Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate

EC Number: 247-525-3
CAS Number: 26225-79-6

CLH-O-0000001412-86-196/F

Adopted

9 March 2018

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CLH-O-0000001412-86-196/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 Regulation (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:

Chemical name: **ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate**

EC Number: **247-525-3**

CAS Number: **26225-79-6**

The proposal was submitted by **Austria** and received by RAC on **23 February 2017.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **4 April 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **19 May 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Pietro PARIS**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **9 March 2018** by **consensus**.

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	607-314-00-2	ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate	247-525-3	26225-79-6	Aquatic Chronic 2	H411	GHS09	H411			
Dossier submitters proposal	607-314-00-2	ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate	247-525-3	26225-79-6	**Add** Aquatic Acute 1 **Modify** Aquatic Chronic 1	**Add** H400 **Modify** H410	**Retain** GHS09 **Add** Wng	**Modify** H410		**Add** M=1 M=1	
RAC opinion	607-314-00-2	ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate	247-525-3	26225-79-6	**Add** Aquatic Acute 1 **Modify** Aquatic Chronic 1	**Add** H400 **Modify** H410	**Retain** GHS09 **Add** Wng	**Modify** H410		**Add** M=1 M=1	
Resulting Annex VI entry if agreed by COM	607-314-00-2	ethofumesate (ISO); (*RS*)-2-ethoxy-2,3-dihydro-3,3-dimethylbenzofuran-5-yl methanesulfonate	247-525-3	26225-79-6	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=1	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Ethofumesate is a racemic mixture of two enantiomers. The herbicidal activity of the two enantiomers has been shown to be equivalent and not different from the racemic mixture. In degradation studies (non-guideline lysimeter study and in a water sediment study) no significant changes in the ratio of the racemate (1:1) were observed, indicating that the degradation and distribution of both enantiomers is the same in the environment. Therefore it was considered adequate that all studies on the active substance where performed using the racemic mixture.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Ethofumesate, an active substance for plant production products (herbicide), is currently classified under Annex VI of the CLP Regulation (Regulation (EC) 1272/2008) with hazard class Aquatic Chronic 2. In view of new information and after a re-evaluation of the existing studies, the DS proposes to classify ethofumesate as Aquatic Acute 1 (M=1) and Aquatic Chronic 1 (M=1).

Degradation

A hydrolysis study conducted according to OECD TG 111 and in compliance with GLP at pH 4, 7 and 9 at 50 °C for 5 days, showed that ethofumesate is hydrolytically stable.

Two studies of the photodegradation of ethofumesate in water were submitted. The first study with radio-labelled ethofumesate in water was conducted according to the guidelines OECD TG 316, US EPA OCSPP Test Guideline No 835.2240, and Japanese MAFF New Test Guidelines Annex No 2-6-2, simultaneously. This study, in compliance with GLP, was carried out at 25 °C in a sterile phosphate buffer solution (pH 7) with continuous artificial light. The study resulted in an experimental DT_{50} of 15.6 d (environmental DT_{50} (Phoenix, Arizona, USA) = 53.2 d). A multitude of transformation products was formed; none of them exceeding 10 % AR. A similar degradation pattern is observed in the second study investigating the photolysis of ethofumesate in water. A large number of minor metabolites were formed, one of them occurred at 9.57 % after 12 hours. The direct phototransformation in water was also investigated in another study whose results showed that environmental half-life relevant to Central Europe was above 1 year and that therefore photochemical degradation of ethofumesate might play a minor role under such conditions.

Two ready biodegradability studies, both carried out according to OECD TG 301D and in compliance with GLP, indicated that ethofumesate is not readily biodegradable. In the first one, ethofumesate was added to the inoculum from the secondary effluent of a municipal sewage treatment plant at a concentration of 1 and 3 mg/L over a period of 28 days at 20 ± 1 °C. The degree of biodegradation expressed as ThOD was -14 % and -4 % within 28 days, in contrast to the reference substance, sodium acetate, which degraded to 65 %. In the second study, ethofumesate was added to the inoculum (activated sludge from a sewage plant treating predominantly domestic sewage) at a concentration of 3 mg/L over a period of 28 days at 20 ± 1 °C. The degree of biodegradation was 10 % after 28 days, in contrast to the reference substances, sodium benzoate and aniline, which degraded to 88 % and 68 %, respectively.

