Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole

EC Number: 205-725-8
CAS Number: 148-79-8

CLH-O-0000001412-86-143/F

Adopted

15 March 2017

15 March 2017

CLH-O-0000001412-86-143/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: **thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole**

EC Number: **205-725-8**

CAS Number: **148-79-8**

The proposal was submitted by **Spain** and received by RAC on **23 March 2016.**

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

PROCESS FOR ADOPTION OF THE OPINION

Spain 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 **31 May 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **15 July 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Zilvinas Uzomeckas**

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 **15 March 2017** 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	613-054-00-0	thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole	205-725-8	148-79-8	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410			
Dossier submitters proposal	613-054-00-0	thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole	205-725-8	148-79-8	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Wng	**Retain** H410		**Add** M=1 M=1	
RAC opinion	613-054-00-0	thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole	205-725-8	148-79-8	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Wng	**Retain** H410		**Add** M=1 M=1	
Resulting Annex VI entry if agreed by COM	613-054-00-0	thiabendazole (ISO); 2-(thiazol-4-yl)benzimidazole	205-725-8	148-79-8	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Wng	**Retain** H410		**Add** M=1 M=1	

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Thiabendazole is a systemic benzimidazole fungicide used as an active substance in plant protection products, currently listed in Annex VI of CLP. The CLH report presents a classification and labelling proposal based on the information presented in the assessment of thiabendazole under the PPP Regulation. The proposal for changing the current harmonised classification and labelling seeks to amend the existing Annex VI entry and does not address all hazard classes. The existing harmonised entry includes a classification for the environment of Aquatic Acute 1; H400 - Very toxic to aquatic life and Aquatic Chronic 1; H410 - Very toxic to aquatic life with long lasting effects. The dossier submitter (DS) proposed to retain this classification and add acute and chronic M-factors of 1 and 1 respectively. No REACH registration dossier was available for thiabendazole at the time of submission of the CLH dossier.

The DS mentioned "*photolysis seems to play a role in the degradation of Thiabendazole in water*", but this was not considered relevant for the degradability of the substance. The DS further noted that thiabendazole is hydrolytically stable at environmentally relevant temperatures and pH values and, based on the available information (screening and simulation tests), thiabendazole is considered as not rapidly degradable in the aquatic environment for the purposes of classification.

The measured whole fish BCF value of 96.45 is below the CLP trigger value of 500 and the Log K_{OW} of 2.43 (at pH 7) is below the CLP trigger value of 4, both of which indicate a low potential for bioaccumulation.

The DS indicated invertebrates as the most sensitive trophic level. The lowest reliable acute/short-term endpoint for classification purposes is the EC_{50} for *Mysidopsis bahia* of 0.34 mg/L. This is in the range >0.1 to ⩽1.0 and, therefore, thiabendazole should be classified as Aquatic Acute 1 (H400) with an M-factor of 1. The lowest reliable chronic/long-term endpoint for classification purposes is the NOEC for *Daphnia magna* of 0.041 mg/L. This is in the range >0.01 to ⩽0.1 and, therefore, thiabendazole should be classified as Aquatic Chronic 1 (H400) with an M-factor of 1 (not-rapidly degradable).

Degradation

Thiabendazole is hydrolytically stable at pH values of 5, 7 and 9 at 25ºC under sterile conditions in the dark for 30 days (K. Kabler and J. Dikes, 1989) and stable under the high temperature of processing conditions (pH 4, 5, 6 at 90ºC, 100ºC and 120ºC respectively) (Adam, 1999). The K. Kabler and J. Dikes (1989) study was conducted at nominal test concentrations of 10 µg/L in four aqueous buffer solutions (pH 5, 7 and 9). Confirmation of the percentage of ^{14}C-thiabendazole in each test sample was achieved with HPLC and thin-layer chromatography. Based on data generated during this study, the compound ^{14}C-thiabendazole does not hydrolyse in the 5 – 9 pH range. The DT50 was 357.1 at pH 5, 203 at pH 7 and 270.8 at pH 9. In Adam (1999), the hydrolysis of thiabendazole was investigated at pH 4, 5 and 6 at 90ºC, 100ºC and 120ºC for 20, 60 and 20 minutes, respectively. The total recoveries for all samples ranged from 98.8% to 103.5% of the applied radioactivity.

