Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

flufenoxuron

ECHA/RAC/DOC No CLH-O-0000001741-79-01/F

Adopted

10 June 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: ***flufenoxuron***

EC Number: ***417-680-3***

CAS Number: ***101463-69-8***

The proposal was submitted by ***France***
and received by RAC on ***31 March 2010.***

Harmonised classification originally proposed by the dossier submitter:

	Directive 67/548/EEC (criteria)	CLP Regulation (EC) No 1272/2008
Current entry in Annex VI CLP Regulation	none	none
Proposal by dossier submitter for consideration by RAC	Repr. Cat 3; R63 R64 Xn; R48/22 N; R50/53	Repr. 2 – H361d Lact. – H362 STOT Rep. 2 – H373 Aquatic. Acute 1 – H400 M-factor = 10 000 Aquatic. Chronic 1 – H410 M-factor = 10 000
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Repr. Cat 3; R63 R64 Xn; R48/22 N; R50/53	Repr. 2 – H361d Lact. – H362 STOT RE 2 – H373 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410

PROCESS FOR ADOPTION OF THE OPINION

France 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 ***31 March 2010***. Parties concerned and MSCAs were invited to submit comments and contributions by ***14 May 2010***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Boguslaw Baranski***
Co-rapporteur, appointed by RAC: ***Alicja Andersson***

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 ***10 June 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 ***flufenoxuron*** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

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 state ment Code(s)	Suppl. Hazard statement Code(s)		
	flufenoxuron	417-680-3	101463-69-8	Lact. Aquatic Acute 1 Aquatic Chronic 1	H362 H400 H410	GHS09 Wng	H362 H410		Acute M = 10 000 Chronic M = 10 000	

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	flufenoxuron	417-680-3	101463-69-8	R64 R33 N; R50/53	N R: 33-64-50/53 S: 2-22-36-37-46- 60-61	C≥0.0025% N; R50/53 0.00025%≤C<0.0025% N; R51/53 0.000025%≤C<0.00025% R52/53	

SCIENTIFIC GROUNDS FOR THE OPINION

Flufenoxuron is an active ingredient in agricultural pesticides and biocidal products and therefore it requires harmonised classification of all hazard classes.

Physical Hazards

Explosivity

Based on the results of the study performed in accordance with A.10 of Regulation (EC) No 440/2008 “Explosive properties” and in compliance with Principles of Good Laboratory Practice (GLP) the dossier submitter concluded that no classification for explosivity of flufenoxuron is justified.
RAC is sharing this opinion.

Flammability

In the study performed in accordance with A.10 of Regulation (EC) No 440/2008”Flammability (solid)” and conducted in compliance with the GLP flufenoxuron could not be ignited with a flame. Flufenoxuron has no self-ignition temperature. Therefore the dossier submitter proposed no classification for flammability.
RAC supports this conclusion.

Oxidising properties

Based on the results of the study performed in accordance with A.17 of Regulation (EC) No 440/2008 ”Oxidizing properties” conducted in compliance with GLP the dossier submitter proposed not to classify flufenoxuron in respect of its oxidising properties.
RAC supports this conclusion.

Health Hazards

Acute Toxicity

Based on the results of the available acute toxicity studies, the Dossier Submitter proposed no classification for acute toxicity. This is supported by RAC.

Skin and eye irritation

Based on the results of available studies, the Dossier Submitter proposed no classification for skin and eye irritation. This is supported by RAC.

Respiratory or Skin sensitisation

The results of the Guinea pig maximisation test indicate that flufenoxuron is not a skin sensitizer, therefore no classification was proposed by the Dossier Submitter, and this is supported by RAC.
No experimental or epidemiological data are available for respiratory sensitisation: no classification is proposed.

Germ cell mutagenicity

Flufenoxuron did not induce reverse gene mutations in three bacterial studies. Flufenoxuron did not induce mitotic gene conversion in a Sacharomyces gene conversion assay. It was also not mutagenic in two *in vitro* gene mutation tests in Chinese hamster V79 cells. A positive, although not dose-dependent, response was noted in one *in vitro* chromosomal aberration test with CHO cells in the presence of S-9 mix. However this positive result was not reproduced in the repeat test in this study. Furthermore, clear negative results were reported in two other *in vitro* chromosomal aberration assays employing rat liver cell line (RL4) and human lymphocytes, respectively.
In vivo, two chromosomal aberration assays and one micronucleus assay all produced negative results. Additionally, a negative result was obtained in an *in vivo* rat liver unscheduled DNA synthesis assay.