Two aerobic mineralisation in surface water studies were performed according to OECD TG 309 and in compliance with GLP. In the first study, ethofumesate was found to be stable in natural surface water until day 62 of incubation and the mineralisation was marginal with a maximum of 1.1 % (high-dose test) and 0.8 % (low-dose test) at the end of the incubation period. The second study showed ethofumesate was degraded slowly. After a lag-phase of 60 days a degradation of ethofumesate was observed: the remaining amounts of ethofumesate after 88 days were 58.3 % AR and 79.3 % AR in the low- (10 µg/L) and high-dose (100 µg/L) experiment, respectively. The main metabolite formed was NC20645 (ethofumesate carboxylic acid) with a maximum amount of 18.3 % AR. The metabolite identified as BCS CW35117 (ethofumesate acetic acid) was formed at 13.4 % AR and 2.4 % AR in the low-dose and high-dose experiment, respectively. The formation of carbon dioxide due to mineralisation was low (0.9 % and 0.8 % for the low and high concentration, respectively).

The aerobic transformation of radiolabelled ethofumesate was investigated in two water/sediment studies, according to BBA (Biologische Bundesanstalt für Land- und Forstwirtschaft) Guideline Part IV, 5-1, 1990. In the first study, after 103 days of incubation, 32 and 27 % AR (13 and 18 % parent compound) was recovered in the river and pond water phase, respectively, while 57 and 64 % (37 and 41 % parent compound) was associated to the sediments. In the second one, after 234 days of incubation in Waldwinkel and 225 days in Ruckhaltebecken, 5.1 and 26 % (1.5 and 21 % parent compound) of applied radioactivity was recovered in the water phase, while 81 and 58 % (53 and 30 % parent compound) was associated to the sediments. The dissipation half-lives of ethofumesate from the water phases in Waldwinkel and Ruckhaltebecken were 7 and 50 days, respectively. For the whole systems, the half-lives were extrapolated to 285 and 242 days. In other two more recent water/sediment studies, mineralisation of ethofumesate ranged between 1.2 % AR and 15.3 % AR after 103 and 125 days, respectively. Non-extractable residues in the sediment compartment ranged between 14.2 % AR and 43.2 % AR at study end. Whole system half-lives ranged between 89 and 294 days (geomean 170 d; n = 8).

Based on the information above, the DS concludes that ethofumesate is not considered to be rapidly degradable.

Bioaccumulation

Based on experimental data, ethofumesate has a measured log K_{ow} of 2.7 (method OECD TG 107, 25 °C and pH 6.44).

In a bioaccumulation study, carried out according to U.S. EPA guideline 165-4 and in compliance with GLP, bluegill sunfish (*Lepomis macrochirus*) were continuously exposed to radio-labelled ethofumesate at a nominal concentration of 0.124 mg/L for 28 days in a flow-through system and thereafter the depuration of radioactivity followed in untreated water for 14 days. In whole fish, apparent steady-state was achieved after 24 h of exposure to the test material. The steady-state bioconcentration factor for whole fish was 144 L/kg based on total radioactivity. After exposure, a rapid depuration was observed (> 99 % within 3 days).

The actual bioaccumulation of [^{14}C]-ethofumesate in bluegill sunfish (*Lepomis macrochirus*) was also investigated in a flow-through system at a nominal exposure concentration of 0.56 mg/L (no test guideline). In whole fish, a steady-state was achieved after 1 day of exposure to the test material. The steady-state bioconcentration factor for whole fish was 67 L/kg based on total radioactivity. Based on one compartment kinetics for whole fish, a BCF of 72 was determined. After exposure, a rapid depuration similar to the first study was observed (99 % within 3 days).

Based on this information, the DS concludes that ethofumesate does not bioaccumulate.

Aquatic toxicity

Several acute and chronic aquatic toxicity data are available for all three trophic levels. New, valid ecotoxicological data are available.

The ecotoxicological test results are summarised in the following tables (the key data are highlighted in bold).

Method	Test organism	Test system	Results			Test [c]	Reference
			Endpoint	LC_{50}/EC_{50} [mg/L]	NOEC [mg/L]		
OECD TG 203 (1984), US EPA guideline (1985) GLP	*Lepomis macrochirus*	Semi-static 96 h	Mortality	21.2		nom	Anonymous, 1991b
OECD TG 203 (1984), US EPA guideline (1985) GLP	*Cyprinodon variegatus*	Static 96 h	Mortality	25.0		nom	Anonymous, J.B., 1992
US EPA guideline (Guideline E, Subdivision 72-1) GLP	*Oncorhynchus mykiss*	Semi-static 96 h	Mortality	11.91		mm	Anonymous, 1989
US EPA guideline (Guideline E, Subdivision 72-1) GLP	*Cyprinus carpio*	Semi-static 96 h	Mortality	10.92		mm	Anonymous, 1989
OECD TG 203, EEC Directive 79/831, Annex V GLP	*Oncorhynchus mykiss*	Semi-static 96 h	Mortality	26.5		nom	Anonymous, 1991*
OECD TG 203, EEC Directive 79/831, Annex V GLP	*Leuciscus idus*	Static 96 h	Mortality	22.0		nom	Anonymous, 1993*
OECD TG 210 (1992), OECD TG 215 (2000), OECD draft guideline "Fish 2-generation test" (2002) GLP	*Danio rerio*	Flow-through 28 d	Growth		0.156	nom	Anonymous, 2013
US EPA guideline 72-4 GLP	*Pimephales promelas*	Flow-through 28 d	Growth		4.17	mm	Anonymous, 2013
OECD TG 202 (1984), US EPA 540/9-85-005 (1985) GLP	*Daphnia magna*	Static 48 h	Immobilisation	13.52		nom	Barber, I., 1991
OECD TG 202 (1984), EEC Directive 79/831, Annex V GLP	*Daphnia magna*	Static 48 h	Immobilisation	28.1		nom	Thun, S., 1993*
FIFRA Guideline 72-3 GLP	*Mysidopsis bahia*	Static 96 h	Mortality	5.4		mm	Schupner, J.K., Stachura, B.J., 1992

