Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

fenamiphos

ECHA/RAC/CLH-O-0000001374-78-03/F

Adopted

15 September 2011

Annankatu 18 | P.O. Box 400 | 00121 Helsinki | Finland
www.echa.eu | Tel.: + 358 9 68.61.80

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

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

Substance Name: ***fenamiphos***

EC Number: ***244-848-1***

CAS Number: ***22224-92-6***

The proposal was submitted by ***the Netherlands*** and received by RAC on ***19 October 2010.***

The proposed harmonised classification

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	Acute Tox 2* H300 Acute Tox 3* H311 Aquatic Acute 1 H400 Aquatic Chronic 1 H410 M-factor: 100	T+; R28 T; R24 N; R50/53 Specific Concentration limits: Concentration Classification C≥0.25% N; R50/53 0.025%≤C<0.25% N; R51/53 0.0025%≤C<0.025% R52/53
Current proposal for consideration by RAC	Acute Tox 2 H300 Acute Tox 2 H310 Acute Tox 2 H330 Eye irrit 2 H319 Aquatic Acute 1 H400 Aquatic Chronic 1 H410	T+; R26/28 T; R24 Xi; R36 N; R50/53 Specific Concentration limits:

	M-factor: 100	Concentration Classification C≥0.25% N; R50/53 0.025%≤C<0.25% N; R51/53 0.0025%≤C<0.025% R52/53
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	Acute Tox 2 H300 Acute Tox 2 H310 Acute Tox 2 H330 Eye irrit 2 H319 Aquatic Acute 1 H400 Aquatic Chronic 1 H410 M-factor: 100	T+; R26/28 T; R24 Xi; R36 N; R50/53 Specific Concentration limits: Concentration Classification C≥0.25% N; R50/53 0.025%≤C<0.25% N; R51/53 0.0025%≤C<0.025% R52/53

***** Minimum classification

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on ***19 October 2010***. Parties concerned and MSCAs were invited to submit comments and contributions by ***03 December 2010***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Norbert Rupprich***
Co-rapporteur, appointed by RAC: ***Hans-Christian Stolzenberg***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***15 September 2011,*** in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.
The RAC Opinion was adopted by ***consensus.***

OPINION OF RAC

The RAC adopted the opinion that ***fenamiphos*** should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
	fenamiphos	244-848-1	22224-92-6	Acute Tox. 2 Acute Tox. 2 Acute Tox. 2 Eye irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H300 H310 H330 H319 H400 H410	GHS06 GHS07 Dgr	H300 H310 H330 H319 H410		Acute M=100 Chronic M=100	

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	fenamiphos	244-848-1	22224-92-6	T+; R26/28 T; R24 Xi; R36 N; R50/53	T+, Xi, N R: 24-26/28-36-50/53 S: ½-23-26-28-35-36/37-45-60-61	C≥0.25% N;R50/53 0.025%≤C< 0.25% N;R51/53 0.0025%≤C <0.025% R52/53	

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by ***the Netherlands***.

Background

Fenamiphos was included in Annex VI to the CLP regulation in 2004 (29. ATP; Commission Directive 2004/73/EC of 29 April). A discussion regarding a change of the classification took place at the TC C&L in November 2006 (Summary record ECB/20/07). The TC C&L discussion was only related to acute toxicity and eye irritation. TC C&L agreed to additionally classify fenamiphos as to acute toxicity and eye irritation. However, the TC C&L conclusion was not implemented in Annex I of Directive EC 67/548 and consequently not included in Annex VI of Regulation EC 1272/2008. Therefore, a proposal for changing the current harmonised classification and labelling was prepared. This proposal focuses on the changes in the classification of fenamiphos as discussed by the TC C&L in November 2006. However, information on all other hazard classes is included in the background document as additional information.

ECHA's Committee for Risk Assessment (RAC) has developed this opinion after entry into force of the 2nd ATP to Regulation EC 1272/2008 in March 2011. On request of the European Commission, RAC has scrutinised decisive information on environmental hazard assessment, focusing only on necessary amendments for classification according to the criteria introduced by the 2nd ATP.

