Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

tebuconazole

CAS number: 107534-96-3

EC number: 403-640-2

CLH-O- 0000002717-69-02/A2

Adopted

5 June 2013

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via the internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensively as possible. Please note that some of the comments might occur under several headings, when splitting the information provided is not reasonable.

Substance name: Tebuconazole
EC number: 403-640-2
CAS number: 107534-96-3
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
04/10/2012	France		MSCA	1

Comment received

In the absence of details and justifications in the CLH report, it is not possible to comment the current harmonized classification.
However, we consider that carcinogenicity and reproductive toxicity are the critical toxicological endpoints for tebuconazole: the relevance of Phenobarbital-like mechanism for carcinogenicity classification and a more severe classification for reproductive toxicity should be discussed.

Cyproconazole (CAS 94361-06-5)
• Harmonized classification
o 67/548/EC: Xn, R22; Repr cat 3, R63; N, R50/53
o CLP: Acute Tox 4 (H302); Repr 2 (H361d); Aquatic Acute 1 (H400); Aquatic Chronic 1 (H410)
• Proposed classification in the CAR
o 67/548/EC: Xn, R22; carc cat 3, R40; Repr cat 2, R61; N, R50/53
o CLP: Acute Tox 4 (H302); Carc 2 (H351); Repr 2 (H361); Aquatic Acute 1 (H400); Aquatic Chronic 1 (H410)

Propiconazole (CAS: 60207-90-1) et tébuconazole : no harmonised classification nor proposed.

Those are only specific examples available but this Mode of Action (MoA) is not specific to triazoles. The relevance of the MoA Phenobarbital-like for human should be discussed in order to ensure fair treatment.

FR agrees with the general conclusion dealing with the environmental classification of the substance.

Dossier Submitter's Response

The dossier on tebuconazole has been prepared because a review of the currently available aquatic toxicity data for tebuconazole has revealed that the classification listed in Annex VI of Regulation EC no.1272/2008 (including the 1st ATP) is not in agreement with the data. There are no new data indicating that an update for the other endpoints (including reproductive toxicity and carcinogenicity) is required. Therefore, these endpoints are not discussed in this CLH dossier and no assessment of the other hazard classes by RAC is requested.

RAC's response

Noted. In line with the DS response: assessment of the additional endpoints is not required and as the hazards were not assessed by the DS, their assessment by RAC is not warranted.
RAC noted the support for environmental classification.

Date	Country	Organisation	Type of Organisation	Comment number
05/10/2012	Germany	Bayer CropScience AG	Company-Manufacturer	2

Comment received

All comments from Bayer CropScience AG are made in the format of a 3-page PDF document, submitted as a public attachment.

*ECHA comment: The attachment **20121004_TBZ_CLH_Bayer Public Comments.pdf** is copied below and in the section OTHER HAZARDS AND ENDPOINTS.*

European Chemicals Agency Classification of the active substance Tebuconazole – Public Consultation Comments from Bayer CropScience AG, notifier of tebuconazole under Directive 91/414/EEC

Part A, Chapter 2, Background:
Page 11, Line 7: While tebuconazole had been included in Annex I to Directive 98/8/EC in 2008, it has been included in Annex I to Directive 91/414/EEC only one year later, in 2009.
Page 11, Line 13: In the justification for the classification according to Directive 67/548/EEC, the R63 is listed alongside the statement "Embryotoxic and teratogenic effects seen without marked maternal toxicity", with a reference to the 29th ATP. However, the related Directive 2004/73/EC does not contain such a statement. Bayer CropScience therefore proposes to delete this statement in the CLH report, or to replace it with the phrase that has been used in the EU Draft Assessment Report: "developmental toxicity occurred at doses that are associated with some maternal toxicity" (Version as of February 2007, Vol. 1, page 36).
Page 11, next-to-last line: Should read "Acute Tox 4" instead of "Acute Chronic 4".
Page 18, last line: Only uses as a fungicide in foliar and seed treatment applications are listed. We recommend that uses in material protection are mentioned as well, to be in line with the background chapter, where Directive 98/8/EC has been discussed.

Part B, Chapter 4, Human Health Hazard Assessment
Page 22, Dermal toxicity: Reference should read "Ohta, 1991" instead of "Heimann and Pauluhn, 1983", and "Heimann and Pauluhn, 1983" instead of "Sheets, 1988".

Dossier Submitter's Response

Part A
Page 11, Line 7: Noted
Page 11, Line 13: In the DAR it is stated that 'developmental toxicity occurred at doses that are associated with some maternal toxicity. However, the toxicity to the dams could not in all cases be categorised in severity to a degree that would influence the development of the offspring via non-specific secondary mechanisms to effects such as malformations'. The conclusion that 'Embryotoxic and teratogenic effects seen without marked maternal toxicity' is therefore correct.
Page 11, next-to-last line: Agreed
Page 18, Noted

Part B
Page 22: Noted

RAC's response

Noted

ACUTE TOXICITY

Date	Country	Organisation	Type of Organisation	Comment number
05/10/2012	Spain		MSCA	3

Comment received

p. 26 Conclusions on classification and labelling for acute toxicity

Tebuconazole is listed in Annex VI of 1272/2008/EEC Regulation (CLP) – included in 29th ATP of Directive 67/548/EEC (DSD).

The current classification for acute oral toxicity is as follows: Acute Tox. 4* H302 (minimum classification), under the CLP Regulation and Xn; R 22 under the DSD.

The Spanish CA supports the proposed classification of tebuconazol as Xn, R22: Harmful if swallowed (limits 200< LD50 ≤ 2000 mg/kg bw) and as Acute Tox 4 (H302: Harmful if swallowed) (limits 300< LD50 ≤ 2000 mg/kg bw) according to DSD and CLP classification criteria, respectively.

Considering the results from oral toxicity studies (LD50 value in female rats = 1700 mg/kg bw; Ohta K, 1991 and LD50 value in male mouse = 1615 mg/kg bw; Heimann KG, 1993) it is no longer

necessary to maintain the current reference that indicates a minimum classification (*).
Dossier Submitter's Response
Thank you for the support
RAC's response
Noted

AQUATIC TOXICITY

Date	Country	Organisation	Type of Organisation	Comment number
17/09/2012	United Kingdom		MSCA	4

Comment received

The aquatic chronic toxicity classification is based on NOECs ≤ 0.1mg/l for fish, invertebrates (Daphnia magna and Mysidopisis bahia), algae and aquatic plants. The chronic toxicity to Daphnia study (Noack, 1999) is used as the key study for determining the chronic M-factor. This is based on a NOEC derived from nominal data,(0.01mg/l) however the mean measured data for this exposure concentration (0.014 mg/l -136 % of nominal) would change the M factor.

The DAR considers the use of nominal data acceptable as analytical detection limits varied.

However we feel it would be useful to present further analytical information to support the M factor used as the chronic NOECs for other taxa are in the range 0.01 mg/l - 0.1 mg/l and the NOEC for the second chronic Daphnia test is 0.12 mg/l (measured data).

Dossier Submitter's Response

In the studies described in our CLH report, the NOEC values in fish and algae fall within the 0.01 mg/L < NOEC ≤ 0.1 mg/L band. However, the lowest NOEC value of 0.01 mg/L (nominal) is obtained for *Daphnia Magna*; this value falls in the toxicity range 0.001 mg/L < NOEC ≤ 0.01 mg/L and supports M-factor 10. This value 0.01 mg/l (nominal) is considered valid in both the DAR and the CAR for tebuconazole. In the DAR, the use of nominal concentrations is justified under table Table B.9.2.5-5 as follows: "Detection limit (DL) varies between 0.014 and 0.037 mg/l which may indicate that the measured values in the lowest concentration are more indicative than actual and the reason for the larger variation. Therefore, the use of nominal values is acceptable." The lowest exposure concentration used is 0.01 mg/l, which is under the detection limit. The uncertainty in the measured concentrations at the lowest concentration is therefore high. As is explained in the DAR, the measured value at the lowest concentration may therefore only be indicative for the real value, which justifies the use of nominal concentrations. We have no reason to disregard this justification and have accepted the results of this study based on nominal concentrations. As the value 0.01 mg/l is the lowest reliable aquatic chronic toxicity value, it is used as basis for classification and determining the M-factor.

As suggested by the UK – MSCA additional information on the chronic toxicity NOECs for tebuconazole as provided in the DAR is shown below.
Daphnia magna reproduction test (21d), (Noack, 1999).Table B.9.2.5-5 Nominal and measured concentrations. The test results based on nominal values as the measured values (mean recovery rates) in old and new media varies between 87 and 136%. Detection limit (DL) varies between 0.014 and 0.037 mg/L that may indicate that the measured values in the lowest doses are more indicative than actual and the reason for the larger variation. Therefore, the DAR considered the use of nominal values acceptable. Based on nominal concentrations the 21-d NOEC was 0.01 mg/L and the LOEC was 0.03 mg/L.