Method	Test organism	Test system	Results			Test [c]	Reference
			Endpoint	LC_{50}/EC_{50} [mg/L]	NOEC [mg/L]		
OECD TG 202 (Part 2, 1984) GLP	*Daphnia magna*	Semi-static 21 d	Reproduction		0.32	nom	Douglas, M.T., James, C.M., Macdonald, I.A., 1990
OECD TG 202 (Part 2, 1984) GLP	*Daphnia magna*	Semi-static 21 d	Reproduction		1.06	mm	Bellmann, W., 1992
OECD TG 202 (Part 2, 1984) GLP	*Daphnia magna*	Semi-static 21d	Reproduction		0.25	mm	Adema, D.M.M., de Rulter, A., 1989
OECD TG 201	*Pseudokirchneriella subcapitata*	Static 72 h	Growth rate	16.347	5.91	mm	Bruns E. and Dorgerloh M., 2008
OECD TG 201	*Anabaena flos-aquae*	Static 96 h	Growth rate	> 20	20	nom	Banman C.S. et al., 2009a
OECD TG 201	*Skeletonema costatum*	Static 96 h	Growth rate	> 20 (72 h)	5 (72 h)	nom	Banman C.S. et al., 2009b
ASTM guideline E 1415-91	*Lemna minor*	Semi-static 14 d	Growth rate	> 52.8	4.3	mm	Scheerbaum D., 1998
ISO guideline (2000) and draft OECD TG 221	*Lemna minor*	Semi-static 14 d	Growth rate	> 42	26	mm	Bogers M., 2001
higher tier study based on OECD TG 221	*Myriophyllum spicatum*	Static 14 d	Growth rate	**0.479**	**0.036**	mm	Banman C.S., 2013
mm – mean measured concentration im – initial measured concentration nom – nominal concentration							

Four acute toxicity studies in fish are reported by the DS. All of the provided reliable LC_{50} values, ranging from 10.92 to 25.0 mg/L, are above the cut-off of 1 mg/L for classification as Aquatic Acute 1. The other studies, by Anonymous (1991) and Anonymous (1993), respectively, are reported as unreliable and marked in the CLH Report as additional information only, due to the deficiencies concerning data on mean measured concentrations in the study reports.

Two chronic toxicity studies to fish are included in the CLH report and are assessed as appropriate and acceptable by the DS. The study by Anonymous (2013) was conducted according to three different test guidelines, OECD TG 210 (1992), OECD TG 215 (2000) and the OECD draft guideline "Fish 2-generation test" (2002); for the evaluation of this study the validity criteria of all used test guidelines were considered. Based on the most sensitive endpoint (growth of parental early life stages and adults) the overall NOEC was 0.156 mg a.i./L, (nominal concentration). In the early life stage toxicity test study by Anonymous (1991) the overall chronic 28-day-NOEC observed was 4.17 mg/L (mean measured concentrations), based on the most sensitive endpoint for growth (standard length and wet weight); a statistical re-evaluation of the original study data performed by Meller M. and Bruns, E. (2013) was reported by the DS, indicating the full reliability of study results from Anonymous (1991).

Three acute toxicity studies for aquatic invertebrates are available and included in the CLH report. The study by Thun S. (1993) is reported as unreliable by the DS as some validity criteria with respect to analytical measurement of the test concentrations are not met. In the fully acceptable

study by Schupner, J.K., Stachura, B.J. (1992), a 96 h LC_{50} value of 5.4 mg/L was determined under static conditions, based on mean measured concentrations.

Three 21 d semi-static *D. magna* studies are reported by the DS, all with NOEC values > 0.1 mg/L.

In total, six toxicity studies to aquatic algae and plants are reported by the DS. All five studies using monocotyledononus aquatic plants (*Lemna* sp.) and algal species providing reliable E_rC_{50} values, ranging from 16.347 to > 52.8 mg/L, give values above the cut-off of 1 mg/L for classification as Aquatic Acute 1. Also, the NOEC values from these studies are all > 0.1 mg/L.