Acute toxicity

Proposal of the dossier submitter

As outlined in chapter 5.2 of the background document and in the corresponding table of the opinion document the dossier submitter proposes to revise the classification for acute toxicity oral, dermal and by inhalation) and to classify fenamiphos for acute toxicity for all three routes of exposure. The dossier submitter's proposal is based on new experimental information on acute toxicity and corresponds to the TC C&L conclusion in November 2006.

Comments submitted by concerned parties

All comments received during public consultation support the dossier submitter's classification proposal for acute toxicity.

Outcome of the RAC assessment

RAC considered the information in the background document sufficient and scientifically sound, checked the corresponding justifications for acute toxicity (oral, dermal and by inhalation), and concluded to support the dossier submitter's proposal as well.

Please find the relevant key data, classification criteria and classification proposals in the following table:

	Key data	CLP	DSD
Acute oral	LD 50 of 6 mg/kg, rat, oral	Acute Tox. 2 (H300)	T+, R28

		(5-50 mg/kg)	(up to 25 mg/kg)
Acute dermal	LD 50 of 72 mg/kg, rat, dermal	Acute Tox. 2 (H310) (50-200 mg/kg)	T, R24 (50-400 mg/kg)
Acute inhalation	LC 50 (aerosol) of 0.065 mg/l, rat	Acute Tox. 2 (H330) (0.05-0.5 mg/l)	T+; R26 (up to 0.25 mg/l)

Eye irritation

Proposal of the dossier submitter

As outlined in chapter 5.3 of the background document and in the corresponding table of the opinion document the dossier submitter proposes to revise the classification for eye irritation and to classify fenamiphos as an eye irritant. The dossier submitter's proposal is based on new experimental information on eye irritation and corresponds to the TC C&L conclusion in November 2006.

Comments submitted by concerned parties

All comments received during public consultation support the dossier submitter's classification proposal for eye irritation.

Outcome of the RAC assessment

RAC considered the information in the background document sufficient and scientifically sound, checked the corresponding justification for eye irritation, and concluded to support the dossier submitter's proposal as well.

The key results of the relevant rabbit eye irritation study are summarised in the following table. All irritation effects observed proved to be fully reversible:

Type of effect	Irritation scores 24 hours	Irritation scores 48 hours	Irritation scores 72 hours
Cornea opacity	1,1,1,1,1,1	1,1,1,1,1,1	1,1,1,1,1,1
Iris lesion	1,1,1,1,1,1	1,1,1,1,1,1	0,1,1,1,1,1

The classification criteria considered relevant for these types of eye irritation are summarised in the next table:

	CLP criteria for eye irrit. 2 (H319)	DSD criteria for Xi; R36
Corneal opacity	>= 1	>= 2
Iris lesions	>= 1	>= 1
in at least x/y animals	2/3 or 4/6	2/3 or 4/6

Based on these relevant data, following comparison with the relevant classification criteria, RAC supports the proposal of the dossier submitter to classify fenamiphos for eye irritation

(CLP: eye irrit. 2 (H319); DSD: Xi; R36). The DSD criteria for Xi; R36 are fulfilled for iris lesions, while the CLP criteria for eye irrit. 2 (H319) are fulfilled both for iris lesions and corneal opacity.

Hazardous to the aquatic environment

Proposal of the dossier submitter

As there is already an existing Annex VI entry for the environmental hazard classification of fenamiphos (table 3.1: H400, H410, M=100; table 3.2: N;R50/53, SCL: C ≥ 0.25% N;R50/53 / 0.025% ≤ C <0.25% N;R51/53 / 0.0025% ≤ C <0.025% R52/53), the dossier provided the data on environmental hazard just for information, and no comments during public consultation referred to this hazard class and its underlying information.

Outcome of the RAC assessment

The submitted dossier provides only sparse information about the aquatic toxicity tests with fenamiphos, far from comparable to the standard requirement of robust study summaries (RSS). Therefore RAC consulted the original study reports from the two decisive studies, namely the acute daphnia test denoted as Irvita Study R-18525 (2005), and the 21d chronic daphnia study under flow-through conditions identified as Surprenant Study 98431 (1988).

While the complete presented information apparently justifies the existing hazard classification, RAC applied particular scrutiny to the aforementioned studies for verifying adequate M-factors and the chronic hazard category in accordance with the new criteria of the 2nd ATP to Regulation EC 1272/2008.