The dossier submitter concluded that the negative results obtained *in vivo* were sufficient to counter the weak evidence arising from the isolated positive finding in one of the *in vitro* chromosomal aberration assay. No classification for mutagenicity was proposed.
This view was shared in all comments received during public consultation. RAC is of the opinion that flufenoxuron does not show relevant mutagenic properties and should not be classified for mutagenicity.

Carcinogenicity

The Dossier Submitter presented and evaluated the data of three carcinogenicity studies: one on rats and two on mice.

In the study on rats, no treatment related increases in the incidence of tumours were observed.

In the first study on mice there was a non-dose-dependent increased incidence of hepatocellular carcinoma in all groups of males and in low dosed females in comparison with concurrent control, which was paralleled by decrease of hepatocelular adenomas in exposed groups. The combined incidence of adenomas and carcinomas in liver were comparable in the treated and concurrent control group. The incidence of hepatocellular carcinomas in the exposed mice were, however, well within the historical control values, while the incidence in control animals were below the historical control range. As such, the increase of hepatocellular carcinoma could have occurred by chance as result of lowered incidence of carcinomas in control animals. The incidence of splenic hemangiosarcoma in the female mice exposed at the highest dose of flufenoxuron of ca. 7 500 mg/kg bw/day in diet (50 000ppm) was increased. At this dose level flufenoxuron elicited also excessive hepatocellular toxicity (single cell necrosis, hepatocellular hypertrophy and aggregation of Kupffer cells) and

pronounced decrease in body weight of males and females demonstrating that the maximum tolerated dose of flufenoxuron in this long term carcinogenicity study was exceeded.

In the second study on mice with the highest dose level in the range of 1592-1890mg/kg/bw/day (10 000ppm) flufenoxuron did not induce an increased incidence of hepatocellular carcinoma or any other malignant and benign tumours in males or females.

In conclusion, the Dossier Submitter evaluated that the available evidence do not warrant classifying flufenoxuron as carcinogen. This opinion was shared in all comments received during public consultation.

In the opinion of RAC the results of three long term carcinogenicity studies in two animal species do not provide sufficient evidence that this chemical has carcinogenic properties that fulfill the classification criteria, therefore no classification is proposed.

Reproductive Toxicity

Adverse effects on sexual function and fertility

Based on the results of the two-generation study the dossier submitter concluded that flufenoxuron is not affecting fertility of animals.

RAC is of the opinion that results of appropriate experimental data reviewed in the background document provide evidence that flufenoxuron is not affecting sexual function and fertility.

Adverse effects on development of the offspring

No developmental toxicity was reported in standard developmental toxicity studies on rats and rabbits. The only results that indicated a possible effect on development came from a two-generation study in rats, in which dams were exposed from 10 weeks prior to mating until the post-weaning period. In this study, increased post-natal pup mortality, reduced pup body weight development during the lactation period and alterations in adjusted weights of brain, heart and liver in weanling pups were reported, mostly from day 8 of lactation. There were no such effects when flufenoxuron was administered to rats from day 3 of gestation until weaning; nor when it was administered from 10 weeks before mating until parturition but not during lactation.

Taking into account the data presented in the background document, it is concluded that a necessary pre-requisite for flufenoxuron to induce these effects on the offspring is a long-term exposure that spans a period before mating, during pregnancy and extends through lactation. Thus, it is evident that in order to observe any developmental effects in the offspring, the exposure of dams has to continue throughout these three periods.

The Dossier Submitter originally proposed a classification of Repr. 2 – H361d in accordance with CLP and of Repr. Cat. 3; R63, in accordance with Directive 67/548/EEC. However, the Dossier Submitter did not propose this classification in the dossier resubmitted after public consultation. In the public consultation three Member States Competent authorities (MSCA) were in favour of this originally proposed classification, two MSCA considered that such classification was not warranted, and one MSCA requested more detailed data.