Aqueous photolysis studies indicate that photolysis seems to play a role in the degradation of thiabendazole in water (Adam, 2005 and Schmidt, 2002). The experimental half-life (DT50) and

DT90-values show that thiabendazole was rapidly photodegraded in sterile natural pond water with a photolytic half-life of 2.7 days (summer sunlight at latitudes 30-50ºN). The direct and indirect photochemical degradation of 14C-Thiabendazole was investigated under simulated sunlight in sterile natural pond water at about pH 8. Individual samples were continuously irradiated for a period of 11 days at a temperature of 25ºC. During this incubation period, 14C-Thiabendazole was found to be rapidly photolysed, decreasing from 99.6% to 1.1% of the applied radioactivity and a significant number of radioactive fractions were detected. Three major metabolites (M3, M5 and M6) exceeded 10% of the applied radioactivity. M3 was identified as benzimidazole-2-carboxylic acid. It reached maximum amounts of 16.5% on day 3 and decline to 10.7% by the end of the irradiation. M5 was identified as 1,2-dihydro-3-hydroxyquinoxaline. It reached 16.6% after 3 days and decline to 5.3% after 11 days. M6 was identified as benzimidazole-2-carboxamide, represented 10.3% on day 3 and 4.6% on day 11. All other metabolites were below 10% of the applied radioactivity.

Direct aqueous photodegradation in sterile water at 25°C and pH 5 resulted in an estimated DT50 of 29 hours (Flynn, 1994). Only one metabolite, benzimidazole-2-carboxamide, was observed at levels > 10% (10.22%).

In Schmidt (2002), half-lives were determined at 0.6 to 1.5 days based on a 24-hour day. All these results indicate that direct photolysis by sunlight has to be considered a relevant process for the lifetime of the test item when released into the environment. Photodegradation of thiabendazole in aqueous solution was faster during direct photolysis than during natural water photolysis. Overall, due to the lack of toxicity data for the photochemical degradation products, the DS concluded that the rate of photolytic degradation could not be used to demonstrate rapid degradability of the substance.

In a ready biodegradation study following OECD 301 B, biodegradation of thiabendazole was observed to be 6.5% of the theoretical value within 30 days (Van de Kolk, J., 1998). The ready biodegradability criterion stated in CLP considers substances readily biodegradable when 70% biotic degradation takes place in the 10 days window within the 28 days test period. Accordingly, the DS concluded that thiabendazole could be considered as not readily biodegradable.

A Water/sediment simulation test was conducted in two aquatic systems, a river and a pond, for six months at 20ºC (Ulbrich, 1999). The water/sediment study suggests that thiabendazole mainly disappears from aquatic systems by physical-chemical processes and not by microbial degradation with the concentration of thiabendazole in the sediment depending on the sediment properties. Although short DT50 and DT90 values were registered for the water phase (DT50 = 1.09 days and DT90 = 8.31 days, geometric mean), thiabendazole disappears by dissipation processes, binding to sediment (70.9% and 29.3% AR at the end of the study from river and pond systems respectively). Non-extractable residues increased to 25.7% AR for the river system and 65.4% AR for the pond system. At the end of the study, the carbon dioxide increased to 0.5 – 1.8% AR indicating minimal mineralization.

Overall, due to the results summarised above, the DS concluded that thiabendazole can be considered as not rapidly degradable in the environment, according to CLP criteria.

Aquatic Bioaccumulation

A BCF has been determined in a flow-through bioconcentration study in bluegill sunfish (*Lepomis macrochirus*) (Hirsch, M.P., 1991). For whole fish, the BCF was 96.45, which is much below the CLP trigger value of 500. Additionally, the Log K_{OW} of thiabendazole at 25ºC, pH 7 was 2.43, which is below the cut-off value of Log $K_{OW} \geq 4$, also indicating a low potential for bioaccumulation, according to the CLP criteria. Therefore, the DS proposed not to consider thiabendazole as bioaccumulative.

Aquatic Toxicity

The ecotoxicological test results from the available acute and chronic studies for all trophic levels of thiabendazole are summarised in the following table and sections. Only the valid acute and chronic studies on thiabendazole, which are relevant for hazard classification purposes, are included in the following table and relevant endpoints from these studies are discussed in further detail below. Reliable acute and chronic aquatic toxicity data are available for all three trophic levels: fish, aquatic invertebrates and algae.

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Fish			
Bluegill sunfish (*Lepomis macrochirus*) / US-EPA Pesticide Assessment Guidelines 1988 ASTM Standard E729-88	96-h LC_{50} = >12 mg/L (mean measured)	-	Beglinger, J.M. and O'Boyle, R.J., 1989
Rainbow trout (*Oncorhynchus mykiss*) / US-EPA Pesticide Assessment Guidelines 1988 ASTM Standard E729-88	96-h LC_{50} = 0.55 mg/L (mean measured)	96-h NOEC = 0.12 mg/L (mean measured)	Beglinger, J.M. and O'Boyle, R.J., 1989a
Sheepshead minnow (*Cyprinodon variegatus*) / 1988 ASTM Standard E729-88	96-h LC_{50} = >10 mg/L (mean measured)	96-h NOEC = 3.6 mg/L (mean measured)	Surprenant, D.C. 1989
Bluegill sunfish (*Lepomis macrochirus*) / US-EPA Pesticide Assessment Guidelines 1988 ASTM Standard E729-88	96-h LC_{50} = 19 mg/L (mean measured)	96-h NOEC = 5.4 mg/L (mean measured)	Holmes, C.M., Swigert, J.P. Smith, G.J., 1992
Fathead minnow embryos (*Pimephales promelas*) / Pesticide Assessment Guidelines 1988 ASTM Standard E 1241-88	96-h LC_{50} = 1.4 mg/L (mean measured)	28-d NOEC = 0.11 mg/L (mean measured)	Holmes, C.M, Swigert, J.P 1992
Aquatic invertebrates			
Water flea (*Daphnia magna*) / Pesticide Assessment Guidelines 1988 ASTM Standard E729-88	48-h EC_{50} = 0.81 mg/L (mean measured)	24-h NOEC = 0.75 mg/L (mean measured) 48-h NOEC = 0.48 mg/L (mean measured)	Holmes, C.M., Bellantoni, D.C. and Peters, G.T. 1990
Eastern oyster (*Crassostrea virginica*) / US EPA 72-3	96-h EC_{50} = >0.26 mg/L (mean measured)	-	Surprenant D.C. 1989a
Mysid shrimp (*Americamysis bahia*) / US EPA 72-3	96-h EC_{50} = **0.34** mg/L (mean measured)	96-h NOEC = 0.25 mg/L (mean measured)	Surprenant D.C. 1989b

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)	Reference
Water flea (*Daphnia magna*) / OECD 211, OPPTS Test Guideline 850.1300	21-d EC_{50} = 0.11 mg/L (mean measured)	21-d NOEC = **0.041** mg/L (mean measured)	Liedtke, A., 2013
Algae			
Algae *(Pseudokirchneriella subcapitat)* / OPPTS 850.5400, JMAFF Test Guidelines, 2-7-3,	72-h E_rC_{50} = 12.3 mg/L (mean measured) 96-h E_rC_{50} = 14.7 mg/L (mean measured) 72-h E_bC_{50} = 3.5 mg/L (mean measured) 96-h E_bC_{50} = 3.3 mg/L (mean measured)	96-h NOE_rC = 0.53 mg/L (mean measured) 96-h NOE_bC = 0.53 mg/L (mean measured)	Baetscher R. 2004
Other aquatic organisms (including sediment)			
Midge larvae (*Chironomus riparius*) / BBA 1995	-	NOEC = 2 mg/L (nominal) (3 mg/kg sediment)	van der Kolk J., 1998

The most sensitive organisms for acute toxicity aquatic invertebrates. All toxicity values for the different trophic levels differ slightly; however all of them are below 1 mg/L to derive aquatic acute toxicity and still in same range for M factor determination.

The most sensitive trophic level for chronic toxicity was invertebrates (*Daphnia magna* with 21-d NOEC of 0.041 mg/L). This is a study, which was included in the CLH report as additional information relevant for classification and labelling proposal according to requirement update dossier with new information.

Overall, the DS assessed thiabendazole as very toxic to aquatic life with long lasting effects, based on the following acute and chronic ecotoxicity data to invertebrates:

Aquatic Acute 1 (H400), based on a 96-h EC_{50} value of 0.34 mg/L for *Americamysis bahia*. As this value is in the range of 0.1 mg/L <L(E)C50 ≤1 mg/L, the acute M-factor should be 1.

Aquatic Chronic 1 (H410), based on a 21-d NOEC of 0.041 mg/L for *Daphnia magna*. As this value is in the range of 0.01 mg/L <L(E)C50 ≤0.1 mg/L and the substance is not rapidly degradable, the chronic M-factor should be 1.