The acute test with *Daphnia magna* (Irvita, 2005) has been conducted according to standard test guidelines (EU Testing Method C.2 and OECD Test Guideline 202) and in compliance with the standards of Good Laboratory Practice. Fenamiphos was tested as technical grade with 95.7% active ingredient (BD section 1.2 on substance ID states minimum purity of 920 g/kg [which should read ≥ 92% w/w]). Considering the rapid photolytic degradability of fenamiphos, the actual test was conducted in darkness. Safelight conditions were applied during media preparation and observations. At test beginning, LC-MS/MS measured concentrations ranged 74...86% of the nominal concentrations. After 48h at test termination, the measured concentrations ranged 81...91% of the initial measured concentrations, with exception of the medium level treatment (65% of initial concentration, i.e. 1.15 µg/L measured for nominal 2.07 µg/L treatment). For test evaluation the measured concentration levels were expressed as geometric means.

The concentration effect curve was very steep with no effect up to 0.939 µg/L, 90% immobile animals at the next treatment level of 1.43 µg/L, and 100% immobilisation at higher test concentrations. Hence, the calculated **EC50 of 1.06 µg/L** has a quite broad 95% confidence interval, ranging 0.943...1.43 µg/L (profile likelihood method). At the first measurements after 24h test duration, the EC50 was 2.48 µg/L (95% confidence interval 2.23...3.34 µg/L), with no effect at the concentration causing 90% immobilisation after 48h test duration, thus showing a pronounced increase of fenamiphos toxicity during the course of the test.

The chronic study with *Daphnia magna* (Surprenant, 1988) has been operated according to the "Protocol for Conducting a Flow-Through Life Cycle Toxicity Test with *Daphnia magna* following FIFRA Guide Lines, SLS Protocol #091087/DM-LC.FIF" and in compliance with the standards of Good Laboratory Practice. Diluter stock solutions were prepared with ^{14}C-Fenamiphos Technical (99.6% active ingredient) and acetone as solvent. Maximum acetone

concentration was 24 µL/L in solvent control and highest treatment level, flow rate was approximately six aquarium volumes per 24h equalling a 90% test solution replacement rate of ca. 6h. Weekly radiometric analyses for ^{14}C-fenamiphos established proper diluter system function throughout the 21d test period and mean measured concentrations which ranged 100...114% and averaged 106% of nominal levels. Weekly HPLC analyses of the highest test concentration (0.47 µg/L nominal) rendered 0.59 µg/L (standard deviation: ± 0.086) fenamiphos, i.e. 125% of the nominal level.

Survival rates of control treatments after 21d were 95% (pooled; control 98%, solvent control 93%), well fulfilling the 80% validity criterion of OECD Test Guideline 211 (2008), whereas the cumulated numbers of 49 offspring per female (pooled; control 46, solvent control 53) did not meet the criterion of the recent guideline requirements (≥ 60 offspring per surviving parent animal). No parent animal survived in the highest treatment level (0.49 µg/L mean measured), while survival rates in all other treatment levels did not differ statistically ($P \leq 0.05$) from the control survival rates. Apart from the highest treatment level, neither reproduction was affected, yielding 49...68 offspring per parent animal in all other treatments.

The most sensitive endpoint has been growth, measured as individual body lengths. The study report stated that at 0.24 µg/L mean measured fenamiphos concentration (i.e. the highest treatment level with unaffected survival rates), the mean body length of 4.2 mm was significantly ($P \leq 0.05$) lower than in controls with a mean length of 4.6 mm (pooled; control 4.5 mm, solvent control 4.7 mm); the mean lengths in the other three treatment levels (0.032, 0.066, 0.12 µg/L) were 4.5 mm, statistically not different from the pooled controls. The study report concludes a NOEC of 0.12 µg/L (mean measured).