RAC Opinion

During the public consultation and RAC discussions, several comments were received that questioned the originally proposed classification for developmental toxicity. The following factors were considered in reaching a decision:

Studies on rats and rabbits did not reveal any pre-natal toxicity of flufenoxuron at doses up to 1000 mg/kg bw/day. At birth, there were no differences in the reproductive indices between control and treated groups. Effects on the growth and survival of pups only became evident during the later stages of lactation, largely from day 8; there were no prominent effects in the first 3 to 4 days after birth. For this effect on pup viability to be exhibited, exposure of the dams had to continue during lactation in addition to throughout gestation (and also before mating): pre-natal exposure alone was not sufficient to induce the effect. Exposure of the dams did not result in embryolethality or malformations; rather, it is postulated in the background document that the adverse effects on pup growth and survival were the result of reduced milk quality. Thus, the critical exposure phase for the induction of the toxicity appears to be lactation.

Although CLP states that 'developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth', it continues 'classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity.' (Annex I section 3.7.1.4.) The hazard statement (H361d) associated with the classification Repr. 2 is 'Suspected of damaging the unborn child'. This would appear to be inappropriate for flufenoxuron, since the substance did not result in developmental toxicity of pups exposed only *in utero*; it was only through lactational exposure that the effects became evident.

In view of these considerations, the RAC does not support a classification of flufenoxuron for developmental toxicity.

Effects on or via lactation

Evidence for flufenoxuron having effects on or via lactation was provided by a two-generation study in rats, in which dams were exposed from 10 weeks prior to mating until the post-weaning period. In this study, increased post-natal pup mortality, reduced pup body weight development during the lactation period and alterations in adjusted weights of brain, heart and liver in weanling pups were reported, mostly from day 8 of lactation. There were no such effects when flufenoxuron was administered to rats from day 3 of gestation until weaning; nor when it was administered from 10 weeks before mating until parturition but not during lactation. Thus, it was evident that in order to observe any effects in the offspring during lactation, the exposure of dams had to continue throughout a long pre-mating period, gestation and during lactation. Since lactational exposure is the critical phase for observation of the effects, the toxicity observed is considered to be an effect on or via lactation, rather than developmental toxicity.

Further evidence in support of the hypothesis that flufenoxuron has an effect on or via lactation is provided by some of the data included in the background document. Toxicokinetic studies indicate that flufenoxuron absorbed from the gastrointestinal tract reaches its highest

concentration in fat. The exposure time to reach steady-state is expected to be in the order of 1-2 months in rats. The mean elimination half-life in rats after 28 days of exposure is 34 days. Flufenoxuron was detected and measured in the milk of exposed female rats, with a high level measured after parturition, although cessation of maternal exposure after parturition led to a rapid decrease of its concentration in the milk. There is limited evidence that flufenoxuron can reduce the quantity of milk, based on the observation of a few dead pups with no or a reduced amount of milk in the stomach. A more plausible hypothesis is that long-term exposure before and during pregnancy and lactation can affect the milk quality as the result of reduced triglyceride levels in the dams.

The possibility of pup toxicity as a consequence of direct pup exposure to flufenoxuron in mothers fed has largely been excluded. Firstly, the mortality of pups in the two-generation study was increased before post-natal day 12, suggesting that direct dietary exposure by ingestion of the dams' food (or via coprophagia; both of these occur from post-natal day 16) was not responsible. Secondly, no increase in mortality of pups between post-natal days 0 and 21 was observed in a study in which pregnant rats were fed until weaning with a diet that contained a high dose of flufenoxuron. Thirdly, the toxicity observed in pups (death) was not consistent with that observed during repeated dose studies in adult animals (mild anaemia).

Comparison with the classification criteria

Under the CLP classification criteria, a substance can be classified for effects on or via lactation based on one of the following findings:

(a) human evidence indicating a hazard to babies during the lactation period

There is no human evidence to inform on the potential of Flufenoxuron to cause adverse effects on or via lactation.

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk

In a two-generation study, there was an increase in the incidence of pup deaths and total litter losses in the four offspring generations (F_{1a}, F_{1b}, F_{2a}, F_{2b}) at dose levels equal to and above 61.6 mg/kg bw/day. Lactational exposure of the pups was essential for the induction of the effects. Flufenoxuron was detected in the milk of exposed dams after parturition, although the concentrations decreased rapidly after cessation of treatment. The most plausible explanation for the adverse effects is that reduced triglyceride levels in the dams, as a consequence of flufenoxuron exposure, result in a decreased fat quantity in the milk, which is thus of a poorer quality. This would be consistent with the observed effects in the pups (reduced growth and death).

