)	243.0 (5.5)
300	276.4	301.3 (24.9)	335.9 (59.6)	317.5 (41.2)	241.3	250.6 (9.3)	264.7 (23.4)	245.6 (4.3)
1000	275.3	282.3* (7.0*)	296.4* (21.2*)	270.4* (-4.9*)	240.4	236.7 (-3.8)	237.8* (-2.6*)	212.3* (-28.2*)

Bodyweight and bodyweight changes:

In the 13-week dog study, bodyweight gain was significantly reduced in the females at the highest dose (50 mg/kg bw/d), but there were no significant changes in bodyweight. The same was seen in the 52-week dog study where the males show a significant reduction in bodyweight gain in the highest dose group (15 mg/kg bw/d).

In the 13-week oral rat study a significant reduction in both bodyweight and bodyweight gain were seen in the two highest dose groups, 100 and 500 ppm (~7 and 37 mg/kg bw/d, respectively).

In the 4-week rat inhalation study there was seen a slight but significant reduction in bodyweight in the highest dose group (50 mg/m^3) after 4 weeks of exposure, but this had fully recovered after a 2-week recovery period. In the 21-day rat dermal study, a slight but significant reduction in both bodyweight and bodyweight gain were seen in both females and males in the highest dose group (1000 mg/kg bw/d).

Leucocyte counts:

In the 13-week oral study in dogs there were statistically significant but inconsistent changes in haematology, including total leucocytes counts in females in the highest dose group. The same was seen in the 4-week rat inhalation study in the highest dose group in females.

Comparisons with the classification criteria:

Whether the two dogs in the 13-week oral study would have died if they had not been euthanised cannot be resolved, but these were the only treatment related deaths that were seen among all the animals in the repeated dose toxicity studies.

The changes in the haematology are considered consistent with 3.9.2.8.1.(b) of Annex I to the CLP Regulation, which lists effects that do not justify classification, i.e. "small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance".

The observed effects are considered to be reversible. Overall the proposal of classification STOT RE 2, H373 (CLP) and Xn; R48/22 (DSD) is therefore not supported.

No specific organ toxicity was observed in the carcinogenicity studies. This also indicated to RAC that no classification for specific organ toxicity (STOT RE) was required.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

No evidence of genotoxicity has been observed in a battery of OECD TG–compliant tests in bacteria and mammalian cells.

In vivo: There was no evidence of induced chromosomal or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice 24, 48 or 72 hours after oral administration of fenpyroximate, even at a dosage which caused marked clinical symptoms and some evidence of toxicity to the bone marrow.

No classification for genotoxicity is required.

Comments received during public consultation

None.

Assessment and comparison with the classification criteria

Since no evidence of mutagenicity was seen in a battery of OECD TG-compliant genotoxicity studies in vitro or in vivo, RAC agreed with the Dossier Submitter that no classification for germ cell mutagenicity was warranted.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No evidence of oncogenic potential was observed in an OECD TG 453–compliant study in rats (doses of 6.2 and 8.0 and mg/kg/d in males and females, respectively) or an OECD TG 451–compliant study in mice (doses of 70 and 73 mg/kg/day, respectively). Therefore no classification for carcinogenicity was proposed by the DS.

Comments received during public consultation

None.

Assessment and comparison with the classification criteria

Since no evidence of carcinogenicity was seen in the submitted studies, RAC agreed with the Dossier Submitter that no classification for carcinogenicity was warranted.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Fertility:
In a two-generation reproductive toxicity study conducted with Sprague-Dawley rats, fenpyroximate technical did not affect reproductive performance. The NOAEL for reproductive performance and fertility was 100 ppm (corresponding to approximately 8 mg/kg bw/d). Based on reductions in bodyweight gain in the adults and in the offspring during lactation the NOAEL for general toxicity toxicity was 30 ppm (equivalent to approximately 2 mg/kg bw/d).

Development:
Developmental toxicity studies with fenpyroximate, conducted in Sprague-Dawley rats and in NZW rabbits, showed no evidence of teratogenic effects for foetuses and no evidence of developmental toxicity in the absence of maternal toxicity.

In the rat developmental toxicity study, the NOAEL for maternal toxicity was 5 mg/kg bw/d based on decreased bodyweights and food consumption at 25 mg/kg bw/d. The NOAEL for developmental toxicity was 5 mg/kg bw/d, based on an increased incidence in supernumerary ribs at 25 mg/kg bw/d.

In rabbits a preliminary developmental toxicity study was conducted with only three or four animals per dose group. Based on decreased bodyweight gain, slightly reduced food and water consumption and reduced faecal output in the high dose group (5 mg/kg bw/d) the NOAEL for maternal toxicity was 2.5 mg/kg bw/d. Increased post-implantation loss in two females and smaller foetuses with anomalies from one female were observed in the 5 mg/kg bw/d dose group. The NOAEL for developmental toxicity was 2.5 mg/kg bw/d.

