Committee for Risk Assessment

RAC

Annex 1
Background document
to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

15 March 2017

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Thiabendazole

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

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

Index Number: **613-054-00-0**

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CONTENTS

Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Thiabendazole
EC number:	205-725-8
CAS number:	148-79-8
Annex VI Index number:	613-054-00-0
Degree of purity:	≥ 98.5%

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Aquatic Acute 1, H400 Aquatic Chronic 1, H410
Current proposal for consideration by RAC	Aquatic Acute 1, H400 M = 1 Aquatic Chronic 1, H410 M=1
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Aquatic Acute 1, H400 M = 1 Aquatic Chronic 1, H410 M=1

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.2.	Flammable gases	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.3.	Flammable aerosols	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.4.	Oxidising gases	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.5.	Gases under pressure	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.6.	Flammable liquids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.7.	Flammable solids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.14.	Oxidising solids	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.15.	Organic peroxides	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification

3.1.	Acute toxicity - oral	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
	Acute toxicity - dermal	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
	Acute toxicity - inhalation	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.4.	Skin sensitisation	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	n.a.	n.a.	Currently not classified	Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic acute 1; H400 Aquatic chronic 1; H410	Acute M - factor = 1 Chronic M – factor = 1	Aquatic acute 1; H400 Acuatic chronic 1; H410	
5.1.	Hazardous to the ozone layer	n.a.	n.a.	Currently not classified	

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

GHS Pictograms:

GHS09

Signal word: Warning

Hazard statements:
H410 - Very toxic to aquatic life with long lasting effects

Precautionary statements:
P273 – Avoid release to the environment
P391 – Collect spillage

Proposed notes assigned to an entry: none

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Thiabendazole is a systemic benzimidazole fungicide used as an active substance in plant protection products **included in the Annex I of the Directive 91/414/EEC** by Commission Directive 2001/21/EC of 5 March 2001. The European Commission review report for thiabendazole (7603/VI/97-final of 22 March 2001) is considered to provide the relevant review information. The active substance is currently approved under Commission Regulation (ECC) 1107/2009 as specified in Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011.

Based on information presented in the assessment of thiabendazole under Directive 91/414/EEC a harmonised C&L was agreed at the former Commission Working Group on Classification and Labelling of Dangerous Substances Pesticides of the European Chemical Bureau (ECB). Thiabendazole was discussed in November 1995, May 1997, November 1997 Commission Working Groups and the Specialised Experts (1993). At the November 1998 meeting (ECBI/12/99 Rev.1), the group agreed to classify thiabendazole with N; R50-53 and concluded that not classification was justified for health effects. Summary record of the meeting at which the human health and environmental classification of thiabendazole was concluded is attached in IUCLID dossier.

Spain as RMS of thiabendazole received on 30.05.2012 a supplementary dossier of this active substance from Syngenta. Commission Regulation (EU) No 1141/2010, laying down the procedure for the renewal of the inclusion of a second group of active substance (AIR II) in Annex I to Council Directive 91/414/EEC, states that “Applications shall state which sections of the dossiers submitted for the first inclusion of the active substance require updating with new information”. The dossier supporting the approval renewal includes the following additional information relevant for classification and labelling proposal:

Physical/chemical/technical properties

- Explosive properties study; original study no longer meets current guidelines.
- Spectra for Thiabendazolee (UV, MS, NMR , IR); not all spectra were available in the original submission.

Animal metabolism and mammalian toxicology

Since the Annex I inclusion of Thiabendazolee, a number of studies were performed in order to comply with updated guidelines. Besides, a number of the studies were carried out to in order to support the review of Thiabendazolee in the US and they are also appropriate for review in Europe.

- Toxicokinetics: Single dose, oral route in rats: Thiabendazolee: Comparative pharmacokinetics following oral and dietary administration in the rat. Jones BK., 2005.
- Toxicokinetics: Repeated dose, oral route, in rats: Thiabendazolee-The Distribution of Total Radioactivity Following Repeated Daily Oral Administration of [14C]-Thiabendazolee to the Rat. Tomlinson J, Maclean R, 2011.
- Acute oral toxicity in rats (up and down procedure): Acute oral toxicity up and down procedure in rats with thiabendazolee technical. Merkel, 2005.
- Acute percutaneous toxicity: Acute dermal toxicity study in rats – limit test with thiabendazolee technical. Merkel, 2005a.
- Acute inhalation toxicity: 4-Hour acute inhalation toxicity study in rats. Rattray, 2004.
- Acute inhalation toxicity: Thiabendazolee (AMK360D) - Acute inhalation toxicity in rats. Durando, B.S., 2007.
- Skin irritation: Primary skin irritation study in rabbits. Merkel, 2005b.
- Eye irritation: Primary eye irritation study in rabbits. Merkel, 2005c.
- Skin sensitization: Dermal sensitization study in guinea pigs (Buehler method) with Thiabendazolee technical. Merkel, 2005d
- In vitro genotoxicity testing – bacterial assay for gene mutation: Thiabendazolee-Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay. Sokolowski A, 2012.
- In vitro genotoxicity testing – test for clastogenicity in mammalian cells: Thiabendazolee: in vitro cytogenetic assay in human lymphocytes. Fox V., 2005.
- In vitro genotoxicity testing – test for gene mutation in mammalian cells: Thiabendazolee: L5178Y TK+/- mouse lymphoma mutation assay. Clay P, 2005.
- In vivo genotoxicity testing: Micronucleus Test, Mouse in vivo study. Deparade E., 1998.
- Acute Neurotoxicity: Thiabendazolee – An oral (gavage) Acute Neurotoxicity Study in Rats. Herberth M.T., 2012.
- Subchronic Neurotoxicity: Subchronic Neurotoxicity: Thiabendazolee – Subchronic (13-Week) Dietary Neurotoxicity Study in Rats. Mark T. Herberth, 2012.
- Immunotoxicity: Thiabendazolee - A 28-Day Dietary Immunotoxicity Study in CD-1 Female Mice. Wasil, J. M, 2012.
- Acute reference dose (ARfD): Thiabendazolee (MK-360): Acute reference dose study. Noakes J. (2004).
- Acute reference dose (ARfD): Thiabendazolee (MK-360): Repeat acute reference dose study for the determination of a NOEL (oral gavage). Noakes J.P., 2005.
- Acute reference dose (ARfD): B.6.8.2.1.3. Thiabendazolee (MK-360): Acute reference dose study in the rat (dietary). Noakes J., (2005a)

Environmental fate and behaviour

- Thiabendazolee - Rate and Route of Degradation of 14C-Phenyl-Labelled Thiabendazolee under Aerobic Laboratory Conditions, in Four Soils, at 20 °C. Adam D., (2011).
- Thiabendazolee - Photodegradation of 14C-Phenyl Labelled Thiabendazolee on Soil Surface. Adam, D., (2011).
- Thiabendazolee - Calculation of Kinetic Modelling and Trigger Endpoints in Soil from Laboratory Study Data according to FOCUS Kinetics Guidelines. Wang M., (2011).
- Thiabendazolee - Normalisation of field studies and kinetic evaluation of the degradation behaviour of thiabendazolee in soil according to FOCUS Kinetics Guidelines. Loll M., (2011).
- Thiabendazolee - Calculation of Kinetic Modelling and Persistence Endpoints in Water and Sediment from Laboratory Study Data according to FOCUS Kinetics Guidelines. Wang M., (2011).
- Thiabendazolee - A Leaching Assessment for Thiabendazolee Using the FOCUS-PEARL 4.4.4 and FOCUS-PELMO 4.4.3 Groundwater Models Following the Sowing of Treated Seed Potatoes. Loll M., (2011).
- Thiabendazolee - A European Environmental Fate Assessment Using the FOCUS Surface Water Models Following the Sowing of Treated Seed Potatoes. Loll M., (2011).
- Thiabendazolee: Study of Adsorption and Desorption Properties in Six Soils. Hurt A., Mason G. (2004).
- Photolysis of 14C-MK360 (Thiabendazolee) in Sterile Natural Water Under Laboratory Conditions. Adam D., (2005).

Ecotoxicology

- Thiabendazolee - Effect on Survival, Growth and Reproduction of Daphnia magna in a Semi-Static Test over Three Weeks. Liedtke, A.(2013).