Nominal Conc. (mg/L)	Mean recovery rate (mg/L	Recovery rate (%)
0	>DL*	
0.01	0.014	136%
0.03	0.028	95%
0.1	0.087	87%
0.3	0.317	106%
0.9	0.888	99%

RAC's response

The information is included in the ODD, RAC agrees with the DS's argumentation that the use of nominal values is acceptable.

Date	Country	Organisation	Type of Organisation	Comment number
01/10/2012	Belgium		MSCA	5

Comment received

Based on the results of the aquatic toxicity test (most sensitive species : Acute : Aquatic plants 7dEC50 Lemna gibba=0.237mg/l, Chronic : invertebrates 21dNOEC Daphnia magna=0.01mg/l) the fact that the substance is NOT rapidly degradable, it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410.

In view of the proposed classification and the toxicity band for acute toxicity between 0. 1 mg/l and 1mg/l, an M-factor for acute toxicity of 1could be assigned, and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and 0.001<NOEC≤0.01 mg/l).

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, LC50 <1 mg/l, BCF<100 but not readily degradable, Tebuconazole should be classified as N, R51/53 with SCL :
N, R50/53 : Cn ≥25%
N, R51/53 : 2.5%≤Cn<25%
R52/53 :0.25%≤Cn<2.5%

In conclusion: we support the proposed classification for the environment by the NL MSCA.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
04/10/2012	Germany		MSCA	6

Comment received

Environmental hazard:
The German CA supports the proposed (more stringent) environmental classification and corresponding SCL and M-factors.

p. 29 & 30 (biodegradation): In the CLH Report is mentioned that no data on ready biodegradation are available. The CA Report of Tebuconazole as a biocide contains description of two tests on ready biodegradability. This information should be included in the CLH Report.

P. 32 Aquatic toxicity – fish long term toxicity: Additional Study not considered in the dossier:
Reference: Title: Tebuconazole – fish sexual development test (FSDT) with fathead minnow
Author, (year): Bomke, C. (2007)
Report number: E 286 3254-3
Guideline: OECD FSTD Draft (Version of 26 July 2006)
GLP: yes
Deviations: none
Validity: Acceptable

Test substance: Tebuconazole (tech.) – HWG 1608, purity: 96.8 %
METERIALS AND METHODS
Test Species: Pimephales promeals, freshly fertilized eggs (< 24 hours old)
Treatments: Nominal: 3.13, 6.25, 12.5, 25.0, 50.0 and 100 µg a.s./L
mean measured: 2.65, 5.78, 11.2, 22.1, 45.0 and 89.6 µg a.s./L
According to the OECD draft the mean measured concentrations are used.
No. of replicates: 4 replicates with 100 eggs each per treatment, 8 replicates per control
Test type / duration: flow-through, 122-125 days
Test conditions: Temperature: 23.2 - 26.4 °C
pH: 6.7 – 7.6
dissolved oxygen: 75 – 110 %

FINDINGS
Analytical results: Mean measured concentrations ranged from 85 to 93 %
Test results:
NOEC (mean measured)
Egg survival: 89.6 µg/L (d 0-5)
Larval survival: 22.1 µg/L (d 5-33)
Adult survival: 22.1 µg/L (d 33-125)
Cumulative mortality: 22.1 µg/L (d 0-125)
Length (mean): 22.1 µg/L m (d 122-125)
> 45.0 µg/L f (d 122-125)
Wet weight (mean): > 45.0 µg/L m/f (d 122-125)
Sex ratio (gonadal tissue): > 45.0 µg/L (d 122-125)

Mortality: in the highest tested concentration (89.6 µg/L) all test animals were dead after 53 days.
Sex ratio: the predicted virilisation (due to the mode of action of tebuconazole) of the animals did not occur in this study.

Pathological findings:
Sex: distinction and sex ratio were not influenced by the test substance. In test concentration 11.2 µg/L two sexual undifferentiated fish were found, whose length and weight were slightly lower (not significant).

At concentrations starting of and above 5.78 µg/L non-adverse liver changes occurred in male fish and at concentrations of and above 11.2 µg/L also in females. Liver toxicity with degenerative changes and inflammation were observed in male and female fish at concentrations of and above 11.2 µg/L. In female fish degenerated oocytes were observed at concentrations of and above 5.78 µg/L (without clear dose-response).

NOEC (mean measured)
Degenerative liver toxicity: 5.78 µg/L m/f (d 122-125)
Testis maturation (faster maturation): 11.2 µg/L (d 122-125)
Reduction yolk-accumulation: 5.78 µg/L (d 122-125)
Pancreas effects: 5.78 µg/L m/f (d 122-125)
Kidneyaneurysma: 22.1 µg/L m/f (d 122-125)

Toxic effects and potential endocrine triggered effects overlap in this study. Measurement of vitellogenin-concentrations possibly could have emphasised endocrine effects.