In the main developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 2.5 mg/kg bw/d based on decreased bodyweight gain and food and water consumption and reduced faecal output at 5 mg/kg bw/d.

An increased incidence compared to that of the control group of slightly folded retinas was observed at 5 mg/kg bw/d, which may indicate that a potential for malformations at higher doses has been observed in the highest dose group. The NOAEL for developmental toxicity was 2.5 mg/kg bw/d. The incidence of folded retinas is presented below. Folded retinas are considered a malformation, but the incidence is in the range of historical control data and the findings are only significant in presence of maternal toxicity (bodyweight loss, reduced food and water consumption and reduced faecal output). The observations following sectioning of foetal heads are presented in the table below (percent incidence and number of litters).

Group:	1 (Control)	2 (1 mg/kg bw/d)	3 (2.5 mg/kg bw/d)	4 (5 mg/kg bw/d)	Historical control (mean value)	Historical control (range)
Observation	% incidence (no of litters)					
Unilateral slightly folded retina	8.1 (3)	6.1 (2)	5.9 (2)	25.8 (6) *	9.91	0-33.3
Bilateral slightly folded retina	10.8 (3)	6.1 (2)	14.7 (4)	16.1 (5)	4.82	0-16.7

Comments received during public consultation

None.

Assessment and comparison with the classification criteria

No effects on fertility were observed. Where development is concerned, an increased incidence of folded retina compared to that of the control group, which may indicate a potential for malformations at higher doses, was only observed in the highest dose groups together with maternal toxicity. Therefore, RAC considers that no classification for reproductive toxicity is required.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of Dossier submitter's proposal

The Dossier Submitter proposed to classify the substance as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) in accordance with CLP, with an M-factor of 100 and 1000, respectively. The corresponding classification according to the DSD is N; R50/53 (with appropriate concentration limits). The proposal is based on acute toxicity to fish (96-h LC_{50} of 0.00105 mg/L) and invertebrates (48-h EC_{50} of 0.00328 mg/L) for the acute CLP and DSD classifications, and a long-term fish toxicity result (34-d NOEC of 0.0001 mg/L for *Pimephales promelas*) for the chronic classification under CLP, together with the fact that the substance is not rapidly (or readily) biodegradable and has a fish bioconcentration factor (BCF) above 500 L/kg.

Comments received during public consultation

One MSCA asked for clarification of the concentration measurements for the fish early life stage (FELS) test with *P. promelas*, as it appeared that they might fall outside of the acceptability criteria. Two MSCAs also queried why a chronic M-factor of 1000 (rather than 100) was used when the long-term fish NOEC was reported as 0.00011 mg/L. The Dossier Submitter replied that three

analytical methods had been used in this test, and whilst one of these (HPLC/RAM, used for the highest dose only) suggested a significant loss of concentration (mean 25%) at the highest dose, this finding was not supported by a second method (Liquid Scintillation Counting (LSC), which indicated that concentrations were 110% of nominal for all doses). Given that the methods indicated that concentrations were well maintained in general, the Dossier Submitter preferred to use the nominal concentration of 0.0001 mg/L for classification, and the value of 0.00011 mg/L (a mean measured value using LSC) was referred to in the report in error. In addition, a new fish full life cycle (FFLC) test has become available, with a mean measured NOEC of 0.000063 mg/L (nominal 0.00008 mg/L), supporting the original proposal for the chronic M-factor.

One MSCA agreed with the proposal but highlighted that specific concentration limits (SCLs) should be assigned under the DSD, and a second MSCA pointed out some missing information from the description of physico-chemical properties that are not directly relevant to this opinion.

Assessment and comparison with the classification criteria

***Degradability*:**
Fenpyroximate is hydrolytically stable under standard conditions at pH 4, 7 and 9. The experimental aquatic photodegradation half-life at pH 7 was 1.5 hours according to first order kinetics; the DAR indicates that a major degradant was the Z-isomer of the parent substance (although not relevant for classification, this could be important for the interpretation of the algal toxicity study).

Fenpyroximate failed a test for ready biodegradation (achieving at most 1.5% mineralization in 29 days), although the substance appeared to be inhibitory to microorganisms at the concentration used (17.5 mg/L, which significantly exceeds the measured solubility in pure water of around 0.025 mg/L).

Simulation tests in two aerobic water-sediment systems using the radiolabelled substance indicated rapid elimination from the water phase (with a dissipation half-life of around 3 days) due to a combination of primary degradation and adsorption to sediment (around 40 % of the applied radioactivity was found in the sediment immediately after application). Degradation in sediment was slower, with DT_{50} values of 24 – 28 days. A maximum of 1.9 % mineralization occurred over 105 days, and bound residues were increasingly formed during the study period (up to 28 % after 105 days). No information was provided in the CLH dossier about primary degradant identities, concentrations or properties, although further details are available in the DAR (which mentions three major metabolites, and identifies a data gap for the formation of other possible metabolites). The EFSA opinion indicates that the whole system geometric mean DT_{50} was 28.8 days for the sediment compartment and 1000 days for the water compartment.