A statistical re-evaluation of the raw data listed in the study report reveals however the following results:

Both control and solvent control are normally distributed (Shapiro-Wilks-Test), and an F-test confirms variance homogeneity. However, a t-test reveals that the controls show significantly ($p < 0.01$) different body length means and should not be pooled. This is also confirmed by non-parametric tests as Levene-, U-, and Kruskal-Wallis- tests. Nevertheless, statistical evaluation confirms that the mean of the pooled control differs significantly from at least one of the four 0.032, 0.066, 0.12, and 0.24 µg/L treatments means (Kruskal-Wallis-Test, $p << 0.001$), and that both the 0.24 µg/L and the 0.066 µg/L treatments show significantly different body length means than the pooled control (level of significance $\alpha = 0.0125$, multiple U-test). Applying the same evaluation procedure with reference to the solvent control only, which is adequate according to statistical state-of-the-art processing, reveals that all four treatment means are significantly different ($p < 0.0125$). Hence no NOEC can be derived for body length reduction in this 21d study as the lowest treatment level differs already significantly from the solvent control. The LOEC = 0.032 µg/L.

Table: *Daphnia magna* mean body lengths [mm] of adults after 21d exposure to fenamiphos

	mean [mm]	coefficient of variation [%] (all single values)	reduction of body length compared to solvent control [%]
control	4.53	4.7	
solvent control	4.67	4.0	
[*pooled control*]	*4.59*	*4.6*]	
0.032 µg/L	4.55	3.3	2.6
0.066 µg/L	4.45	3.9	4.7
0.12 µg/L	4.53	3.3	3.0
0.24 µg/L	4.24	3.5	9.2
0.49 µg/L	-	note: no adults survived in this treatment level	

During its further discussion RAC concluded that despite the statistical significance there is no clear concentration-response relation and the biological relevance of the body length reductions below 5 % is not sufficient for classification purposes, and the 9.2 % reduction at 0.24 µg/L is borderline. With a view to the other parameters, i.e. survival (no significant effect up to 0.24 µg/L, 100% mortality at 0.49 µg/L) and reproduction (no significant effect up to 0.24 µg/L; for the 0.49 µg/L treatment, the percentage of reduction could not be calculated as 'cumulated offspring per surviving female' due to the 100% mortality of parent animals), some uncertainty remains about the precise effect threshold. However RAC concludes that for classification purposes it is sufficient to confirm the evidence for this threshold being above 0.12 µg/L and below 0.49 µg/L.

Conclusions according to 2nd ATP

The existing Annex VI entry is based on the main facts that fenamiphos is not rapidly degradable according to classification criteria and is very toxic to aquatic organisms with effect concentrations well below 1 mg/L. RAC considers the reported bioconcentration factor (BCF) value equivocal as it is based on radiolabel and hence potentially overestimated, and as no specifications on lipid normalisation are reported. However, the BCF is not decisive for classification under 2nd ATP criteria, as chronic data for all three trophic levels (fish, crustaceans, algae) are available. The 2nd ATP introduced independent application of the acute and chronic classification categories with additional criteria for long-term effects, and requires indicating appropriate M-factors for both classification categories 1.

Acute Category 1 requires the lowest LC50 or EC50 from all three tested trophic levels to be ≤ 1 mg/L. The acute *Daphnia* test with EC50 = 0.00106 mg/L confirms this hazard category. Regarding selection of an appropriate M-factor, this value is very close to the decision criterion 0.001 mg/L and RAC notes the broad 95% confidence interval, the particular analytical deviation just in the key concentration range adding further uncertainty to the steep

regression curve, and the pronounced toxicity increase from 24h to 48h test duration. However, based on 0.001 < 0.00106 ≤ 0.01 mg/L, **M = 100**.

Chronic Category 1 requires the lowest NOEC from long-term tests with all three trophic levels to be ≤ 0.1 mg/L for not rapidly degradable substances. The 21d *Daphnia* test with effect thresholds well below 1 µg/L thus confirms hazard category Chronic 1, and for 0.0001 < NOEC ≤ 0.001 mg/L a corresponding **M = 100**.

Under DSD criteria, the basis for the acute M-factor above corresponds to SCL (specific concentration limits) as follows:

Concentration	Classification
C≥0.25%	N;R50/53
0.025%≤C<0.25%	N;R51/53
0.0025%≤C<0.025%	R52/53

where C is the concentration of fenamiphos in the preparation.

This SCL compilation matches the existing entry as in table 3.2 of Annex VI to CLP Regulation EC 1272/2008.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[1]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter.