Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

tebuconazole

EC number: 403-640-2
CAS number: 107534-96-3

CLH-O-0000002717-69-02/F

Adopted

5 June 2013

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: tebuconazole

EC number: 403-640-2

CAS number: 107534-96-3

The proposal was submitted by **the Netherlands** and received by the RAC on **21/08/2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **21/08/2012**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5/10/2012**.

ADOPTION OF THE OPINION OF THE RAC

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

Co-rapporteur, appointed by RAC: **Pietro Paris**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **5 June 2013** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **tebuconazole** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factor	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	Repr. 2 Acute Tox. 4* Aquatic Chronic 2	H361d*** H302 H411	GHS08 GHS07 GHS09 Wng	H361d*** H302 H411			
Dossier submitters proposal	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	**Modify:** Removal of (*) from Acute Tox 4 **Add:** Aquatic Acute 1 Aquatic Chronic 1	**Add:** H400 H410		**Add:** H410		**Add:** M=1 M=10	
RAC opinion	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	**Modify:** Removal of (*) from Acute Tox. 4 **Add:** Aquatic Acute 1 Aquatic Chronic 1	**Add:** H400 H410		**Add:** H410		**Add:** M=1 M=10	
Resulting Annex VI entry if agreed by COM	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	Repr. 2 Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H361d*** H302 H400 H410	GHS08 GHS07 GHS09 Wng	H361d*** H302 H410		M=1 M=10	

Classification and labelling in accordance with the criteria of DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	Repr. Cat. 3; R63 Xn; R22 N; R51-53	Xn; N R: 22-51/53-63 S: (2-)22-36/37-61		
Dossier submitters proposal	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	**Add:** N; R50-53	**Add:** N; R50/53	N; R50-53: C ≥ 25 %; N; R51-53: 2,5 % ≤ C < 25 %: N; R52-53: 0,25 % ≤ C < 2,5 %:	
RAC opinion	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	**Add:** N; R50-53	**Add:** N; R50/53	N; R50-53: C ≥ 25 %; N; R51-53: 2,5 % ≤ C < 25 %: N; R52-53: 0,25 % ≤ C < 2,5 %:	
Resulting Annex VI entry if agreed by COM	603-197-00-7	tebuconazole (ISO); 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	403-640-2	107534-96-3	Repr. Cat. 3; R63 Xn; R22 N; R50-53	Xn; N R: 22-50/53-63 S: (2-)22-36/37-61	N; R50-53: C ≥ 25 %; N; R51-53: 2,5 % ≤ C < 25 %: N; R52-53: 0,25 % ≤ C < 2,5 %:	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Tebuconazole is currently listed in Annex VI of Regulation (EC) No 1272/2008 as Xn; R22 in table 3.2 (DSD) and as Acute Tox 4 (*); H302 in table 3.1 (CLP; index number 603-197-00-7). Tebuconazole was added to Annex I to Directive 67/548/EEC in the 29th ATP (Commission Directive 2004/73/EC of 29 April 2004). The classification as Acute Tox. 4(*); H302 according to the CLP Regulation is the minimum classification arising from the translation of the classification in Annex I to Directive 67/548/EEC. The classification as Acute Tox. 4; H302 is now proposed to be confirmed based on data. No classification via other exposure routes is proposed.

Acute toxicity: oral

For acute oral toxicity, there are three studies in rats, two in mice and one in rabbits.

The lowest LD_{50} values in rats are from a study that was performed according to OECD test guideline (TG) 401 and were 1700 mg/kg bw and 4000 mg/kg bw for females and males, respectively (Sprague-Dawley rats). In all three studies, female rats were more sensitive than male rats.

The lowest LD_{50} value for mice was from a study based on relevant OECD/EU guidelines with doses of 100, 500, 1000, 1800, 2500, 3150 and 3550 mg/kg bw for males and 500, 1000, 1800, 2500, 3550 and 5000 mg/kg bw for females. The lowest LD_{50} value from these two studies was 1615 mg/kg bw for males and 3023 mg/kg bw for females (NMRI mice). In mice, males were more sensitive than females in both studies.

In the only study in rabbits (HC:NZW), the LD_{50} value was found to be > 1000 mg/kg bw in both males and females but only two dose levels were tested, i.e. 500 mg/kg bw and 1000 mg/kg bw. Therefore, the current classification Acute Tox. 4*; H302 under CLP is proposed to be changed to Acute Tox. 4; H302, with the removal of the * indicating removal of the minimum classification for this category.