A Renewal Assessment Report (**RAR**) was prepared in accordance with Article 15(1) of the Commission Regulation (EU) N° 1141/2010. The RAR was submitted by Spain (RMS) and The Netherlands (Co-Rapporteur) to EFSA, on May 2013, to support the renewal (AIR II) of inclusion of the active substance thiabendazole under Regulation (EC) No 1107/2009. Thiabendazole was discussed in the pesticides peer review meeting 114 in May 2014.

Final Addendum to the RAR on thiabendazole was made public on September 2014.

The Addendum includes the following relevant information:

Physical and chemical properties

The physical and chemical properties of the active substance have been evaluated as part of the EU evaluation of thiabendazole for inclusion in Annex I to directive 91/414/EEC, and are summarised in the Commission Review Report for thiabendazole (Thiabendazole 7603/VI/97-final of 22 March 2001).

Acute toxicity, irritancy and skin sensitisation

In the assessment for Annex I inclusion, Thiabendazole was considered not to be acutely toxic via oral, dermal and inhalation routes of exposure, neither as skin or eye irritant and was considered as not skin sensitizer.

Acute studies presented for thiabendazole Annex 1 inclusion were considered not to be suitable for the renewal of the approval, therefore new acute toxicity studies were submitted; these studies, GLP and Guideline compliant nowadays, were carried out in order to support the review of Thiabendazole in the US, and are also suitable for review in Europe.

After assessment of new acute toxicity studies it can be concluded that: thiabendazole showed a low oral and dermal acute toxicity with LD50 oral and dermal in rats higher than 5000 mg/kg. In accordance with Regulation (EC) Nº 1272/2008 of the European Parliament and of the Council, Thiabendazole does not require classification for acute oral or dermal toxicity. The single exposure acute inhalation LC_{50} of Thiabendazole is greater than 0.53 mg/L in rats. According to Regulation (EC) 1272/2008, Thiabendazole does not require classification for acute inhalation toxicity.

Thiabendazole is non-irritant when applied topically to rabbits and did not cause eye irritation in rabbits. According to Regulation (EC) Nº 1272/2008, Thiabendazole does not require classification for as skin or eye irritant

Based on the results of the modified Buehler test, Thiabendazole does not induce delayed contact hypersensitivity in guinea pigs. Therefore, according to Regulation (EC) Nº 1272/2008 Thiabendazole does not require classification as skin sensitizer.

Short-term toxicity

No new data or assessment was provided.

Genotoxicity

The overall outcome of genotoxicity studies with Thiabendazole indicates that it was not genotoxic. In the battery of tests submitted for the previous assessment, Thiabendazole was not genotoxic in a variety of in vitro and in vivo point mutation and DNA damage assays. At very high concentrations in vitro (3.9 to 25 g/ml and above) thiabendazole, in common with other anti-fungal benzimidazoles, has been shown to produce non-disjunction and aneuploidy in fungi and mammalian cells. These concentrations are about an order of magnitude above those found at toxic dose levels in vivo and so are not achievable in the whole animal. This is supported by the fact that thiabendazole is uniformly negative for induction of chromosomal anomalies in vivo in rats and mice at toxic dose levels.

For the re-evaluation process an additional bacterial reverse mutation assay, an in vitro mouse lymphoma and a chromosome aberration assays were conducted to update the thiabendazole genotoxicity database. Additionally an in vivo micronucleus assay was conducted subsequent to the previous submission. All of these newly included studies were negative and add to the weight of evidence that thiabendazole is not genotoxic.

Long-term toxicity and carcinogenesis

No new data or assessments are provided.

Reproductive and developmental toxicity

No new data or assessment has been submitted.

Neurotoxicity

New acute neurotoxicity study showed decreased motor activity at all doses testes in rats at time peak effect (≈3h). The FOB findings were transient, no test substance-related findings were observed on study days 7 and 14.

Immunotoxicity studies

A 28-Day Dietary Immunotoxicity Study in Mice was carried out to in order to support the review of Thiabendazole in the US. This study was considered also appropriate for review in Europe and was required by RMS. Data indicates a depression of antibody response in mice administered with thiabendazole at 1027.0 mg/kg bw/day with a NOEL for the AFC assay (humoral immune response) of 205.6 mg/kg bw/day.

Supplementary studies on the active substance

Three studies (2004, 2005a & 2005b) were specifically conducted to derive an Acute Reference Dose (ARfD) for Thiabendazole. In the gavage studies, neuroactive effects were observed in animals treated at doses ranging from 20 to 1000 mg/kg. These effects (slightly decreased activity, tiptoe gait and slightly reduced splay reflex) have not been considered as adverse effects because they are not dose-related, besides a full recovery from these observations occurred not later than 4 days post-dosing. Additionally, reduced motor activity included, statistically significant were observed in animals treated up 100 mg/kg. In the dietary study, no treatment-related effects on clinical signs, FOB assessment, motor activity or bodyweight were observed at up to 600 ppm, equivalent to 48.2 mg/kg for males and 45.8 mg/kg for females, the highest dose tested.

EFSA (European Food Safety Authority), 2014, Conclusion on the Peer Review of the pesticide risk assessment of the active substance thiabendazole. In its evaluation EFSA recommends classification only for environmental effects with H400, H 410.

This CLH dossier presents a classification and labelling proposal based on the information presented in the assessment of thiabendazole under PPP regulation. Data referred to assessment made under PPP regulation are attached to the IUCLID Dossier.

Thiabendazole was included in Annex I of Directive 98/8/EC (Commission Directive 2008/85/EC). An assessment report (February 2008) was established as a result of the evaluation of thiabendazole as product-type 8 (wood preservatives) in order to ensure authorisations for biocidal products used as wood preservatives. An Evaluation Report was submitted on May 2006. Currently, thiabendazole is being reviewed in accordance with the Regulation 1062/2014 for the following product-types: 7-Film preservatives; 9-Fibre, leather, rubber and polymerised materials preservatives and 10-constrution materials preservatives.

No REACH registration dossiers are available for thiabendazole at time of submission of the present CLH dossier.

2.2 Short summary of the scientific justification for the CLH proposal

Being thiabendazole an active substance in the meaning of Directive 91/414/EEC is subject to harmonised classification labelling, in accordance with Article 36(2) of EC Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP).

There is an existing entry in Annex VI to the CLP Regulation. Thiabendazole is currently listed in Annex VI of Regulation 1272/2008 (CLP Regulation) with Aquatic Acute 1: H 400 and Aquatic Chronic 1: H410.

New data has become available since the harmonised classification was agreed. Review of these documents has revealed that the classification listed in Annex VI of CLP Regulation need to be revised.

A proposal for changing the current harmonised classification and labelling has been prepared in the present CLH dossier. This proposal seeks to amend the existing Annex VI entry and does not address all hazard classes.

Regarding human health, additional data do not give rise to classify thiabendazole for health effects.

With respect to environmental hazards, the current entry in Annex VI Table 3.1 as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) should not be changed; only acute and chronic M factors should be added. For this environmental hazard category correspond an M for acute toxicity of 1 and an M factor for chronic toxicity of 1, justified due to the invertebrates' acute EC value of 0.34 mg/l and chronic NOEC value of 0.041 mg/l and the fact that the substance is not rapidly degradable in the aquatic environment.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification:

Aquatic Acute 1, H400
Aquatic Chronic 1, H410

Labelling:

GHS09, Wng
H410

Specific concentration limits and M factor:

None

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

The self-classification according to the ECHA inventory of notified classification and labelling on 21 March 2016 was:

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)			
Aquatic Acute 1	H400			GHS09			135
Aquatic Chronic 1	H410	H410		Wng			
Aquatic Acute 1	H400	H400		GHS09			81
Aquatic Chronic 1	H410	H410		Wng			
Aquatic Acute 1	H400			GHS09			38
Aquatic Chronic 1	H410	H410		Wng			
Aquatic Acute 1	H400	H400		GHS09			35
Aquatic Chronic 1	H410	H410		Wng			
Aquatic Acute 1	H400			GHS09			35
		H410		Wng			
Aquatic Acute 1	H400			GHS09			4
Aquatic Chronic 1	H410	H410 (H410)		Wng			
Aquatic Acute 1	H400			GHS09	M=1		3
Aquatic Chronic 1	H410	H410		Wng			
Aquatic Acute 1	H400			GHS09			2
Aquatic Chronic 1	H410	H410		Wng			
		H400		GHS09			2
		H410		Wng			
Aquatic Acute 1	H400	H400		GHS09			1
Aquatic Chronic 1	H410	H410		Dgr			
		H400		Wng			1
		H410					
Not Classified							1
Aquatic Acute 1	H400	H400		GHS09			1
		H410		Wng			
		H361		GHS07			1
				GHS08			
		H302		Wng			

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Thiabendazole is an active substance included in the list of active substances approved under Regulation (EC) no. 1107/2009 and therefore no justification is required.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

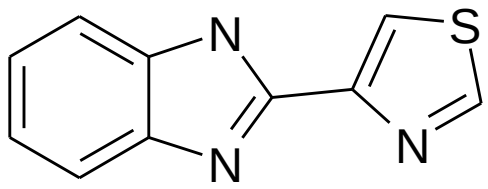
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	205-725-8
EC name:	Thiabendazol (ISO) ; 2-(thiazole-4-yl)benzimidazole
CAS number (EC inventory):	148-79-8
CAS number:	148-79-8
CAS name:	
IUPAC name:	2-(1,3-thiazol-4-yl) -1H-benzimidazole
CLP Annex VI Index number:	613-054-00-0
Molecular formula:	$C_{10}H_7N_3S$
Molecular weight range:	201.3 g/mol

Structural formula:



1.2 Composition of the test substance

Table 5: Constituents

Constituent	Typical concentration	Concentration range	Remarks
Thiabendazole	≥ 985 g/kg		-

Current Annex VI entry: H400, H410.

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
No relevant impurities			

There are a number of process impurities in the substance that have been taken into consideration and are not considered to impact on the classification proposed in this dossier. Further information on the impurities is considered to be confidential but full details are provided in the technical dossier.

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives	-	-	-	-

1.2.1 Composition of test material

See confidential information (IUCLID section 1.2).

1.3 Physico-chemical properties

Table 8: Summary of physico-chemical properties

Property	Value	Reference/Comment
State of the substance	At room temperature (25°C) thiabendazole is a dry powder Off-white to yellow-tan.	
Melting/freezing point	297-298 ºC (purity 99.16%)	Meeus,1997 EEC A1
Boiling point	Not applicable. Thiabendazole is a solid.	
Relative density	1.3989 (purity 99.16%)	Meeus,1997
Vapour pressure	5.3 x 10^{-7} Pa at 25 ºC	Boos, R.N., 1973
Surface tension	72.7 mN/m (90% of the saturation concentration)	
Water solubility	Solubility (g/l at 20 ± 0.5ºC) (purity 99.16%): pH5: 0.16 pH7: 0.03 pH10: 0.03	Meeus,1997 EEC A6
Partition coefficient n-octanol/water	Temperature: 23ºC ±1 and purity of 99.16% Stock solution 1.5 g teste substance / 1L n-octanol saturated with distilled water: n-octanol/water pH4: Pow:42.01, log Pow: 1.62 n-octanol/water pH7: Pow:271.58, log Pow: 2.43 n-octanol/water pH10: Pow:221.94, log Pow: 2.35	Meeus,1997 EEC A8
Flash point	Not applicable. The active substance is non-volatile and high melting powder.	Meeus,1997 EEC A6
Flammability	The test substance is not considered as highly flammable. (purity 99.16%).	Jackson, 2003 ECC A10
Explosive properties	Not an explosive substance (theoretical assessment).	Jackson, 2011
Self-ignition temperature	Not available.	
Oxidising properties	Thiabendazole active substance is a free flowing powder. The chemical structure of thiabendazole does not indicate oxidising properties or capability of reacting exothermically with a combustible material.	
Granulometry	Not available.	
Solubility in organic solvents, including the effects of temperature on stability	Purity: 99.16 % w/w at 25 ºC g/L n-heptane: <0.01 xylene: 0.13 methanol: 8.23 1,2-dichloroethane: 0.8 Acetone: 2.43 Ethyl acetate: 1.49 n-octanol: 3.91	Meeus,1997 EEC A6
Dissociation constant	Thiabendazole has two sets of dissociation constants at 22 ºC : pKa: 4.73 and 12.00 (from protonation of either of the benzimidazole nitrogens and thiazolyl nitrogen).	Farrow, 1977; Book, 1988
Viscosity		

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for Classification and Labelling.

2.2 Identified uses

Thiabendazole is an active substance used in plant protection products as systemic benzimidazole fungicide.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

No proposal for revision or amendment to the existing harmonised classification is made.

Table 9: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Flash point EEC A6	Not applicable. The active substance is non-volatile and high melting powder.	None	Meeus,1997
Flammability ECC A10	The test substance is not considered as highly flammable. (purity 99.16%).	None	Jackson, 2003
Explosive properties	Not an explosive substance (theoretical assessment).	None	Jackson, 2011
Self-ignition temperature	Not available.		
Oxidising properties	Thiabendazole active substance is a free flowing powder. The chemical structure of thiabendazole does not indicate oxidising properties or capability of reacting exothermically with a combustible material.	None	

4 HUMAN HEALTH HAZARD ASSESSMENT

No proposal for revision or amendment to the existing harmonised classification is made.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Thiabendazole was included in Annex I of Council Directive 91/414/EEC in 2011 (Inclusion Directive 2001/21/EC of March 2001. The active substance is currently approved under Commission Regulation (EC) 1107/2009 as specified in Commission Implementing Regulation (EU) 540/2011.

Available environmental fate and ecotoxicology studies have been considered and summarised in Draft Renewal Assessment Report, October, 2013 (RAR, Volume 3, Annex B8 and Annex B9) and its final addendum, September 2014. The key information pertinent to determining the environmental hazard classification for Thiabendazole is presented below and the summaries included in this proposal are partly copied from the revised RAR, its addenda and the EFSA Conclusion of this active substance, finalised on October 2014. References to the RAR are provided.

Regarding the classification according to CLP Regulation, no changes are needed, only acute and chronic M - factors should be included.

5.1 Degradation

Table 10: Summary of relevant information on degradation

Method	Results	Remarks	Reference
EPA/FIFRA subdivision N guidelines 161-1, 1982	Hydrolytically stable		K. Kabler, J. Dikes, 1989
Not specified	Hydrolytically stable		Adam, 1999
EPA/FIFRA subdivision N guidelines 161-1, 1982	DT_{50} = 29 hours		Flynn, 1994
OECD Guidelines for the testing of chemicals, Draft, August 2000	DT_{50} = 1.5 days		Adam, 2005
OECD 301B	Not ready biodegradable		Van de Kolk, J., 1998
OECD 308 (Guidelines for Testing of Chemicals, Aerobic-Anaerobic Transformation in Water-Sediment Systems, Draft Document, November 1998)	DT_{50} - DT_{90} water phase = 1.09-8.31	DT_{50} and DT_{90} values of dissipation.	Ulrich, 1999

5.1.1 Stability

Hydrolysis

Studies on the hydrolysis of Thiabendazole demonstrate that it is hydrolytically stable at pH values of 5, 7 and 9 at 25ºC under sterile conditions in the dark for 30 days. Thiabendazole was also shown to be stable under the high temperature of processing conditions (pH 4, 5, 6 at 90ºC, 100ºC and 120ºC.

One of the hydrolysis studies (K. Kabler, J. Dikes, 1989) was conducted at nominal test concentrations of 10 µg/l in four aqueous buffer solutions (pH 5, 7 and 9). Confirmation of percent ^{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 hydrolyze in the pH range 5 – 9:

pH	DT50

5	357.1
7	203.0
9	270.8

In the other study (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 set up ranged from 98.8% to 103.5% of the applied radioactivity. The results showed that Thiabendazole is hydrolytically stable under the conditions of the test.

pH	**Incubation**		**Radioactivity Fractions after hydrolysis determined by HPLC analysis (% applied)**
	Temp, (ºC)	**Time, (min.)**	
4	90	20	103.5
5	100	60	101.2
6	120	20	98.8

Photolysis

Flynn, 1994.

The direct aqueous photolysis of Thiabendazole was studied under sterile conditions in a buffer solution (pH 5) at 25ºC. Based on the results of this study, Thiabendazole in aqueous solution will undergo photlytic degradation, following first-order kinetics, in the presence of sunlight with a short half-live of 29 hours. Formation of several photodegradates can be expected, however only benzimidazole-2-carboxamide, as the major product (10.22%), exceeded 10% of the applied radioactivity.