CONCLUSION:
NOEC = 0.00578 mg/L; mean measured concentration, based on sublethal effects

Additional comments to the study:
1. With Pimephales promelas a species has been chosen that – in comparison to Danio rerio – reacts less sensitive to certain mechanisms.
In this case Danio rerio would have been the more appropriate species.
2. Instead of 135 only 100 eggs per concentration have been tested. In return six concentrations have been tested (required are at least 3)
3. Vitellogenin-concentrations (important indicator for endocrine effects/changes) have not been analyzed!
However, this study is considered acceptable.

This new endpoint does not change the proposed classification and the respective M-factor for Tebuconazole.

Dossier Submitter's Response

Thank you for your supporting remarks, comments and additional information.

<u>Biodegradation</u>
We do not have the two tests on ready biodegradability referred to by the German CA. The CA Report we have states that "*tebuconazole is not readily biodegradable*" and study descriptions are not provided (Assessment Report Product-type PT 8 Wood Preservative 8, Annex I, Denmark, November

2007). For this reason, they were not included in the CLH report. Despite the omission of these two studies we do not foresee a change in the conclusion that tebuconazole is not rapidly degradable.

Fish sexual development study
Thank you for the information and we agree that this new study does not change the proposed classification and M-factor for tebuconazole.

A potential point of discussion is that the guideline for fish sexual development studies is relatively new and not many of these studies have been included in CLH reports. The goal of these studies is to assess early life-stage effects and potential adverse consequences of putative endocrine disrupting chemicals on fish sexual development. In addition to the more "traditional" effects (mortality, growth, fertility etc), effects that have traditionally not been used as basis for classification are measured in these studies; sometimes these effects lead to a lower NOEC than the more generally used effects. The CLP Guidance does not yet specifically address which effects can be used as the basis for classification . At present CLP Guidance mentions that the lowest NOEC is generally used. It might be useful to gather experiences with the interpretation of Fish Sexual development studies with regard to classification and evaluate whether guidance can be refined.

RAC's response

Biodegradation: noted
Fish sexual development study: RAC comments are considered in the ODD.

Date	Country	Organisation	Type of Organisation	Comment number
05/10/2012	Germany	Bayer CropScience AG	Company-Manufacturer	7

Comment received

*ECHA comment: The attachment **20121004_TBZ_CLH_Bayer Public Comments.pdf** is copied below and in the section General Comments.*

Part B, Chapter 5, Environmental Hazard Assessment

General remark: 1,2,4-Triazole (M26) is a relevant metabolite of tebuconazole. The compound is mentioned occasionally, but inconsistently throughout the CLH report. Reference is missing e.g. in chapter 5.1.2.3, "Biodegradation in soil", or in chapter 5.2 "Environmental distribution", in Table 15 and in the reference list. We recommend that the missing references are added to the CLH report to bring the document in line with other documentation resulting from the EU review of tebuconazole. Ultimately, of course, data on 1,2,4-triazole is not relevant for the classification of the parent molecule.

Page 28, Table 15, Line 2: Needs to read "§162-1" instead of "§161-2". Furthermore, study has been carried out at pH 7 only, not at pH 5 or 9.

Page 28, Table 15, Line 3: Entry in Results field needs to read "20.9 %" instead of "20 %" and "52 weeks" instead of "52 days".

Page 28, Table 15: As quantum yield has been discussed in the text, we recommend that the results be included in the table, see proposal below:

Method	Results	Remarks	Reference
ECETOC method	The UV absorption data showed that aqueous solutions of tebuconazole do not absorb any light at wavelengths above 290 nm	No contribution of direct photo-degradation to the overall elimination of tebuconazole in the environment	Hellpointner, 1990

Page 28, Table 15: The same applies to 1,2,4-triazole (M26), see proposal for inclusion below:

M26	Results	Remarks	Reference
No hydrolytic degradation after 30 days incubation at pH 5.0, pH 7.0 and pH 9.0 at 25°C.		Hydrolytically stable	Spare, 1983

Page 29, "Aerobic water/sediment system", 2nd paragraph: Twice it should read "Lienden" instead of "Leinden".

Page 29, "Aerobic water/sediment system": For clarification, we propose that the following statement

from the EU review under 91/414/EEC, consisting of two paragraphs, is included after the 2nd paragraph (i.e. after the sentence ending "slow ongoing degradation process for tebuconazole").

