Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole -3-carbonitrile

EC Number: 424-610-5
CAS Number: 120068-37-3

CLH-O-0000001412-86-53/F

Adopted

5 June 2015

05 June 2015

CLH-O-0000001412-86-53/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 harmonized classification and labelling (CLH) of:

Chemicals name:	**Fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile**
EC Number:	**424-610-5**
CAS Number:	**120068-37-3**

The proposal was submitted by **France** and received by RAC on **30 June 2014.**
All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS).

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/harmonised-classification-and-labelling-consultation*** on **26 September 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14 November 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Ritta Leinonen**

Co-rapporteur, appointed by RAC: -

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 harmonized classification and labelling was reached on **05 June 2015** and the comments received are compiled in Annex 2.

The opinion was adopted by **consensus**.

Existing Annex VI entry (CLP, Table 3.1)

OPINION OF THE RAC

The RAC adopted the opinion on Fipronil (ISO) that 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)**		
Current Annex VI entry	608-055-00-8	fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile	424-610-5	120068-37-3	Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H301 H311 H331 H372** H400 H410	GHS06 GHS08 GHS09 Dgr	H301 H311 H331 H372** H410		M=10	
Dossier submitters proposal	608-055-00-8	fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile	424-610-5	120068-37-3	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Dgr	**Retain** H410		**Modify** M=10000 M=10000	
RAC opinion	608-055-00-8	fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile	424-610-5	120068-37-3	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Dgr	**Retain** H410		**Modify** M=1000 M=10000	
Resulting Annex VI entry if agreed by COM	608-055-00-8	fipronil (ISO); 5-amino-1-[2,6-dichloro-4-(trifluoromethyl) phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile	424-610-5	120068-37-3	Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H301 H311 H331 H372** H400 H410	GHS06 GHS08 GHS09 Dgr	H301 H311 H331 H372** H410		M=1000 M=10000	

RAC EVALUATION OF ENVIRONMENTAL HAZARDS

Summary of the Dossier submitter's proposal

Fipronil is used as an insecticide. The substance is currently listed in Table 3.1 of Annex VI to the CLP Regulation with the classification Aquatic Acute 1; H400, Aquatic Chronic 1; H410 with an M-factor of 10 for both. The dossier submitter (DS) proposed to revise the existing harmonised classification of the substance as Aquatic Acute 1; H400 with an acute M-factor of 10 000 and Aquatic Chronic 1; H410 with a chronic M-fatcor of 10 000. The classification proposal was based on the substance not being rapidly degradable, non bioaccumulative and very toxic to aquatic organisms. The lowest acute aquatic toxicity value was a 96 hours EC_{50} of 0.0325 µg/L for the invertebrate *Chironomus dilutus* and the lowest chronic aquatic toxicity value was a 28 days NOEC of 0.0077 µg/L for the invertebrate *Mysidopsis bahia*.

Degradation

Fipronil was shown to be hydrolytically stable at pH 5 and 7. At pH 9 fipronil has a hydrolysis half-life of 28 days with only RPA 200766 as breakdown product. The photolysis in water was studied at pH 5 at 25±1 °C. Two major degradation products were formed. The half-life was 3.63 hours under the xenon lamp corresponding to 0.33 days of summer sunlight in Florida. The DS concluded that photolysis can be considered a major route of fipronil degradation in aqueous environment.

In a 28 days OECD 301B biodegradation test fipronil reached 47 % degradation and was not considered readily biodegradable.

[^{14}C]-fipronil degradation in two water/sediment systems showed that in the aerobic aquatic environment fipronil partitions steadily into the underlying sediment where it degrades further by hydrolysis and oxidation. Amongst all metabolites identified RPA 200766 is a major metabolite in water and MB 45950 is a major metabolite in sediment. Two other water/sediment studies showed similar results. There was no information available about the degree of mineralisation for any of the tests.

Table: Half-lives of fipronil in water/sediment tests

	DT_{50}, water (20 °C) [days]	**DT_{50}, total system (20 °C)** [days]	**DT_{50}, water (12 °C)** [days]	**DT_{50}, total system (12 °C)** [days]
Water/sediment, sand	32.8	76.0	62.2	144.1
Water/sediment, clay loam	22.7	39.1	43.0	74.1
Water/sediment, sandy clay loam			10.55	16.68
Water/sediment, sandy loam			4.25	23.00
Water/sediment, mixture of sandy loam sediment and pond water				41.2 14.5 (25 °C)

The degradation of [^{14}C]-fipronil was also investigated in two soils under aerobic conditions. Degradation proceeded mainly via hydrolysis and oxidation. The non-extractable soil residues remained low reaching a maximum of ca. 15 %. In another study [^{14}C]-fipronil degradation was

studied in four soils at 20°C and two soils at 10°C. The degradation pathway followed the lines of the previous study. The degradation rate was temperature dependent with more rapid degradation at 20°C than 10°C. The two major metabolites of finpronil identified in the soil were RPA 200700 and MB 46136.

