

Committee for Risk Assessment
RAC

Opinion

proposing harmonised classification and labelling
at EU level of

**2,2'-methylenebis(6-(2H-benzotriazol-2-yl)
-4-(1,1,3,3-tetramethylbutyl)phenol)**

EC Number: 403-800-1
CAS Number: 103597-45-1

CLH-O-0000001412-86-177/F

Adopted

5 December 2017

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

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

Chemical name:

2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetra methylbutyl)phenol)

EC Number: 403-800-1

CAS Number: 103597-45-1

The proposal was submitted by **Germany** and received by RAC on **30 September 2016**.

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

PROCESS FOR ADOPTION OF THE OPINION

Germany 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 **16 December 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **9 February 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Katalin Gruiz**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **5 December 2017** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	604-052-00-0	2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)	403-800-1	103597-45-1	Aquatic Chronic 4	H413	-	H413			
Dossier submitters proposal	604-052-00-0	2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)	403-800-1	103597-45-1	Remove Aquatic Chronic 4	Remove H413	-	Remove H413			
RAC opinion	604-052-00-0	2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)	403-800-1	103597-45-1	Retain Aquatic Chronic 4	Retain H413	-	Retain H413			
Resulting Annex VI entry if agreed by COM	604-052-00-0	2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)	403-800-1	103597-45-1	Aquatic Chronic 4	H413	-	H413			

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS proposed to remove the existing harmonised classification as Aquatic Chronic 4 (H413) based on new experimental data demonstrating that 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) does not show acute aquatic toxicity in fish, aquatic invertebrates and algae. The substance is also not toxic in long-term studies available for aquatic invertebrates and algae up to its level of water solubility. Furthermore, the DS concluded that the bioaccumulation potential is expected to be low based on available information from BCF QSAR calculations, mammalian toxicokinetic studies, a high log Kow (12.7 at 25 °C) and low water solubility (<5 ng/L).

The CLH dossier was prepared by industry and submitted by the German CA, in accordance with Article 37(6) of the CLP Regulation.

Degradation

Hydrolysis: the substance is not expected to hydrolyse in water at environmentally relevant conditions.

Biodegradation: The substance is not considered rapidly degradable for classification purposes based on the results of a reliable (Klimisch 1) ready biodegradability study (EEC, L 251 Vol. 27, comparable to OECD TG 301B by CIBA-GEIGY Ltd., 1991c) and confirmed by an inherent biodegradability test (OECD TG 302C, RCC Ltd., 2005) (The DS has not included a reliability assessment for this test).

Ready biodegradability: 0–10% CO₂ evolution after 28 days;

Inherently biodegradable: 0% O₂ consumption after 28 days.

Aquatic bioaccumulation

Measured bioaccumulation: The only available study on bioconcentration (Kyushu Chemical Biotesting Center, 1986) was conducted according to a former Japanese standard test method (July 13, 1974) for bioaccumulation in fish. This test was not in compliance with OECD TG 305 C, and has been assessed by the DS as not reliable (Klimisch 3) due to high solvent content and too high substance concentration in the test medium (0.1 and 1.0 mg/L) compared to the water solubility (<5 ng/L). The DS considered the study not valid compared to the recent OECD TG 305 (2012), as the solvent might have significantly altered the dissolved concentrations in the medium.

The measured values: BCF=0.1–1.5 for the higher substance concentration of 1 mg/L, and BCF=0.14 for the lower substance concentration of 0.1 mg/L (whole body w.w., time of plateau: 2 weeks, steady state).

The predicted BCF values from QSAR models showed large variability between <1–2.4E+11 (the extremely high values resulted from simplified models not considering other substance properties). The substance did not comply with the demands of most of the models, being out of their applicability domains. One QSAR model (US EPA T.E.S.T. v4.1: Bioaccumulation, Consensus method by BASF SE, 2014g) has an applicability domain covering 2,2'-methylenebis(6-

(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol, but with low confidence. This modelling resulted in an estimated BCF=101.9.

The DS assessed the bioaccumulation potential in a weight of evidence (WoE) approach due to the lack of valid bioaccumulation test data. Thus, while the limitations concerning the reliability of the QSAR results were recognised and depending on the degree of the criteria violations, the DS concluded that the estimated BCF values can be used in the assessment of the bioaccumulation potential in combination with other data, – e. g. log Kow and water solubility – in a weight-of-evidence approach".

The DS concluded that neither an experimental nor a calculated BCF could be determined.

Toxicokinetic study in Wistar rat

The DS introduced data from mammalian studies in Rat in an effort to further assess bioaccumulation.

After 6 hours of topical exposure, the dermal absorption was not more than 0.8% and 0.4% of the applied dose. The topically applied substance did not achieve systemically measurable concentrations, *i.e.* was not bioavailable. After oral administration, the systemic availability was negligible and the substance was quantitatively and rapidly excreted as parent compound via the faeces. Based on these findings the DS concluded that the substance is not bioavailable as it does not significantly cross biological membranes. Subsequently the DS also concluded that a significant bioaccumulation in fish is not expected either.