"It must be stressed that the findings derived from water-sediment studies indicating a slow degradation are not representative for the behaviour of tebuconazole under natural conditions. In contrast to the laboratory degradation studies which are conducted in the dark, field ecosystems have an additional sink for chemicals, in the form of secondary photoreactions. Though degradation of tebuconazole by direct photolysis can be excluded, reactions under the influence of sensitizers or with photolytically activated substances, e.g. free radicals, are possible. The relevance of this route becomes evident from studies with solutions of tebuconazole in natural water under exclusion of light on the one hand, and in the presence of nitrate or humic acids under irradiation with UV-light on the other hand. While degradation in water sediment systems and in natural water under exclusion of light is a slow process, it occurs more rapidly under the influence of natural sunshine. In an experiment with natural water under exposed conditions, the percentage of tebuconazole had been reduced to 15% of the applied amount. In an experiment with nitrate as a sensitizer commonly present in surface water from areas with intense agriculture this value was down to 2%. Three metabolites, HWG 1608- lactone (M17), HWG 1608-pentanoic acid (M25) and 1,2,4 triazole (M26) occurred as major metabolites under these conditions.

It became evident that both abiotic light induced degradation and microbial degradation take part in the overall degradation of tebuconazole. Studies measuring the effects of photolysis and biotic degradation in the dark performed according to the guidelines cannot produce a concise picture of the behaviour of tebuconazole in the aquatic environment. Therefore, higher-tier pond studies were performed in an outdoor environment in which the dissipation of tebuconazole from the aquatic system was monitored. The analytical results of the most recent outdoor microcosm study showed that the disappearance of tebuconazole can be described by first-order kinetics and that the average half-life for the disappearance from the water body was 42.6 days, and for the disappearance from the total system (water plus sediment) 54.4 days." (to be continued with next paragraph "Heimbach (2003) conducted an outdoor microcosm to study…").

Page 30, "Field studies": We propose that the following statement should be added after the first paragraph for further clarification:
"According to the PRAPeR Expert Meeting 47 (19 – 23 May 2008) the six latest trials and one of the older trials were used for the assessment of the field DT50 resulting in non-referenced half-lives of 20 - 92 days."

Page 31, Line 1: Should read "adsorption range from 7.67 to 16.39 mL/g" instead of "adsorption range from 7.67 to 19.39 mL/g" and "arithmetic mean of 769" instead of "arithmetic mean of 992".

Page 34, last Line: Should read "*Cyprinodon variegatus*" instead of "*Cyprinodon variegates*". The same typo occurs twice on page 35 (chapter 5.4.1.2, 2nd and 3rd paragraph).

Page 35, last line: Should read "*Oncorhynchus mykiss*" instead of "*Onchorhynchus mykiss*".

Page 38, Summary acute toxicity: Should read "*Mysidopsis bahia*" instead of "*Mysidopisis bahia*".

Page 38, "CLP Acute aquatic hazard", Line 4: Should read "aquatic plants" instead of "aquatic algae".

Page 41, Reference list on acute toxicity: The reference "Sheets LP (1988). Primary dermal irritation of technical Folicur in rabbits" needs to be replaced with "Ohta K (1991). HWG 1608 technical - Acute dermal toxicity study on rats (study no. 91A012)".

Dossier Submitter's Response

Thank you for your comments.

General comments
Thank you for pointing out the inconsistencies and editorial mistakes.

Specific comments
Metabolites: For the sake of completeness, we included information on metabolites to the CLH report. Information on metabolites is useful in cases where information on primary degradation is available.

In this case, acute and chronic toxicity studies in fish and invertebrates show that the toxicity of metabolites is lower than the parent compound. Therefore, the metabolites are not relevant for the classification of tebuconazole. *Degradation, page 29*: All available data on degradation relevant for classification and labelling (e.g. biodegradation in water/sediment systems, biodegradation in soil) including information on photochemical degradation was taken into account in the evaluation of tebuconazole. Information on photolysis is difficult to interpret and is generally not used for classification (see, Guidance on the application of the CLP criteria section II.2.3.9). Interpretation of the degradability data (following the CLP) lead to the conclusion that tebuconazole does **not** rapidly degrade in the aquatic environment. Consequently, no changes were proposed to the current classification on degradation for tebuconazole.
RAC's response
General comments: noted Specific comments *Metabolites*: noted and agreed with DS's response. *Degradation, page 29*: noted and agreed with DS's response.

ATTACHMENTS RECEIVED: 1

1. 20121004_TBZ_CLH_Bayer Public Comments.pdf
Submitted by Germany / Bayer CropScience AG / Company-Manufacturer. *Document is copied in the table.*