In addition, a study has been conducted to investigate both the direct and indirect photolysis properties of Thiabendazole (Adam, 2005), and a new study is also available to evaluate the quantum yield of the direct photochemical degradation of Thaibendazole (Schmidt, 2002).

Adam (2005).

The direct and indirect photochemical degradation of ^{14}C-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 25ºC. During this incubation period, ^{14}C-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. Only three of these radioactive fractions (M3, M5 and M6) exceeded 10% of the applied radioactivity. Nearly all of them were further mineralised to $^{14}CO_2$. The amount of radioactive carbon dioxide in the irradiated samples increased continuously amounting to 19.6% if the applied radioactivity at the end of the irradiation.

The most significant photodegradates were M3, characterised 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 but was faster degraded compared to M3 reaching 5.3% after 11 days. M6, the third major metabolite benzimidazole-2-carboxamide, represented 10.3% on day 3 and 4.6% on day 11. M7 the most

prominent minor metabolite increased throughout the irradiation amounting to 7.9% after 11 days. Since it was well below 10% of the applied radioactivity, its structure was not further elucidated. All other metabolites were below 4.7% of the applied radioactivity.

The rate of photolytic degradation of Thiabendazole and its major metabolites were described using a first-order reaction kinetic model. The experimental half-life (DT_{50}) and DT_{90}-values show that Thiabendazole was rapidly photodegradated in natural pond water with a photolytic half-life of 2.7 days (summer sunlight at latitudes 30-50ºN).

Calculated Half-life (DT_{50}) and DT_{90} in Days

Compound	k-value	Suntest *		Sunlight ** 50°N		Tokyo *** 35°N	
		DT_{50}	DT_{90}	DT_{50}	DT_{90}	DT_{50}	DT_{90}
MK360	0.476	1.5	4.8	2.7	8.5	11.7	37.6
Benzimidazole carboxylic acid (M3)	0.095	7.3	24.2	12.9	42.9	57.1	189.4
1,2-dihydro-3-hydroxy-quinaxoline (M5)	0.156	4.5	14.8	8.0	26.3	35.2	115.8
Benzimidazole carboxamide (M6)	0.165	4.2	14.0	7.4	24.8	32.9	109.5

* continuous irradiation
** natural summer sunlight at 30 to 50°N
*** natural Tokyo spring sunlight at 35°N
Note: The degradation rate of the parent molecule was additionally fitted with the software MicroCal Origin to confirm the results obtain by ModelMaker. DT_{50} and DT_{90} values obtained with Origin were 1.3 days and 4.5 Suntest days, respectively (see Figure 4).

Schmidt, E., 2002.

The direct photolysis quantum yield of Thiabendazole has been determined in dilute neutral and acidic aqueous solutions, pH of 7.3 and 2.7 respectively. For geographical latitudes 30°N, 40°N and 50°N in spring and summer, half-lives were determined between 0.5 and 1.5 days. Photolysis under acidic conditions proceeds at a higher rate than in neutral solutions. Overall, direct phototransformation in aqueous systems is considered to be a relevant process for the lifetime of Thiabendazole when released into an aqueous environment.

		predominantly neutral form	predominantly protonated form
Mean rate constant k_p [s^{-1}]:		9.87×10^{-5}	9.18×10^{-5}
Mean half-life DT_{50} [h]:		1.93	2.1
Quantum yield		0.00136	0.00110
Environmental half-lives* [days]:			
Latitude 30°N	Spring	0.83	0.52
	Summer	0.68	0.44
Latitude 40°N	Spring	1.07	0.65
	Summer	0.76	0.48
Latitude 50°N	Spring	1.52	0.87
	Summer	0.89	0.55

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

5.1.2.2 Screening tests

The ready biodegradability was tested according to OECD301B. In this test the biodegradation of Thiabendazole accounted for 6.5 % of the theoretical value within 30 days. The results demonstrated further that no abiotic degradation (hydrolysis) took place under the test conditions. The toxicity control flask results gave clear evidence that Thiabendazole did not adversely affect the degradation of the reference substance sodium benzoate, since the CO2 evolution was comparable to that one in the pure reference substance flask without the addition of Thiabendazole.

5.1.2.3 Simulation tests

Water/Sediment

Ulbrich, 1999.

Aerobic degradation of Thiabendazole in two aquatic systems, a river (Rhine) and a pond, has been investigated for six months at 20ºC.

- River system: the radioactivity in the river water phase decreased from 96.5% on day 0 to 2.1% of the applied radioactivity on day 14. Thereafter, the radioactivity was below 0.8% of the applied radioactivity until study end.

  The extractable radioactivity from the river sediment increased to 76.1% at day 42 after application. Thereafter, it remained almost constant until study end (70.9% on day 181). The non-extractable radioactivity increased from 1.8% (day 0) to 23.1% (day 14). And kept this level until day 181: 25.7%.

- Pond system: the radioactivity in the pond water phase decreased from 92.2% (day 0) to 7.0% of the applied radioactivity on day 14. Thereafter, the radioactivity was below 0.8% of the applied radioactivity until the end of incubation.

  The extractable radioactivity from the pond sediment increased within 42 days of incubation to 44.3% of the applied radioactivity and, thereafter, decreased to 29.3% on day 181. The non-extractable radioactivity increased from 1.1% h (day 0) to 52.7% on day 14 and further to 65.4% at study end.

More than half of the non-extractable radioactivity (57 to 73% of non-extractable) could be released as parent compound from both sediments after treatment with 0.5N NaOH.

After 181 days of incubation, all volatile radioactivity in the river and pond systems were characterised as carbon dioxide. It was reached to low percents (0.5 – 1.8 %) indicating little mineralization.

Taking into account the above results, the degradation of Thiabendazole in the aquatic systems was characterized by two phases.

In a first phase, a relatively fast and complete migration of the test substance from water to sediment (adsorption) took place already within a relatively short time period of two weeks after application (the radioactivity in water phase decreased rapidly over the incubation period). Depending on the

sediment properties (mainly organic matter content, clay content and cation exchange capacity), a distinct proportion of the migrated substance was then strongly bound/adsorbed (non-extractable) to the sediment. The amount of strongly bound radioactivity was after two weeks with 52.7% more than two times higher for the pond sediment than for the river sediment (23.1%). These data are not surprising since the pond sediment was the system with the more than two times higher binding capacity due its higher organic carbon content, clay content and cation exchange capacity.

In the second phase a very slow decline of Thiabendazole from the Rhine river and Pond system was observed with a dissipation time of >4000 and 375 days, respectively. Here again the higher binding capacity of the pond system might be responsible for the shorter dissipation time.

In conclusion, the negligible mineralization rate (CO_2,-formation), the extremely poor pattern of metabolites and the fact that with sodium hydroxide considerable amounts of the parent compound can be released from the "bound-residue", suggest that Thiabendazole mainly disappears from aquatic systems by physico-chemical processes and not by microbial degradation. However, the rapid and almost complete and permanent disappearance of radioactivity from the water suggests that the compound is rather safe for the aquatic environment.

The data from the above study was re-evaluated according to the FOCUS Kinetics guidance for persistence and modeling endpoints (FOCUS, 2006). (**Wang, M. and Löll, M., (2011a))**

Whole system DT_{50} values according to SFO kinetics are 499.8 days for river system and 117.4 days for pond system. However residuals are not distributed randomly around zero in the SFO fits. The other kinetic models show better fits but are statistically not acceptable. FOMC shows better fit however it not possible to obtain a reliable endpoint. This has no consequence on the SW modeling since a worst-case DT50 value of 1000 days was used further in the water and sediment compartment.

The fitting obtained for Thiabendazole of water column provided a FOMC persistence DT_{50} and DT_{90} water values of 1.32 and 6.91 days, respectively, from the river system and DT_{50} and DT_{90} water values of 2.09 and 10 days, respectively, from the pond system.

Water/Sediment system	**t. °C**	**DT_{50} - DT_{90} Whole system (days)**	**DT_{50} - DT_{90} Water phased (days)**	**DT_{50} - DT_{90} Sediment phase (days)**	**Method of calculation**
River (Rhine river at Möhlin, Switzweland)	19.4	-	1.32 – 6.91	-	FOMC
Pond (Fröschweiher at Rheinfelden, Switzweland)	15.8	-	2.09 - 10	-	FOMC
Geometric mean		No acceptable fits.	1.09 – 8.31	No acceptable fits.	

5.1.3 Summary and discussion of degradation

The fate and behaviour of Thiabendazole in water were evaluated during the initial EU review. Additional data were submitted and the kinetic analysis of the data from the water /sediment system study of Ulbrich (1999) was re-evaluated.

Photolysis seems to play a role in the degradation of Thiabendazole in water (Adam,2005 and Schmidt, 2002) with a photolytic half-life of 2.7 days (summer sunlight at latitudes 30-50ºN) and three major metabolites have been identified (M3, M5 and M6) but not toxicity data are available for them. Due to this lack of photochemical degradation data for metabolites, photolysis is not considered into the degradability of the substance.

In contrast to photolysis, Thiabendazole shows hydrolytic stability at pH values of 5, 7 and 9 at 25ºC under sterile conditions in the dark for 30 days and is also shown to be stable under the high temperature of processing conditions (pH 4, 5, 6 at 90°C, 100°C and 120°C), and is not rapidly biodegradable. Thiabendazole is considered hydrolytically stable at environmentally relevant temperatures and pH values.

The water/sediment study suggests that Thiabendazole mainly disappears from aquatic systems by physical-chemical processes and not by microbial degradation and the concentration of Thiabendazole in the sediment will depend on the sediment properties (mainly organic matter content, clay content and cation exchange capacity). Partitioning to sediment is the main route of dissipation of thiabendazole in water sediment systems primarily binding to sediment. No significant metabolites were formed. Depending on the sediment properties a distinct proportion of the migrated substance was then strongly bound to the sediment. The amount of strongly adsorbed radioactivity was more than two fold higher for the pond sediment than the river sediment.

Thiabendazole can be considered as not rapidly degradable in the aquatic environment from the water/sediment system study carried out. Although short DT50 and DT90 values were registered for the water phase (DT50 = 1.09 days and DT90 = 8.31 days), Thiabendazole disappears by dissipation process, 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. And at the end of the study the carbon dioxide increased to 0.5 – 1.8% AR indicating minimal mineralization.

Thiabendazole is considered not readily biodegradable according to the result of the biodegradation test presented (6.5 %), following OECD 301 B guideline. The ready biodegradability criterion stated in this guideline considers substances readily biodegradable when 70% biotic degradation takes place in the 10 days window within the 28 days long duration test.

Due to the results summarized above, Thiabendazole can be considered as a not rapidly degradable substance in the environment, according to the CLP criteria.

5.2 Environmental distribution

Table 11: Summary of relevant information on distribution

Method	Results	Remarks	Reference
OECD 106	Koc ads = 2108.3 (mg/l)	Thiabendazole has low mobility in soil	Mason & Hurt, 2004
OECD 106	Koc ads = 2072.7 (mg/l)	Thiabendazole has low mobility in soil	Hurt and Völkel, 2004
-	Thiabendazole is considered as inmobile in soil		WARF Institute, Inc., 1976
-	Thiabendazole is considered as inmobile in soil		Schroeder and Steele, 1978

5.2.1 Adsorption/Desorption

Results obtained show that Thiabendazole aerobically aged in soil is not leached by water in any of the representative soil types investigated. Thiabendazole was found to be immobile in all the physicochemically different soil classes investigated and there was also no difference in this immobile behavior of Thiabendazole under either rapid or slow experimental leaching conditions. This has been confirmed in field dissipation studies, as well as no residues of Thiabendazole were detected below 20-cm depth in soil.

According to the Mason (2004) study, the adsorption and desorption properties of Thiabendazole were studied in six soils. Thiabendazole showed high adsorption with average adsorption partition coefficients (Kd) ranged from 26 to 120, Freundlich adsorption coefficients (KF) were similar, an average Koc ranged from 1200 to 11000 and KFoc values followed a similar pattern, ranging from 620 to 4400, with a mean value of 2108.3 mg/l.

Furthermore, during the three desorption steps, the adsorption of Thiabendazole was shown to be not entirely reversible resulting in a reduction in the potential mobility of the compound.

According to the Hurt and Völkel (2004) study, Thiabendazole showed high adsorption to the six soils studied. Freundlinch adsorption coefficients (KF) were similar, ranging from 13.1 to 93.3. KFoc values (derived from KF) ranging from 539 mg/l to 4514 mg/l, with a mean value of 2073 mg/l. KF and KFoc mean values increased during the desorption steps indicating that the adsorption of Thiabendazole is not entirely reversible.

According to the classification system of McCall et al., Thiabnedazole has low mobility in soils and is expected to be little mobile o immobile in soils according to the classification system of Guth.

In these studies, 1/n values showed no linearity involved in the adsorption test and due to similarities 1/n values from the adsorption and desorption processes, these behaviours are similar.

Due to the update of OECD protocols and the unreliability of old data, the soils were sterilized with NaN3 there were differences in data treatment and minor representative soils were used, a new study is carried out. The new study is composed of two valid studies, Mason, 2004 (original study) and Hurt 2004 (used to assess the impact of using sub-gram amounts of soil) resulting in a total of 12 Kfoc and 1/n values. RMS considers that only adsorption data from these new studies should be used. The mean of KFOC is 2090 and 1/n is 0.79.

End-points derived in the new evaluation (Mason & Hurt/ Hurt & Völkel studies)

End-point	Soils	Thiabendazole
$K_{oc\ ads}$ (mL/g)	Sandy Loam ("Kenny Hill")	620 /539
	Sandy Loam ("Kagoshima")	1700/ 1833
	Sandy Clay Loam ("18 Acres")	1100/1011
	Silty Clay Loam ("Wisborough Green")	4100/3741
	Sandy Loam ("ERTC")	4400/4514
	Loam ("Gartenacker")	730/798
1/n	Sandy Loam ("Kenny Hill")	0.75/0.77
	Sandy Loam ("Kagoshima")	0.68/0.69
	Sandy Clay Loam ("18 Acres")	0.80/0.82
	Silty Clay Loam ("Wisborough Green")	0.93/0.86
	Sandy Loam ("ERTC")	0.78/0.95
	Loam ("Gartenacker")	0.78/0.65

Results from the adsorption/desorption, column and aged column leaching, field dissipation conducted in several physicochemically different soil types demonstrate that Thiabendazole binds tightly to, and is hence immobile in soil.

5.2.2 Volatilisation

The vapour pressure of thiabendazole at 25ºC is approximately 4 x 10^{-9} mmHg and its Henry´s law constant is 3.7 x 10^{-6} Pa m^3 mol^{-1}. Because of the low vapour pressure, no significant contamination of air can reasonably be expected. The calculation half-life for the atmospheric oxidation of Thiabendazole by hydroxyl radicals was made using the Atkinson calculation and found to be 2 - 3.5 h. No new data or assessments are provided

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

Table 12: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Not given	BCF = 96.45		Hirsch, M.P., 1991

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

There is no indication for bioaccumulation potential of Thiabendazole (log Pow < 4).

pH	Log P_{ow}
4	1.62
7	2.43
10	2.35

5.3.1.2 Measured bioaccumulation data

Since the octanol-water partition coefficient of Thiabendazole is below the cut-off value of log Kow ≥ 4, there is no indication for a bioaccumulation potential of Thiabendazole.

In spite of this, the BCF has been determined in a flow-through bioconcentration study in bluegill sunfish. In this study the concentration of Thiabendazole was monitored in both the fish and water during a 28-days uptake period and the subsequent 14-day depuration period.

The uptake rate constant (k1), depuration rate (k2), and the steady-state bioconcentration factors (BCF) were calculated for whole fish, viscera, and edible tissues. These values for the whole fish are k1 = 29.90 day-1, k2 = 0.31 day-1, and **BCF = 96.45**; for the edible portion, k1 = 7.59 day-1, k2 = 0.33 day-1, and BCF 22.84; and for the visceral tissue are k1 = 153.03 day-1, k2 = 0.24 day-1, and the BCF = 642.

5.3.2 Summary and discussion of aquatic bioaccumulation

Taking into account the above information, no bioconcentration of Thiabendazole in fish is expected, since the log Pow values are lower than 4 and the experimentally bioconcentration factor is also lower than 500.

5.4 Aquatic toxicity

Thiabendazole was included in Annex I of Council Directive 91/414/EEC in 2011 (Inclusion Directive 2001/21/EC of March 2001. The active substance is currently approved under Commission Regulation (EC) 1107/2009 as specified in Commission Implementing Regulation (EU) 540/2011.

A brief summary of the aquatic toxicity studies listed in the Draft Assessment Report (DAR) and Draft Renewal Assessment Report (RAR) are reported below. Only reliable and acceptable ecotoxicity tests from these reports were used.

Table 13: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
Fish			
Acute toxicity to fish: US-EPA, Office of Pesticide Programmes October 1982. Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic organisms, subsection 71-2 ; American Society for Testing and materials 1988 ASTM Standard E729-88	LC_{50} > 12 mg/l (mm) (*L. macrochirus*)		Beglinger, J.M. and O'Boyle, R.J., 1989

Acute toxicity to fish: US-EPA, Office of Pesticide Programmes October 1982. Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic organisms, subsection 71-2 ; American Society for Testing and materials 1988 ASTM Standard E729-88	LC_{50} = 0.55 mg/l (mm) (*O. mykiss*)		Beglinger, J.M. and O'Boyle, R.J., 1989a
Acute toxicity to fish: American Society for Testing and materials 1988 ASTM Standard E729-88	LC_{50} > 10 mg/l (mm) (*C. variegatus*		Surprenant, D.C. 1989
Acute toxicity to fish: US-EPA, Office of Pesticide Programmes October 1982. Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic organisms, subsection 71-2 ; American Society for Testing and materials 1988 ASTM Standard E729-88	LC_{50} = 19 mg/l (mm) (*L. macrochirus*)		Holmes, C.M., Swigert, J.P. Smith, G.J., 1992
Early life stage of fathead minnow: Series 72 of pesticide assessment Guidelines. Subdivision E Hazard Evaluation: Wildlife and aquatic organisms. ASTM Standard E 1241-88	NOEC (32 d) = 0.11 mg/l (mm) (*P. promelas*)		Holmes, C.M, Swigert, J.P 1992
Aquatic invertebrates			
Acute toxicity to Daphnia: Series 72 of pesticide assessment Guidelines. Subdivision E Hazard Evaluation: Wildlife and aquatic organisms. ASTM Standard E 729-88	EC_{50} = 0.81mg/l (mm) (*D.magna*)		Holmes, C.M., Bellantoni, D.C. and Peters, G.T. 1990

Acute toxicity to eastern oyster: US EPA 72-3	EC_{50} > 0.26 mg/l (mm) (*C.virginïca*)		Surprenant D.C. 1989a
Acute toxicity to mysid shrimp: US EPA 72-3	LC_{50} = 0.34mg/l (mm) (*M. bahia*)		Surprenant D.C. 1989b
Chronic toxicity to *D. magna:* OECD 211 (2012) OPPTS Test Guideline 850.1300 (April 1996)	NOEC(21d) = 0.041 mg/l (mm) (*D. magna*)		Liedtke, A., 2013
Algae			
Algal inhibition test: OPPTS 850.5400, (1996); JMAFF Test Guidelines, 2-7-3, (2001)	$ErC_{50\ (96h)}$ = 14.7 mg/l NOErC = 0.53 mg/l (mm); $EbC_{50(96h)}$ = 3.30 mg/l NOEbC = 0.53 mg/l (mm) (*Selenastrum capricornutum*)		Baetscher R. 2004
Sediment dwelling organisms			
BBA 1995	NOEC = 2.0 mg/l (nom) (3 mg /kg sediment) (*C. riparius)*		van der Kolk J., 1998

5.4.1 Fish

According to the conclusions given in the DAR Thiabendazole has been shown to be acutely very toxic to the cold-freshwater fish, rainbow trout (*Oncorhynchus mykiss*, 96-day LC50 < 1 mg/l) which is often the most sensitive indicator of freshwater species. It is less toxic to warm water fish, bluegill sunfish (*Lepomis macrochirus*, 96-day LC50 >19 mg/l).

5.4.1.1 Short-term toxicity to fish

Beglinger, J.M. and O'Boyle, R.J., 1989.

Bluegill sunfish were exposed to Thiabendazole in a 96-hour dynamic test. The mean measured concentrations tested, determined at 96 hours, were 0.345, 0.77, 1.65, 3.6 and 6.96 mg a.s. /l. **The 96-hour dynamic acute LC_{50} was determined to be > 12 or >13 mg a.s/l** for replicate A and B, respectively. The no-effect concentration, based on the presence of transient darker colour in the fish, was reported to be 6.8 mg a.i/l. The 96-hour no-mortality concentration was 9.5 mg a.s/l.

Beglinger, J.M. and O'Boyle, R.J., 1989a.

Rainbow trout were exposed to technical Thiabendazole in a 96 hour dynamic acute test. The pH, dissolved oxygen content, and water temperature were maintained within acceptable levels for this test at all-time points. The nominal concentrations of Thiabendazole in the aquaria were 0.09, 0.19, 0.38, 0.75, and 1.5 mg a.s/l. Mean measured concentrations taken at test times 0 and 96 hours, verified the nominal values, except for the 0.09 mg/l level which was approximately 50% of nominal. **The**

96-hour LC50, based on mean measured concentrations, was 0.55 and 0.56 mg a.s/l for replicate A and B, respectively. The 95% confidence limits were 0.41 and 0.77 mg a.s/l for replicate A and 0.39 and 0.81 mg a.s/l for replicate B. The acute NOEC values for the rainbow trout were determined to be 0.12 mg a.s/l for both replicates based on both lethal and sub-lethal effects. The lowest concentration causing 100% mortality was 1.2 mg a.s/l. The highest concentration causing no mortality was 0.19 mg a.s/l.

Surprenant, D.C. 1989.

The acute toxicity of Thiabendazole, to sheepshead minnow (*Cyprinodon variegatus*) under flow-through conditions was determined. Duplicate test aquaria were maintained at nominal test concentrations of 1.2, 1.8, 2.8, 4.4, and 6.7 mg a.s/l. Each replicate aquarium was analysed for Thiabendazole active ingredient at test initiation and termination. Based on these analyses, the mean measured concentrations were 1.5, 2.2, 3.6, 6.0, and 10 mg a.s/l. Higher test concentrations were not possible due to the limited solubility of Thiabendazole in unfiltered seawater, in spite of effort to obtain higher concentrations of Thiabendazole by employing greater than 0.1 ml triethylene glycol solvent per litre aquaria water. Following 96 hour exposure, 30% mortality was observed among fish exposed to the highest treatment level tested (10 mg a.s/l, measured concentration). **The LC_{50} of Thiabendazole was estimated to be greater than 10 mg a.s//l**. The no-observed effect concentration level (NOEC) established for this study was 3.6 mg a.s/l.

Holmes, C.M., Swigert, J.P. Smith, G.J., 1992.

Bluegill sunfish were exposed to Thiabendazole in a 96 hour static acute test. The pH, dissolved oxygen content and water temperatures were maintained at acceptable levels for this test at all-time points. The temperature of the aquaria was maintained at 22 +/- 1oC. Mean measured concentrations verified the nominal values. **The 96-hour LC_{50}, based on mean measured concentrations, was 19 mg a.s/l.** The 95 % confidence limits were 16 and 26 mg a.s/l. The 96-hour no-mortality concentration, determined by visual examination of the mortality data, was 9.5 mg a.s/l. While there were no mortalities in the 9.5 mg a.s/l treatment group, several bluegill sunfishes appeared discoloured over the 48 - 96 hour observation period. The effect appeared to be dose responsive and treatment-related. The lowest concentration causing 100% mortality was 26 mg a.s/l. The 96-hour NOEC based on discoloration was 5.4 mg a.s/l.

5.4.1.2 Long-term toxicity to fish

Holmes, C.M, Swigert, J.P., 1992

Fathead minnow embryos were exposed to Thiabendazole under flow-through conditions. The exposure period included a 5-day period for viable embryos to hatch, and a 28-day post hatch exposure period. Loading was calculated to be 0.028 grams of fish per litre of water passing through the aquaria during a 24-hour period. Instantaneous loading was 0.34 gram of fish per litre of water at any given time. Nominal test concentrations were 0.12, 0.25, 0.05, 1.0 and 2.0 mg a.s/l. Mean measured concentrations of water samples taken on days 0, 7, 14, 21, 28 and 33 of the test were 0.11, 0.23, 0.50, 0.98, and 1.9 mg a.s/l. Water temperatures and dissolved oxygen concentrations were within acceptable limits for this study. Conductivity, hardness and alkalinity were typical of moderately-hard freshwater.

There were no apparent treatment-related effects upon mean hatching success at any of the concentrations less than or equal to 0.98 mg a.s/l. There was an apparent treatment-related reduction in hatching success at the 1.9 mg a.s/l test concentration.

Mean percentage survival in the four lowest treatment groups was not significantly different from the pooled control group. The reduction in survival to 10% at 1.9 mg a.s/l was dose responsive and statistically significant when compared to the pooled control group. The 28-day LC50 was 1.4 mg a.s/l and the 95% confidence interval ranged from 0.98 to 1.9 mg a.s/l.

Effects of Thiabendazole upon fish growth were evaluated by comparing fish length, wet body weight, and dry body weight. There were no statistically significant effects in the growth parameters of fish exposed to 0.11 mg a.s/l compared with the solvent control group. A statistically significant reduction in fish weight existed at 0.23 and 0.50 mg a.s/l. However, mean lengths and mean dry weights of fish exposed to 0.23 and 0.50 mg a.s/l were similar to those of the solvent control fish. Statistically significant reductions in all growth parameters were found in the fish exposed to 0.98 mg a.s/l.

Based on these findings, **the no-observed effect concentration (NOEC) for the early life-stage toxicity of Thiabendazole to fathead minnows was 0.11 mg a.s/l** and the Lowest-Observed Effect Concentration (LOEC) was 0.23 mg a.s/l. Therefore, the Maximum Acceptable Toxicant Concentration (MATC) was between 0.11 and 0.23 mg a.s/l. The geometric mean of these limits was used as the estimate of the MATC and was calculated as 0.16 mg a.s/l.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Holmes, C.M., Bellantoni, D.C. and Peters, G.T. 1990.

Daphnids were exposed to Thiabendazole at nominal concentrations of 0, 0.22, 0.37, 0.61, 1.02 and 1.70 mg a.s/l. Mean measured (samples taken at 0, 24 and 48 hours) concentrations were 0.48, 0.75, 1.19, 2.36, and 3.72 mg a.s/l. **The flow-through acute 48-hour EC50 value calculated using the mean measured concentrations was 0.81 mg a.s/l**. The 95% confidence limits ranged from 0.72 to 0.91 mg a.s/l. The 24- and 48-hour no-observed effect concentration was 0.75 and 0.48 mg a.s/l, respectively.

Surprenant D.C. 1989a.

The acute toxicity of Thiabendazole to Eastern oysters (Crassostrea virginica) was determined. Eastern oysters were exposed to nominal concentrations of 65, 110, 180, 300, and 500 micrograms a.i/l of Thiabendazole for 96 hours. Analyses of duplicate exposure solutions at test initiation and termination resulted in mean measured concentrations of 64, 98, 130, 180 and 260 micrograms a.i/l. Measurements of shell growth at test termination established that at the two highest concentrations (260 and 180 micrograms a.i/l) shell deposition was reduced by 22 and 19%, respectively. Reduction in shell growth of < or = to 15% was observed at the remaining treatment levels. The presence of a surface film of Thiabendazole indicated that the solubility of Thiabendazole in natural unfiltered sea water had been exceeded. The EC_{50} for Thiabendazole to Eastern oysters was estimated as being greater than the highest mean measured concentration (> 260 micrograms a.i/l, 0.26 mg a.i/l). The NOEC based on reduction in shell growth was established as 65 micrograms a.i/l, 0.065 mg/l. Since the exposure concentration would have to exceed the water solubility of Thiabendazole in unfiltered seawater to obtain > 50% effect (reduction in shell deposition), Thiabendazole should not be considered to be hazardous to the Eastern oyster.

In this study an EC_{50} could not be obtained due to the lack of solubility of Thiabendazole in the unfiltered natural seawater. EC_{50} should be considered > 0.26 mg/l (solubility given in the report).

Surprenant D.C. 1989b.

Mysid shrimps (Mysidopsis bahia) were exposed in a flow-through system to 5 concentrations of Thiabendazole for 96 hours at nominal concentrations of 0, 0.18, 0.27, 0.42, 0.65, and 1.0 mg a.s/l. Mean measured concentrations (samples taken on days 0 and 4 of the test) were 0.15, 0.25, 0.42, 0.64 and 0.88 mg a.s/l of Thiabendazole. **The 96- hour LC50 was 0.34 mg a.s/l**. The 95% confidence limits ranged from 0.25- 0.42 mg a.s/l. The no-observed effect concentration was 0.25 mg a.i/l. The highest concentration showing no mortality was 0.25 mg a.i/l. The lowest concentration showing 100% mortality was 0.64 mg a.s/l.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Liedtke, A., 2013.

The effect of the test item Thiabendazole on the survival, growth (body length) and reproduction of Daphnia magna was investigated in a semi-static test over 21 days. Daphnids were exposed to nominal concentrations of 0.010, 0.022, 0.046, 0.10, 0.22 and 0.46 mg/L (mean measured: 0.0092, 0.020, 0.041, 0.097, 0.20 and 0.43 mg/L). The survival of Daphnia magna after 21 days was reduced at the highest test concentration of 0.43 mg/L. Reproduction (based on number of offspring per surviving female) was unaffected compared to the controls at treatment levels up to 0.041 mg/L. At the highest mean measured concentration of 0.20 mg/L, the mean body length of surviving daphnids was statistically significantly reduced compared to the control.

Based on mean measured concentrations, the 21-day EC50 for reproduction was determined to be 0.11 mg/L, the EC20 was 0.083 mg/L and the EC10 was 0.071 mg/L. Based on reproduction, the 21-day NOEC was determined to be 0.041 mg/L and the 21-day LOEC was determined to be 0.097 mg/L.

5.4.3 Algae and aquatic plants

Baetscher R. 2004.

The toxicity of Thiabendazole to the fresh water green algae, *Selenastrum capricornutum,* was determined using the measured concentrations 0.56, 1.75, 5.5 and 17.2 mg/L for dilutions 1:32, 1:10, 1:3.2 and the undiluted filtrate respectively. At the end of the test, measured test item concentrations were between 85-94% of the initial measured values.

Mean measured test item concentrations were adopted for the calculation and reporting of results.

The algal cell particle densities were measured at 24, 48, 72 and 96 hours and statistically analysed, where appropriate procedures were applied to test for significant differences (p=<0.05) between the controls and test concentrations. The 72 and 96-hour EC50 for biomass and growth rate were calculated.

Microscopic observation of the algal cells after 96 hours exposure showed no difference between algae growing in the test media containing the test item at a concentration of 5.2 mg/L (1:3.2 dilution) and the algal cells in the control. There were no obvious effects on the shape and size of the algal cells growing in the test media containing the test item at up to and including this test item concentration.

Thiabendazole EC50 values over the 96-hour exposure period

Time	Biomass		Growth rate	
	EC50 (mg/L)	95% confidence interval (mg/L)	EC50 (mg/L)	95% confidence interval (mg/L)
72 hours	3.5	n.d	12.3	4.7-n.d.
96 hours	3.3	0.03-n.d.	14.7	7.1-n.d.

*n.d. - could not be determined

Thiabendazole had a statistically significant inhibitory effect on the growth (biomass and growth rate) of Pseudokirchneriella subcapitata after exposure for 72 and 96 hours at test concentrations of 1.62 mg as/L and above. The 72 and 96 hour NOEC was determined to be 0.53 mg/L.

5.4.4 Other aquatic organisms (including sediment)

van der Kolk J., 1998.

A new study (van der Kolk, 1998) on the chronic toxicity of Thiabendazole on midge larvae (Chironomus riparius) has been submitted. The study was conducted following the method published by the BBA (1995) and under GLP. Thiabendazole was added to the water phase and the NOEC and LOEC estimated as nominal water concentration in µg/l. This approach is not considered appropriate for the estimation of the risk of Thiabendazole to sediment dwelling organisms. However, the study includes analytical measurements of Thiabendazole concentrations in both water and sediment on days 0, 7 and 23.

No significant differences versus the control and the highest nominal concentration, 2 mg/l, were observed and this concentration led to sediment concentrations between 3 and 4 mg/kg from day 7 to day 23. The rapporteur considers that a NOEC of 3 mg/kg sediment can be assumed.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Thiabendazole is considered hydrolytically stable at environmentally relevant temperatures and pH values.