The available information indicates that fenpyroximate is neither rapidly degradable (CLP) nor readily biodegradable (DSD) in the aquatic environment.

***Bioaccumulation*:**
Fenpyroximate has a log K_{ow} of 5.01. Measured fish BCF values from one study normalised to a 5% lipid content were 870 L/kg wet weight (steady state) and 1001 L/kg wet weight (kinetic). It is not indicated whether growth correction would have been desirable, but both values exceed the CLP and DSD criteria for bioaccumulation (500 and 100 L/kg, respectively).

***Ecotoxicity*:**
The lowest reliable ecotoxicity results were as follows (the key studies for classification are highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	*Oncorhynchus mykiss*	**96-h LC_{50} = 0.00105 mg/L**	21-d NOEC = 0.00019 mg/L
	Pimephales promelas	-	**34-d NOEC = 0.0001 mg/L**
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} = 0.00328 mg/L	21-d NOEC = 0.00068 mg/L
Aquatic algae and plants	*Scenedesmus subspicatus* [*Desmodesmus*	72-h E_rC_{50} = 0.00554 mg/L	72-h NOE_rC = 0.001 mg/L

	subspicatus]		

Note: All values except the long-term *P. promelas* result and algal study were based on mean measured concentrations.

Two freshwater fish species had acute LC_{50} values within a factor of 5 of the most sensitive result, so there appears to be good consistency in acute sensitivity amongst fish species. *O. mykiss* had a similar sensitivity to *P. promelas* in long-term testing (so lack of acute toxicity data for the latter species does not appear to be relevant for the classification proposal). The lowest long-term fish toxicity result is based on nominal concentrations, because analytical measurements showed that test concentrations were well maintained. This result is supported by the results of a FFLC study for the same species reported by the Dossier Submitter in response to the public consultation comments (30-day NOEC of 0.00008 mg/L (nominal) for the same endpoint of reduced growth). Acute sensitivity of both invertebrates and algae appears to be similar to fish. Algae appear to be around an order of magnitude less sensitive than fish or invertebrates for long-term endpoints.

RAC notes that the CLH dossier presents very little information about the invertebrate and algal studies. However, due to the rapid aquatic photolysis, the parent substance may have been significantly degraded over the duration of the algal test. In addition, the substance is used as an acaricide, so the sensitivity of other invertebrate species could be different to *D. magna*. The DAR mentions some additional studies that are not included in the CLH dossier, including a 'microcosm' study of effects on total abundance and community composition of zooplankton in the presence of sediment, which gave an overall 28-day NOEC of 0.001 mg/L.

Classification according to CLP

Acute aquatic hazard:
The lowest reliable short-term aquatic toxicity result was a 96-h LC_{50} of 0.00105 mg/L for the fish *Oncorhynchus mykiss*. This is supported by acute toxicity data on two other fish species, an invertebrate and algae. Fenpyroximate is therefore classifiable as:

Aquatic Acute 1 (H400), with an M-factor of 100 ($0.001 < L(E)C_{50} \leq 0.01$ mg/L).

Chronic aquatic hazard:
Fenpyroximate is not considered to be rapidly degradable, and has a fish BCF greater than 500 L/kg. Reliable and relevant long-term aquatic toxicity data are available for all three trophic levels. The lowest value is for *P. promelas*, with a 34-d NOEC of 0.0001 mg/L (supported by a 30-day NOEC of 0.00008 mg/L (nominal) for the same endpoint of reduced growth from a FFLC study with the same species). These concentrations are below the threshold value of 1 mg/L for non-rapidly degradable substances, leading to classification as:

Aquatic Chronic 1 (H410) and an M-factor of 1000 ($0.00001 < NOEC \leq 0.0001$ mg/L).

Classification according to DSD

The lack of ready biodegradation, fish BCF above 100 L/kg and 96-h LC_{50} of 0.00105 mg/L for the fish *Oncorhynchus mykiss* (with a similar value for invertebrates and algae) mean that fenpyroximate fulfils the criteria for classification with N; R50-53. The following specific concentration limits are applicable:

Concentration of fenpyroximate in the mixture, C (w/w)	**Classification of the mixture**
$C \geq 0.25\%$	N; R50-53
$0.025\% \leq C < 0.25\%$	N; R51-53
$0.0025\% \leq C < 0.025\%$	R52-53

In summary, the RAC agrees with the original proposal of the Dossier Submitter.

REFERENCES:

Sano, Y., Nokata, M.: Effects on Fenpyroximate in human. Eyes and skin irritation. Nihon Nohyaku Co. September 1992, unpublished report

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).