There is no information available in the CLH report to conclude if the metabolites in water/sediment and soil tests fulfil the criteria for classification as hazardous to the aquatic environment.

Table: Half-lives of fipronil in soil

	DT_{50}, soil (20°C), days	DT_{50}, soil (12°C), days
UK sandy loam soil	128	362
German sandy soil	308	871
Four soils	31-304	
Two soils		358-686 (10°C)

The DS concluded based on the results of the degradation tests that fipronil does not meet the criteria for being rapidly degradable (nor readily biodegradable) in the environment.

Bioaccumulation

The tested log Kow values for fipronil were 4.0 and 3.5 when using the shake flask method and HPLC method, respectively. The bioconcentration factor and bioaccumulation of [^{14}C]-labelled fipronil were measured in a bioconcentration study with fish (*Lepomis macrochirus*) according to the US EPA 165-4 guideline. The test included an uptake phase (continuous flow-through over 35 days) and a 14 days depuration phase. The steady-state bioconcentration factor (BCF) estimated in whole fish was 321. Uptake residues were rapidly and nearly completely eliminated from the whole fish within the depuration phase.

Aquatic toxicity

The available data on aquatic toxicity consist of five acute and two chronic studies for fish, seven acute and four chronic studies on invertebrates, and five acute and two chronic studies for and algae/*Lemna*. All studies are considered valid by the DS. The lowest acute and chronic test results for all three trophic groups are presented in the table below (the key studies are highlighted in bold).

Table: The lowest aquatic toxicity values for fipronil

Substance	**Species**	**Test Guideline**	**Endpoint**	**Toxicity value (µg/L)**	**Conditions**
Fipronil	*Lepomis macrochirus*	US EPA FIFRA 72-1	96h LC_{50}	85.2 (mm)	Flow-through
Fipronil	*Cyprinodon variegatus*	US EPA FIFRA 72-4	35d NOEC	2.9 (mm) corresponds to the highest concentration tested	Early life stage, flow-through
Fipronil	*Chironomus dilutus*	No official guideline	96h EC_{50} (inability to thrash when gently prodded)	0.0325 (initial measured)	Static
Fipronil	*Mysidopsis bahia*	USEPA FIFRA 72-3	96h LC_{50}	0.14 (mm)	Static
Fipronil	*Mysidopsis bahia*	USEPA FIFRA 72-4	28d NOEC	0.0077 (mm)	Flow-through

Substance	Species	Test Guideline	Endpoint	Toxicity value (µg/L)	Conditions
Fipronil	*Scenedesmus subspicatus*	OECD 201 and EEC Dir. 87/302	E_bC_{50}[(1] NOErC	68 40 (nominal, based on measured)	Static

[(1] Study E_rC_{50} not reliable, EC_{50}s from other studies do no specify if it concerned growth or biomass.

Invertebrates are the most sensitive taxonomic group studied. A recent publication by Weston & Lydy (2014) assessed the toxicity of fipronil on 14 benthic macroinvertebrate species. The lowest toxicity for fipronil was seen in a *Chironomus dilutus* test. Actual concentrations were near nominal (median 95 % of nominal, range 66-131 %), but all data were adjusted to reflect actual initial concentrations.

A sublethal (behavioural) endpoint 'inability to thrash when gently prodded' was reported for *C. dilutus*. The 'thrashing' endpoint was assessed using visual analysis. The animal, when it thrashes, creates an S shape in one direction, then a backward S in the other direction, which when they do it fast gives the impression of a figure 8. The ones affected by fipronil did not thrash with the same intensity, giving EC_{50}s of 0.035 and 0.030 µg/L, respectively (based on initial measured concentrations), mean 0.0325 µg/L. The LC_{50}s for both tests were > 0.0815 µg/L. The control showed a mortality of 17 and 13 % respectively. Althought slightly above the usual validation criteria (10 % mortality), the DS considered this value acceptable. The tests followed a non-standard protocol in line with the US EPA guideline for water composition and the OECD guideline for the test conditions. Even if those guidelines refer to long-term exposure with other endpoints, the test conditions used seemed to them to be relevant for the test performed. Furthermore, the test duration matched with the EPA manual recommendations for acute testing for several invertebrate species (2002) which allows 24, 48 or 96 hours exposures. Therefore the DS proposed to consider these studies in the assessment of the acute aquatic hazard classification for fipronil.