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk

Toxicokinetic studies indicate that flufenoxuron accumulates in fat and, additionally, it has been measured in milk from exposed female rats. However, the dose obtained by pups during lactation is likely to be substantially lower than that achieved in the dams, and there is no data to inform on the relative susceptibilities of neonates and adults. The toxicological profile suggests that the effects observed were not the result of direct toxicity via the milk.

Based on a comparison of the data with these criteria, the Dossier Submitter concluded that the available evidence is sufficient to classify flufenoxuron for effects on or via lactation.

For the adverse effects during lactation to occur, long term exposure before, during and after pregnancy is needed for bioaccumulation of flufenoxuron in the maternal body, particularly in fat tissue. The data reviewed in the background document therefore indicate that flufenoxuron fulfils the criteria defined in Annex VI of Directive 67/548/EEC in point 4.2.3.3., stating that substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

RAC Opinion

Based on the criterion (b) above being met, the RAC supports the proposal in the CLH dossier. In the opinion of the RAC, flufenoxuron meets the classification criteria of Hazard Category for Lactation effects: **Effects on or via lactation** with the associated hazard statement **H362**, while within a DSD classification it meets the criteria of the risk phrase **R64 "May cause harm to breastfed babies"** and **R33 Danger of cumulative effects**.

Specific Target Organ Toxicity/Repeated dose toxicity

The dossier submitter proposed CLP classification **STOT RE 2 – H373** "May cause damage to organs (red blood cells) through prolonged or repeated exposure" equivalent to DSD classification **Xn; R48/22**. This classification was supported within public consultation by four MSCA, while one MSCA did not find sufficient experimental data to justify classification.

RAC Opinion

The main effect exerted by flufenoxuron in repeated-dose toxicity study with rats, mice and dogs is anaemia, probably haemolytic, which is characterized by decreases in haemoglobin levels and changes in red blood cell parameters with compensatory haematopoiesis. This effect was associated with bone marrow hyperplasia, reflecting a compensatory response to the anaemia and with pigment deposition (probably hemosiderin) in particular in the liver and the bone marrow.

However, the degree of severity of these changes does not reach the level required for classification specific target organ toxicity repeated exposure within CLP regulation or for classification with R48 for haemolytic anaemia in DSD classification system. In addition these haematological effects were mainly observed at dose levels higher than the guidance values indicated in both classification systems.

Based on the detailed comparison of the haematological effects with classification criteria presented in section 5.5.6 of the Background document the RAC is of the opinion that flufenoxuron should not by classified for Specific Target Organ Toxicity/Repeated dose toxicity.

Environmental Hazards

Hazardous to the aquatic environment

The data presented in the CLH dossier included study results used in the evaluation of the substance according to Dir.98/8/EC. All the studies included were already assessed as reliable and their results were used in the classification.

All stakeholders who participated in the public consultation supported the proposed classification for the aquatic environment. Industry expressed its wish however to include into the part on bioaccumulation also results from water-sediment studies to show a lower bioaccumulation of the substance if measured under realistic conditions. These studies (available in the toxicity part of the report) were not included however since their exposure regime was not appropriate for the determination of the BCF required for the classification.

Based on the available information on the substance, i.e.

(i) Lack of ready biodegradability,
(ii) High bioaccumulation potential (BCF> 500),
(iii) Acute toxicity (48h EC_{50} *Daphnia magna* = 0.04 µg/l), and
(iv)Long-term toxicity (21d NOEC *Daphnia magna* = 0.0049 µg/l)

RAC Opinion

RAC agrees with the submitting MS to classify flufenoxuron as Aquatic Acute I with M factor (acute) of 10 000 and Aquatic Chronic I with M factor (chronic) of 10 000. This classification corresponds to N; R50/53 according to Directive 67/548/EEC with the following specific concentration limits:

C≥0.0025%	N; R50/53
0.00025%≤C<0.0025%	N; R51/53
0.000025%≤C<0.00025%	R52/53

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.