Acute toxicity: inhalation

Two acute inhalation studies are available, both in Wistar rats and performed according to OECD 403. Neither of the studies indicates acute inhalation toxicity, either as an aerosol or as a dust at the maximum dose levels tested. The acute inhalation LC_{50} of tebuconazole was established as greater than 818 mg/m^3 (the maximum concentration tested for aerosol exposure of 1 x 4h) in one study (particle size approx. 50 % < 5 µm, not test-specific data) and > 371 mg/m^3 for aerosol and > 5093 mg/m^3 for dust on another study (no data on particle MMAD). In a range-finding study (exposure 5 x 6 h) performed according to OECD 403, the LC_{50} was established as greater than 240 mg/m3 (maximum dose tested, aerosol exposure with MMAD 4.6-7.1 µm; GSD 1.8-2.0 µm).

Acute toxicity: dermal

Two acute dermal toxicity limit-test studies are available, both in rats (Sprague-Dawley and Wistar) and both performed according to OECD 402. No effects were observed either at a dose of 2000 mg/kg or 5000 mg/kg, respectively.

Comments received during public consultation

The Spanish CA supported the current classification Xn;R22 under the DSD and Acute Tox 4; H302 under CLP as proposed by the DS.

Assessment and comparison with the classification criteria

The lowest acute LD_{50} of tebuconazole (1700 mg/kg bw in rats and 1615 mg/kg bw in mice) via the oral route falls within the range of values for classification for Acute Tox 4; H302 (300 < LD_{50} > 2000 mg/kg bw) and Xn; R22 (200 < LD_{50} > 2000 mg/kg bw), in accordance with the CLP and

DSD criteria, respectively. For the inhalation and dermal routes all estimated LD/LC_{50} values are above the criteria for classification and labelling (CLP and DSD).
RAC agreed on classification for Acute Tox. 4; H302 (Xn, R22) as proposed by the Dossier Submitter (DS).

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Tebuconazole currently has a harmonized classification as Aquatic Chronic 2 according to CLP and N; R51-53 according to DSD. Based on a review of the available data on aquatic toxicity, the dossier submitter (DS) proposes to change the environmental classification of tebuconazole to Aquatic Acute 1 (M=1) and Aquatic Chronic 1 (M=10) according to CLP and N; R50-53 according to DSD, with specific concentration limits: N; R50-53: C ≥ 25 %, N; R51-53: 2.5 % ≤ C < 25% and R52-53: 0.25 % ≤ C ≤ 2.5 %.

Degradation

A hydrolysis study according to U.S. EPA §161-1[1] using radio-labelled tebuconazole was run at pH 5, 7 and 9 at 25 °C for 28 days. At the end of the study no degradation of tebuconazole was observed. A separate hydrolysis study performed with the metabolite 1,2,4-triazole (M26) showed that it is hydrolytically stable (half-life in water at pH 5 – 9 is greater than 30 days).

The photodegradation of tebuconazole in water was studied according to U.S. EPA §161-2[2]. No photolytic degradation was observed after 30 days incubation at pH 5.0, 7.0 and 9.0 at 22 °C (extrapolated half-life was 590 days). According to the ECETOC method, aqueous solutions of tebuconazole did not show absorbance of UV-light at wavelengths above 290 nm, therefore direct photo-degradation does not contribute to the dissipation of tebuconazole in the environment. Two photochemical degradation studies are available for the metabolite M26 in water. In the first study, photolytic degradation was not expected (considering the measured values of the molar absorptivity) and the second study confirmed that no significant degradation of M26 was observed.
No data on ready biodegradation are available.

An aerobic water/sediment simulation study using radio-labelled tebuconazole is available. The study, carried out according to EPA §162-4[3], was run for 52 weeks at 22 °C (± 2%) using two systems: from the drainage ditch of a fruit orchard and from a recultivated gravel pit of agriculturally used areas. The percentage of the applied radioactivity that is transformed into carbon dioxide after 52 weeks of incubation was 10.0% and 20.9%, respectively. The dissipation of tebuconazole in both water-sediment systems is a slowly on-going process. After one year 56% (recultivated gravel pit system) or 67% (drainage ditch system) of the applied radioactivity was attributed to tebuconazole. There was no calculation of actual degradations rates in water; however, the results of the water/sediment study were interpreted as indicating a relatively slow ongoing degradation process for tebuconazole. Moreover, no major metabolites were found in water/sediment systems.