From the available aquatic acute toxicity data, the sixth study shows that aquatic macrophytes are the most sensitive trophic group with E_rC_{50} values < 1 mg/L. In particular, the most sensitive species tested is *Myriophyllum spicatum*, that was exposed to the test substance in a static test system for 14 d. The E_rC_{50} of 0.479 mg/L is based on mean measured concentrations.

Also, for chronic aquatic toxicity, the most sensitive species tested is *Myriophyllum spicatum* with a NOE_rC of 0.036 mg/L (14 d static test), based on mean measured concentrations.

Toxicity studies on other aquatic organisms (one study on *Crassostrea virginica* and three studies on *Chironomus riparius*) were also reported by the DS as reliable information available on ethofumesate. The studies on *C. riparius* provide NOEC values ranging from 3.82 to 14.05 mg/L based on initial measured concentrations. The study on *C. virginica* provides acute and chronic toxicity values (96 h EC_{50} = 1.7 mg/L; NOEC < 0.81 mg/L, both based on new shell growth).

Comments received during public consultation

Three MSCAs commented on the proposed environmental classification. Two of them agreed with the DS's proposal. For one MSCA, it was unclear if the *M. spicatum* 14 days study endpoints were relevant for both acute and chronic classification and in addition it was noted that a sediment phase was included in the study which made interpretation of endpoints difficult. The DS responded by agreeing with the uncertainties raised. They further indicated that *M. spicatum* is commonly used For classification and labelling purposes and that whilst no sediment measures for ethofumesate were made, the concentrations in the aquatic phase were 74 – 83 % of nominal.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal to consider ethofumesate as not rapidly degradable. The substance is hydrolytically stable, not readily biodegradable, and not ultimately degraded to a level greater than 70 % over 28 days in surface water and water/sediment simulation studies.

Bioaccumulation

The measured BCF (for total radioactivity) in whole fish of 144 L/kg is below the decisive CLP criterion (BCF ≥ 500). Therefore, RAC agrees with the DS's proposal to consider that the actual bioaccumulation of ethofumesate is low.

Aquatic toxicity

Myriophyllum spicatum, a rooted macrophyte species, may be considered the target aquatic plant species for ethofumesate. From the other aquatic plants or algae studies reported by the DS, *Lemna* sp. and algae are less sensitive to ethofumesate.

Although the study with *M. spicatum* was conducted according to OECD TG 221 (*Lemna* growth inhibition test) which foresees an exposure period of 7 days, in this case the exposure time was 14 days as recommended by OECD TG 239 (water-sediment *M. spicatum* toxicity test), which is a valid time period to calculate both acute and chronic endpoints. Moreover the study fulfils the validity test criteria reported in OECD TG 239.

Regarding sediment, the OECD TG 239 recommends to determine the concentration at the beginning and the end of the test, at least at the highest test concentrations, unless the water concentration is > 80 % of the nominal. In this study, the condition is not completely verified but the measured concentrations (74 % - 83 % of the nominal) are not too far from this limit. Moreover, at the highest test concentrations the concentrations are > 80 % of the nominal. RAC therefore considers that this study is valid and that *M. spicatum* is an appropriate organism for the classification of ethofumesate.

Acute aquatic hazard

Ethofumesate is of low acute toxicity to fish and aquatic invertebrates with reliable $L(E)C_{50}$ values > 1 mg/L. Instead, the available acute toxicity data on aquatic macrophytes show E_rC_{50} values < 1 mg/L. The most sensitive species tested is *Myriophyllum spicatum* with an E_rC_{50} of 0.479 mg/L, based on mean measured concentrations.

Chronic aquatic hazard

Ethofumesate is of moderate chronic toxicity to fish and aquatic invertebrates with NOEC values of 0.156 mg/L and 0.25 mg/L, respectively. The most sensitive species tested is *Myriophyllum spicatum,* (14 d static test) with a NOE_rC of 0.036 mg/L, based on mean measured concentrations.

Conclusion on the classification

Ethofumesate is considered not rapidly degradable and does not fulfil the criteria for bioaccumulation. The lowest acute toxicity value falls in the range of $0.1 < L(E)C_{50} \leq 1$ mg/L and the lowest chronic toxicity value lies in the toxicity range of $0.01 < NOEC \leq 0.1$ mg/L.

RAC agrees with the DS that ethofumesate fulfils the CLP criteria for classification as **Aquatic Acute 1; H400** with an **M-factor of 1** and **Aquatic Chronic 1; H410** with an **M-factor of 1.**

ANNEXES:

Annex 1 The 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 RAC (excluding confidential information).