Thiabendazole is considered not readily biodegradable according to the result of the biodegradation test presented (6.5 %), following OECD 301 B guideline.

Thiabendazole has a log Kow of 2.43 below the cut-off value of log Kow ≥ 4, so no potential for bioaccumulation is expected, regarding CLP criteria.

Thiabendazole can be considered as not rapidly degradable in the aquatic environment from the water/sediment system study carried out. Short DT_{50} and DT_{90} values were registered for the water phase but Thiabendazolee disappears by dissipation process, binding to sediment. Non-extractable residues increased to during the study, and at the end of the study the carbon dioxide yield indicated minimal mineralization.

Photolysis seems to play a role in the degradation of Thiabendazole in water and three major metabolites have been identified but not toxicity data are available for them. Due to this lack of photochemical degradation data for metabolites, photolysis is not considered into the degradability of the substance.

Taking into account the above, Thiabendazole can be considered as a not rapidly degradable substance in the environment, according to the CLP criteria.

Thiabendazole is assessed as very toxic to aquatic life with long lasting effects, based on the following acute and chronic ecotoxicity data to invertebrates: lowest acute toxicity endpoint is Mysidopsis bahia (96h) EC_{50} = 0.34 mg/l, and lowest chronic toxicity endpoint is Daphnia magna (21d) NOEC = 0.041 mg/l. These two endpoints for invertebrates will also establish the M factors needed for CLP environmental classification categories.

Taking into account the lowest ecotoxicity endpoints obtained from the acute and chronic ecotoxicity studies carried out with invertebrates, Thiabendazole should be classified according to Regulation (EC) No 1272/2008 criteria as:

Aquatic Acute 1 with M factor of **1** (0.1 < LC $(E)_{50}$ ≤ 1 mg/l); CLP criteria for EC_{50} acute toxicity values below or equal to 1 mg/l (EC_{50} = 0.34 mg/l < 1 mg/l), and

Aquatic Chronic 1 with M factor of **1** (0.01 < NOEC ≤ 0.1 mg/l) CLP criteria for NOEC chronic values below or equal to 0,1 mg/l (NOEC = 0.041 mg/l < 0,1mg/l), plus the fact that this substance is not rapidly degradable.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Due to all the results summarized in the previous sections, the following classification categories and M factors can be concluded for this active substance:

Thiabendazole meets the CLP Regulation criteria for being classified as Aquatic Acute 1 with M factor of 1.

Thiabendazole meets the CLP Regulation criteria for being classified as Aquatic Chronic 1 with M factor of 1.

The current entry in Annex VI Table 3.1 of CLP Regulation should not be changed; the acute and chronic M factors of 1 should be added to this entry.

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 25°C, 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

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, 25ºC), which is less than the CLP trigger of ≥ 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} ≤ 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 ≤ 0.1 mg/L range, the **chronic M-factor is 1.**

6 OTHER INFORMATION

7 REFERENCES

Authors	Date	Title	Testing facility	Doc. No. (Report No.)	GLP / GEP	Published
Kabler, K. Dykes, J.	1989	Hydrolysis as a function of pH at 25 °C of ^{14}C-Thiabendazolee	ABC Analytical Bio-Chemistry Laboratories Inc. Columbia, USA.	MK360/0181	Yes	No
Adam	1999	Hydrolysis of ^{14}C-Labelled MK 360 1 CGA 28020	Protection AG Environmental Safety/Ecochemistry Besel, Switzerland	-	-	-
Flynn, J.	1994	Determination of the aqueous Photolysis of ^{14}C-Thiabendazolee.	ABC Analytical Bio-Chemistry Laboratories Inc. Columbia, USA.	MK360/0182	Yes	No
Adam, D.	2005	Photolysis of 14C-MK360 (Thiabendazolee) in sterile natural water under laboratory conditions	RCC Ltd. Itingen, Switzerland	MK360/0938	Yes	No
Schmidt, E.	2002	Quantum yield of the direct photochemical degradation of Thiabendazolee (MK360) in aqueous solution	Solvias AG, Basel, Switzerland	MK360/0589	Yes	No
Van der Kolk, J.	1998	MK 360 B (Thiabendazolee) ready biodegradability CO2 evolution test (modified sturm test)	Springborn Smithers Laboratories (Europe) AG, Horn, Switzerland	MK360/0454	Yes	No
Ulbrich, R.	1999	Degradation and metabolism of 14C-Phenyl-labelled MK 360 in two aerobic aquatic systems under laboratory conditions	Novartis Crop Protection AG, Basel, Switzerland	MK360/0555	Yes	No
Hurt A., Mason G.	2004	Thiabendazolee : Study of Adsorption and Desorption Properties in Six Soils	Syngenta Crop Protection AG, Basel, Switzerland	MK360/0894	Yes	No
not specified	1976	Soil leaching study: column method radiolabeled Thiabendazolee	WARF Institute, Madison, USA	MK360/0179	Yes	No
Schroder, C., Steele J.	1978	Soil mobility of Thiabendazolee aerobically aged in soil and photodegraded Thiabendazolee	WARF Institute	MK360/0180	Yes	No
Hirsch M.P.	1991	Bioconcentration of Thiabendazolee (2-(4-thiazolyl)-1H-Benzimidazole) in bluegill sunfish, *Lepomis macrochirus*	Syngenta Crop Protection AG, Basel Switzerland Eastman Kodak, Rochester, USA	MK360/0204	Yes	No

Authors	**Date**	**Title**	**Testing facility**	**Doc. No.** **(Report No.)**	**GLP / GEP**	**Published**
Beglinger, J.M. O'Boyle, R.J	1989	Acute Aquatic Effects of Thiabendazolee on the Bluegill Sunfish, *Lepomis macrochirus.*	Eastman Kodak, Rochester, USA	MK360/0196	Yes	No
Beglinger, J.M. O'Boyle, R.J	1989a	Acute Aquatic Effects of Thiabendazolee on the Rainbow Trout, *Salmo gairdneri.*	Eastman Kodak, Rochester, USA	MK360/0197	Yes	No
Surprenant, D.C	1989	Acute Toxicity of Thiabendazolee to Sheepshead Minnow (*Cyprinodonn variegatus)* Under Flow-Through Conditions.	Springborn Life Science Inc. Wareham, MA, USA	MK360/0199	Yes	No
Holmes, C.M., Swigert, J.P. Smith, G.J.	1992	Thiabendazolee: A 96-Hour Static Acute Toxicity Test with the Bluegill Sunfish *Lepomis macrochirus.*	Wildlife International, Easton, Maryland, USA	MK360/0200	Yes	No
Holmes, C.M. Swigert, J.P.	1992	Thiabendazolee: An Early Life-Stage Toxicity Test with the Fathead Minnow (*Pimephales promelas*).	Wildlife International, Easton, Maryland, USA	MK360/0202	Yes	No
Holmes, C.M., Bellantoni, D.C. Peters, G.T.	1990	Thiabendazolee: A 48-Hour Flow-Through .Acute Toxicity Test with the Cladoceran (*Daphnia magna)*.	Wildlife International, Easton, Maryland, USA	MK360/0208	Yes	No
Surprenant, D.C.	1989a	Acute toxicity of Thiabendazolee to eastern oysters (*Crassostrea virginica*) under flow-through conditions	Springborn Life Science Inc., Wareham, USA,	MK360/0198	Yes	No
Surprenant, D.C.	1989b	Acute toxicity of Thiabendazolee to mysid shrimp (*Mysidopsis bahia*) under flow-through conditions	Springborn Life Science Inc., Wareham, USA,	MK360/0207	Yes	No
Baetscher, R.	2004	Thiabendazolee (MK360): A 96-hour algal growth inhibition test with *Pseudokichneriella subcapitata* (formerly *Selenastrum capricornutum*)	RCC Ltd., Itingen, Switzerland	MK360/0725	Yes	No
van der Kolk J.	1998	MK 360 B (Thiabendazolee): chronic effects on Midge Larvae (*Chironomus riparius*) in a water / sediment system	Springborn Smithers Laboratories (Europe) AG, Horn, Switzerland	MK360/0481	Yes	No
Liedtke, A.	2013	Thiabendazolee - Effect on Survival, Growth and Reproduction of Daphnia magna in a Semi-Static Test over Three Weeks	Syngenta Harlan Laboratories Ltd., Itingen, Switzerland,	MK360-11593	Yes	No

8 ANNEXES