The lowest chronic toxicity value proposed by the DS is a NOEC of 0.0077 µg/L for *Mysidopsis bahia* in a 28-day life-cycle test.

Comments received during public consultation

Two Member States (MS) supported the proposed classification. One MS requested clarification to decide on the usefulness of the Weston & Lydy (2014) publication. Another MS acknowledged that the DS did provide justifications for including the Weston & Lydy (2014) study, despite it not being conducted according to GLP nor to the usual standard guidelines or timescales. However, they felt that the reliability and relevance of the study should be carefully considered before concluding on the acceptance of these endpoints.

Industry (IND) commented on the reliability indices used in the CLH report. IND also pointed out that both CLP and REACH Regulations state clearly which kind of test methods, standard or non-standard, GLP or not, can be used in relation to classification but eventually IND concluded that non-GLP data could potentially be used in the assessment if they followed internationally accepted guidelines.

IND further stressed that the publication by Weston & Lydy (2014), on which the acute aquatic classification proposal is based, was not conducted by an authority, as implied by a misleading citation in the CLH report, but by two universities and the results were published in a scientific journal. In addition to the low reliability of this study, it is not in line with the data requirements

for classification and labelling. IND also claimed that as valid GLP data on *C. dilutus* were available these should be preferred if insect data were to be used at all. For crustaceans valid acute and chronic GLP studies with *D. magna* and *M. bahia* were also available. As to the algae studies, they pointed out that for comparison with the acute criteria in the CLP Regulation, data should be recalculated to estimate the effects at 72 or 96 hour and growth rate should be used over biomass or yield. IND stated that acute classification should be based on *M. bahia* with a 48h LC_{50} of 0.17 μg/L. This would result in an acute M-factor of 1000. The chronic classification should be also based on *M. bahia* with a 28d NOEC of 0.0077 μg/L and a chronic M-factor of 10 000. The DS explained that the GLP study proposed by IND for acute classification corresponds to "Fipronil - Toxicity to midge (*Chironomus tentans*) during a 10 day sediment exposure". The study was a spiked sediment study carried out during 10 days sediment exposure.

Assessment and comparison with the classification criteria

Degradation

Fipronil is not readily degradable based on 47 % degradation in a 28 days OECD 301B biodegradation test. Fipronil partitions steadily into underlying sediment in a water/sediment test where it further degrades. Amongst all metabolites identified RPA 200766 is a major metabolite in water and MB 45950 is a major metabolite in sediment. The adsorption on sediment was more or less rapid depending on the characteristics of the sediments and in some cases the half-lives were below 16 days. There was no information about the degree of mineralisation nor was there information on metabolites to conclude if they fulfil the criteria for classification as hazardous to the aquatic environment. Hence, fipronil is considered as non readly degradable.

Bioaccumulation

The measured log Kow values for fipronil were 4.0 and 3.5. The cut-off value for classification is log Kow ≥ 4. However, because the measured BCF for fish is 321, the cut-off value for classification being ≥ 500 for the whole fish, fipronil is not considered to be a bioaccumulative substance for classification purposes.

Acute aquatic toxicity

RAC is of the opinion that the key issue for assessing the classification of aquatic acute toxicity, is the reliability of the Weston & Lydy (2014) study. Article 5 of the CLP Regulation states that new scientific information shall be used in determining whether the substance entails a hazard as set out in its Annex I. Regarding the use of *Chironomus* data the CLP Regulation states that fish, crustaceans and algae are considered as surrogate for all aquatic organisms and data on other species shall also be considered if the test methodology is suitable. The most recent CLP Guidance further states that *"Valid data for short- and long-term tests on other species at the same trophic level shall also be considered, provided they are equivalent in terms of species relevance, testing conditions and test endpoints."* Moreover, as fipronil is an insecticide, aquatic insect data can be relevant in this case.

Since RAC is of the opinion that the Weston & Lydy (2014) is not reliable for classification purposes (see Appendix 1) and can be used only as supporting information, the classification of fipronil is based on the lowest reliable acute aquatic toxicity data available in the CLH report, that for *Mysidopsis bahia*.

There are acute aquatic toxicity data available for all three trophic levels. The lowest acute aquatic toxity data is a 96 h LC_{50} of 0.14 μg/L for the invertebrate *Mysidopsis bahia*. For algae and aquatic plants an E_rC_{50} based on growth is preferred in the classification criteria but in case of fipronil the test giving the lowest results had no reliable E_rC_{50}. In fact in none of the five studies available an

E_rC_{50} was reported. All EC_{50}s in these tests were greater than results the lowest being EC_{50} > 0.120 mg/L.