Comments received during public consultation

Four MSs submitted comments. Three of them agreed with the DS proposal without further justification. One MS queried the chronic M-factor, pointing out that in the assessment report there is an available study for fish with a chronic NOEC of 0.012 mg/L (Wilson, leBlanc and Mastron, 1982) which would suggest an M-factor of 10. They asked to consider this study and discuss the derivation of the chronic M-factor. In response, the DS reported that this study has not been taken into account for chronic hazard classification because of several deviations from OECD Guideline No. 210 and was not carried out under GLP. Apart from this, the chronic aquatic toxicity value from *Daphnia magna* was considered more reliable since the study was validated according to OECD Guideline No. 211. Nevertheless, the DS provided a short description on the study. The DS confirmed that the NOEC of thiabendazole for *Oncorhynchus mykiss* embryos and larvae was estimated to be 0.012 mg/L. However, even taking into account this endpoint, the

aquatic chronic classification of thiabendazole and the M-factor would not be modified as 0.012 mg/L would still result in classification as aquatic chronic 1 and M=1 for non-rapidly degradable substances.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal to consider thiabendazole as not rapidly degradable following the current CLP degradation criteria guidance based on:

- hydrolytic stability at environmentally relevant temperatures and pH values (5, 7 and 9 at 25ºC and pH 4, 5, 6 at 90ºC, 100ºC, 120ºC respectively),
- 6.5% biodegradation in a ready biodegradation test (OECD 301B), indicating thiabendazole is not readily biodegradable,
- although short DT50 and DT90 values were registered for the water phase (DT50 = 1.09 days and DT90 = 8.31 days, geometric mean), thiabendazole is distributed in the environment by dissipation processes, binding to sediment (70.9% and 29.3% AR at the end of the study from river and pond systems respectively). Non-extractable residues increased to 25.7% AR for the river system and 65.4% AR for the pond system. At the end of the study, carbon dioxide generation increased to 0.5 – 1.8% AR indicating minimal mineralization.

RAC agrees with the DS that photolysis seems relevant for the degradation of thiabendazole in water with a photolytic half-life of 2.7 days and three major metabolites > 10 % of AR which have been identified. However, due to the limited relevance of photo degradation for classification purposes, RAC presumed that photolysis is not considered into the conclusion on the degradability of the substance.

Consequently, RAC agrees that thiabendazole is considered to be not rapidly degradable for the purpose of classification under the CLP Regulation.

Aquatic Bioaccumulation

A study on Bluegill sunfish (*Lepomis macrochirus*) indicates the whole fish bioconcentration factor (BCF) was 96.45, substantially below the CLP BCF trigger of 500. Although, it should be mentioned that no information has been provided to allow lipid or growth correction. Additionally, thiabendazole has a Log K_{OW} of 2.43 (at pH 7, 25°C), which is less than the CLP trigger of $\geqslant 4$. Despite that, RAC agrees with the DS's conclusion that the substance has a low potential for bioaccumulation.

Aquatic Toxicity

RAC notes that there are reliable acute and chronic aquatic toxicity data for fish, aquatic invertebrates and algae. The most sensitive species for acute toxicity was cold-water fish. Other results were in same range for classification purposes and M-factor derivation. The most sensitive trophic level for chronic toxicity was invertebrates. In addition, during the public consultation it was mentioned that there is one more chronic toxicity study available in the DAR for fish (*Oncorhynchus mykiss*), with the chronic value of 0.012 mg/L (Wilson, leBlanc and Mastron, 1982). This study was not included in the CLH report by the DS as several deviations from the OECD Guideline No. 210 have been identified and it was not carried out under GLP. However, the endpoint derived for embryos is deemed as an accurate estimate of long-term toxicity of thiabendazole in fish. The resulting value for fish of NOEC 0.012 mg/L is in same range as the value for invertebrates (NOEC = 0.041 mg/L) for classification purposes and M-factor derivation.

Acute toxicity

RAC agrees that the lowest most reliable acute (short-term) endpoint for aquatic acute classification purposes of thiabendazole is the invertebrate (*Americamysis bahia*) 96-hour EC_{50}=0.34 mg/L based on mean measured concentrations.

Chronic toxicity

RAC agrees that the lowest most reliable chronic (long-term) endpoint for aquatic chronic classification purposes of thiabendazole is the invertebrate (*Daphnia magna*) 21-day NOEC=0.041 mg/L based on mean measured concentrations.

Conclusion on classification

Thiabendazole is considered as not rapidly degradable and does not fulfil the criteria for bioaccumulation. Based on the available and most reliable information, RAC is of the opinion that thiabendazole should be classified as:

Aquatic Acute 1 – H400 based on EC_{50} = 0.34 mg/L for *Americamysis bahia*. As this acute toxicity value falls within the 0.1 < L(E)C_{50} $\leqslant$ 1 mg/L range, the **acute M-factor is 1**.

Aquatic Chronic 1 – H410 based on NOEC =0.041 mg/L for *Daphnia magna*. As this chronic toxicity value falls within the 0.01 < NOEC $\leqslant$ 0.1 mg/L range, the **chronic M-factor is 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).