Another study, conducted according to OECD guidance document 'Freshwater Lentic Field studies (outdoor microcosms and mesocosms) June 2000 (draft), was carried out on an outdoor microcosm to study of the dissipation of tebuconazole in outdoor stagnant water bodies. The average half-life for disappearance from the water body was calculated to be 30.9 days and for the disappearance from the total system (water plus sediment) 38.7 days. Using the TOXWA

[1] U.S. EPA Pesticide Assessment Guideline, Subdivision N, Chemistry: Environmental Fate. Series 161-1, Hydrolysis Studies.

[2] U.S. EPA Pesticide Assessment Guideline, Subdivision N, Chemistry: Environmental Fate. Series 161-2, Photodegradation in water.

[3] U.S. EPA Pesticide Assessment Guideline, Subdivision N, Chemistry: Environmental Fate. Series 162-4, Aerobic Aquatic Metabolism.

model, the calculated average dissipation DT_{50} for the total water/sediment study is 54 days. The dissipation DT_{50} for the water phase is 43 days and one year (default) for the sediment.

Moreover, the aerobic biodegradation of 14C-tebuconazole was tested in soil. The data suggest a slow degradation in soil with a DT_{50} (lab) longer than 1 year with 67.4% remaining after 1 year. In a total of 24 field dissipation trials, tebuconazole was tested at application rates ranging between 250 and 500 g per hectare. The DT_{50} field-values were transformed to standard conditions to enable comparisons with each other and with laboratory data to be made. As a result the geometric mean of the DT_{50}-values referenced to 20 °C was calculated to be 29.4 days. Tebuconazole appeared to be persistent in soil studies under laboratory conditions, in contrast to the situation in the field, where it has been shown to be moderately degradable.

Based on all available data on degradation that was relevant for classification and labelling, the DS concluded that tebuconazole is considered to be not rapidly degradable.

Bioaccumulation

Tebuconazole has a measured log K_{ow} of 3.70 (Method OECD 107, 20 °C, purity 99.1%).

The DS reported two bioaccumulation studies on tebuconazole. In the first study (EPA-Guideline §165-4[1]) bluegill sunfish (*Lepomis macrochirus*) were exposed to radio-labelled tebuconazole over a 28-day exposure period. A test concentration of 60 µg/l was used. Tebuconazole is bioaccumulated and excreted rapidly by bluegill sunfish yielding a BCF of 78 (whole fish) based on the total amount of radioactivity.

In the second study (OECD TG 305E) bluegill sunfish (*Lepomis macrochirus*) were exposed to radio-labelled tebuconazole over a 3 day exposure period. Mean concentrations in water of approximately 0.211 mg/l or 0.018 mg/l were used. A bioconcentration factor in the range of 55-93 was obtained for the whole fish based on the total radioactivity and a BCF in the range of 35-59 when related to the parent compound.

All BCF values based on the total amount of radioactivity may be overestimated.

The DS concluded that the measured bioaccumulation data show that tebuconazole is not potentially bioaccumulative according to CLP (BCF is below 500) and DSD criteria (BCF is below 100).

Aquatic toxicity

Several acute and chronic aquatic toxicity results are available from studies on tebuconazole and on its major metabolites, which, for the most part, were consistent with the relevant technical guidelines, were GLP compliant and were considered reliable according to the dossier submitter. The available short-term tests for tebuconazole were: four with fish, three with invertebrates and three with algae and aquatic plants. The most sensitive species tested was the aquatic plant *Lemna gibba* with a 7 d ErC_{50} based on frond counts, resulting in a value of 0.237 mg/l based on mean measured concentrations. Studies of acute toxicity of metabolites of tebuconazole showed that the toxicity is lower than that of the parent compound.
The chronic toxicity of tebuconazole was assessed on the basis of three long-term fish tests, three chronic tests with invertebrates and three studies with algae and aquatic plants. The most sensitive species tested was *Daphnia magna* that was exposed to tebuconazole for 21 d under static-renewal conditions that followed the standard OECD test guideline 211. The NOEC for the reproduction was 0.01 mg/l based on nominal concentrations (Noack, 1999). Mean values for recovery rate including new and old media were in the range 87 - 136 %. Available chronic studies on fish and algae of metabolites of tebuconazole showed that their toxicity was lower than that of the parent compound.

[1] U.S. EPA Pesticide Assessment Guideline, Subdivision N, Chemistry: Environmental Fate. Series 165-4, laboratory studies of pesticide accumulation in fish.