The Weston & Lydy (2014) study used as supporting evidence, suggests that the acute toxicity of the substance to insects might be higher than currently seen. If reliable data were to become available in the future the acute M-factor might have to be revised.

Chronic aquatic toxicity

There are chronic toxicity data abailable for all three trophic levels. The lowest chronic toxicity result for invertebrates is a 28 day NOEC of 0.0077 µg/L for *M. bahia*.

Conclusion

The most sensitive trophic level is clearly crustaceans/insects. The classification is based on crustacean data supported by *Chironomus* data. The lowest acute aquatic toxicity value 0.14 µg/L is in the 0.1 < LC_{50} ≤ 1 range giving an **acute** M-factor of 1 000. The lowest chronic toxicity value 0.0077 µg/L is in the 0.001 < NOEC ≤ 0.01 µg/L giving a **chronic** M-factor of 10 000 for non-rapidly degrable substance.

RAC therefore recommends that Fipronil should be classified as follows:
Aquatic Acute 1; H400 with an **acute M-factor** of **1 000** and
Aquatic Chronic 1; H410 with a **chronic M-factor** of **10 000**.

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).

Appendix 1 Assessment of the reliability of the Weston & Lydy (2014) ecotoxicity study

ECHA Guidance on information requirements and chemical safety assessment, chapter R.7a, (version 3.0, 2014) contains guidelines for assessing the reliability of a study.

The key points to assess are: the proven ability of the laboratory to perform the test method; the purity/impurities and origin of the test substance as well as the reference substances must be reported; the availability of the raw data from the study, there must be an adequate description of the study e.g. a complete test report, or a sufficiently detailed description of the test procedure, which must be in accordance with generally accepted scientific standards. When the test procedure used to generate the test data is found to differ significantly from that described by the recognised test method or generally accepted scientific standards, or the reliability of the data cannot be established fully, the assessor must decide, if and how the information can be used, e.g. as supporting information where a reliable study already exists.

In the Weston & Lydy (2014) test for *Chironomus dilutus* (W&L study) the purity of tested fipronil was not mentioned, nor were the impurities. RAC is of the opinion that the availability of the raw data is not sufficient to judge if the study is in accordance with generally accepted scientific standards. RAC uses the acute *Chironomus* test guideline (OECD 235, adopted 28 July 2011) as a reference point in its evaluation. The OECD guideline specifies a preferred test duration of 48 hours (96h in W&L study). According to the guideline 1st instar larvae should be used but there is no information of the stage of larvae in W&L study. The endpoint in the guideline is immobilisation. Those animals that are not able to change their position (by crawling and swimming movements) within 15 seconds after mechanical stimulation are considered to be immobilised. The movement of larvae are erratic and phases of high activity are interrupted by phases of no movement. It seems that there is a fine line between the guideline endpoint and the 'inability to thrash when prodded' endpoint. Water quality parameters are monitored in the W&L study but information is not presented in the article. The feeding of the larvae during the test is not allowed in the guideline test. In W&L test the larvae were fed on the second day after which 80 % of the water was replaced with freshly prepared fipronil-spiked solutions. In the W&L study only water from a concentration step near the expected EC_{50} was analysed for verification of initial concentration with compositing solutions prepared on days 0 and 2. Actual concentrations were from 66 to 131 % of nominal covering all tests in the study and all data were adjusted to reflect initial concentrations without knowing if the concentration had been maintained throughout the test. The raw data for assessing the concentration-response curves are missing in the Weston & Lydy study. One validity criterion of the OECD TG 235 is that in the control, including the solvent control if appropriate, not more than 15 % of the larvae should show immobilisation or other signs of disease or other stress at the end ot the test. In the Weston & Lydy study the control survival was 83 and 87 % and no toxicity was reported in the solvent control. The other validity criterion is that the dissolved oxygen concentration at the end of the test should be ≥ 3 mg/L in control and test vessels. Oxygen concentration had been monitored but not reported in the Weston & Lydy (2014) study article.

In general, RAC concludes that the availability of the raw data is not sufficient to consider the study reliable for classification purposes. When assessing the reliability of the W&L study with *C. dilutus* the main concerns are uncertainty of the stage of the larvae, having only initial measured concentrations available near the expected EC_{50}, the feeding of the larvae, actual concentrations not maintained within ± 20 % of the nominal, no possibility to create a concentration-response

curve due to unsufficient availability of the raw data, unreported water quality parameters including oxygen concentration which is a validity criterion. The results, however, are consistent with other aquatic toxicity results and can be considered as supporting information.