Comments received during public consultation

Four member states (MS) and one industry representative (IND) contributed comments during public consultation. Three MS stated general agreement with the proposed environmental classification.

One MS noted that the CA Report for tebuconazole as a biocide contains a description of two tests on ready biodegradability and proposed to include this information in the CLH report. The DS confirmed that these two tests had not been available but stated that these data did not change the conclusion on the degradability of the substance.

In relation to the aerobic water/sediment studies, IND proposed to insert a statement, taken from the EU review under 91/414/EEC, to emphasise that the findings derived from these studies are not representative of the behaviour of tebuconazole under natural conditions.

A MS presented an additional fish long-term toxicity study (Bomke C., 2007). Both the MS and the DS agreed that the result of the study did not, however, affect the proposed environmental classification.

Another MS suggested that the DS present further analytical information to support the chronic M-factor, as it was based on a NOEC derived from nominal data (Noack, 1999). The DS provided a clear explanation about the acceptability of nominal concentrations for this study.

Assessment and comparison with the classification criteria

Degradation

RAC agreed with the DS proposal to consider tebuconazole as not rapidly degradable, based on hydrolytic stability at all pH from 5 to 9, less than 70% mineralization within 28 days in a water/sediment study (10% and 20.9% in two different systems, after 52 weeks), more than 16 days half-life for the disappearance in one outdoor microcosm study (42.6 days from the water body and 54.4 days from the total system).

Bioaccumulation

Based on experimental data, tebuconazole has a log k_{ow} value of 3.70.
The measured bioaccumulation data based on the total amount of radioactivity and on the parent compound showed that the bioaccumulation potential of tebuconazole is low.

The measured BCFs are below the relevant CLP criterion (BCF≥500) and the DSD criterion (BCF≥100).

Aquatic toxicity

Several studies on acute and chronic aquatic toxicity are available for tebuconazole and its major metabolites.

Acute toxicity

Most acute toxicity test results, for fish, crustaceans and algae, are above the 1 mg/l criterion for CLP Category Acute 1. Two tests, however, give results under 1 mg/l. A 96 h acute test on *Mysidopsis bahia* in a seawater flow-through system results in an EC_{50} value of 0.46 mg/l. The second is a *Lemna gibba* test that reports a 7 d ErC_{50} of 0.237 mg/l (frond count), where the value was recalculated from a 14 d exposure period test, to be more in line with the ECHA recommendations. For the metabolites of tebuconazole, available test results with all three trophic levels indicate a lower toxicity compared to the parent compound.
RAC considers the lowest acute aquatic toxicity value ErC_{50} = 0.237 mg/l suitable for the purposes of classification.

Chronic toxicity

Chronic aquatic toxicity values for tebuconazole are available for all three trophic levels. Fish long-term testing provide the lowest NOEC value of 0.012 mg/l in a study based on larval survival with *Salmo gairdneri* exposed for 83 days under flow-through conditions. Among the three available chronic tests on invertebrates, the lowest NOEC value (0.01 mg/l) is obtained in a 21 d long-term toxicity study with *Daphnia magna* using a static-renewal test design (nominal concentrations). The most sensitive species tested among primary consumers is the aquatic plant *Lemna gibba*, providing a 7 d ErC_{10} value of 0.036 mg/L under static conditions. Available studies of chronic toxicity of metabolites of tebuconazole on fish and algae show that the toxicity is lower than that of the parent compound.
RAC considers the lowest NOEC value of 0.01 mg/l as suitable in order to classify tebuconazole.

Conclusion on classification

Tebuconazole is considered not to be rapidly degradable and does not fulfil the criteria for bioaccumulating potential. The lowest aquatic acute value falls within the range $0.1 < L(E)C_{50} \leq 1$ mg/l, the lowest aquatic chronic value lies within the toxicity range $0.001 < NOEC \leq 0.01$ mg/l. The RAC concludes that tebuconazole fulfils the CLP criteria for classification as **Aquatic Acute 1** with an **M-factor of 1** and **Aquatic Chronic 1** with a **M-factor of 10**. According DSD criteria, tebuconazole is classified **N; R50-53**, the relative specific concentration limits are: N; R50-53: C ≥ 25 %, N; R51-53: 2.5 % ≤ C < 25 % and R52-53: 0.25 % ≤ C ≤ 2.5 %.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. It is based on the CLH report prepared by the dossier submitter; the evaluation performed by the RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and the RAC (excl. confidential information).