The overall WoE conclusion of the DS on the bioaccumulation of 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) is that the low bioavailability, the poor water solubility, and the high log Kow indicate that bioaccumulation of the test item in organisms is not to be expected and a toxicokinetic study demonstrated that the substance is not bioavailable as it does not significantly cross biological membranes.

Aquatic toxicity results

Method	Results	Reliability	Reference
Fish acute toxicity EEC L251 (≈OECD TG 203)	LC ₅₀ (96h) > 28.9 mg/L (measured)	1	CIBA-GEIGY Ltd. (1991b)
Invertebrates acute toxicity EEC L251 (≈OECD TG 202)	LC ₅₀ (48h) > 65.9 mg/L (measured)	1	CIBA-GEIGY Ltd. (1991a)
Chronic toxicity to invertebrates (OECD TG 211)	NOEC (21d) ≥ 25 µg/L (measured)	1	RCC Ltd. (2006)
Toxicity to aquatic algae (OECD TG 201)	EC ₅₀ (72h) > 2 mg/L (measured) NOEC (72h) ≥ 2 mg/L (measured)	1	Safepharma Laboratories Limited

All test results in the table are above the water solubility of the test substance.

The DS did not include any chronic toxicity results for fish in the CLH report, but instead stated that *"neither fish nor aquatic invertebrates seem to be more sensitive. A chronic fish toxicity test is therefore not necessary to assess the toxicity towards aquatic organisms."*

Based on the above evidence the DS concluded that 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) does not fulfil the criteria for classification as Aquatic Chronic 4, thus, proposing the removal of the harmonised environmental classification.

Comments received during public consultation

Four MSCAs commented during the public consultation, three indicating no support for the proposed removal of the 'safety net' classification, whereas one MSCA indicated support.

According to one opposing MSCA, Aquatic Chronic 4 applies due to the following uncertainties:

- Other log Kows than 12.7 (20°C) were reported in different registration dossiers. – The DS responded that only the most reliable and relevant result was included in the CLH report.
- Lack of clarity on the availability of a valid and reliable NOEC for fish available. The MSCA referred to a study result of 56 days NOEC >1 mg/L (mortality) available for *Cyprinus carpio*, which should have been described in the CLH report (even if not reliable, together with the reason why). – The DS responded that this study is the same as used for measuring bioaccumulation and was assessed as not reliable (Klimisch 3) by the DS.
- Many QSAR predictions were included in the CLH report, however, none of them was reliable. It was therefore not sufficiently demonstrated that the substance will not bioaccumulate over time. – In his response, the DS referred to the toxicokinetic study results demonstrating that the substance is not bioavailable and does not significantly cross biological membranes.
- Bioavailability may vary between different organisms.

Another MSCA did not support the removal of the current Aquatic Chronic 4 classification, as there were no data for the chronic toxicity to fish endpoint and the relative chronic toxicity to fish was unclear. In his response, the DS agreed on the lack of chronic fish data. Furthermore, the MSCA stated in its comments that it was not possible to conclude that the substance is not bioaccumulative, as none of the BCF values were considered reliable. The DS responded by referring to the toxicokinetic data showing the opposite.

A third MSCA did not support the removal of the existing harmonised classification as Aquatic Chronic 4 due to uncertainties in the QSAR estimates of the BCF values. – The DS confirmed these uncertainties of the BCF estimates but referred to the low bioavailability, poor water solubility and high log Kow of the substance, based on which bioaccumulation in organisms is not expected.

One MSCA supported the proposed removal of the harmonised classification based on the following comments:

- Despite the QSAR predictions not being valid, the limited bioavailability suggests that the bioaccumulation may be very low.
- Despite a chronic fish toxicity test being absent, it is expected that the substance may not be toxic to fish at the limit of the water solubility. Such potent substances (*i.e.* those showing effects at concentrations < 5 ng/L) have been only demonstrated in a few chemicals like endocrine disruptors.
- The MSCA, however, did not agree with the statement of the DS: "*according to the acute aquatic toxicity data, neither fish nor aquatic invertebrates seem to be more sensitive. A chronic fish toxicity test is therefore not necessary to assess the toxicity towards aquatic organisms.*"

Assessment and comparison with the classification criteria

2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) is poorly soluble as its solubility in water is <5 ng/L. The calculated log Kow of 12.7, which was included in the CLH dossier and considered the most reliable one by the DS, derives from a study for which information on the exact methods used are not known. In addition, other log Kow values (ranging from 4.2 to 14.48) can be found in various registration dossiers available for the substance. Consequently, the log Kow reported in the CLH dossier cannot be considered by RAC as very certain.

RAC agrees with the DS to not consider the substance as rapidly degradable for classification purposes. Only 0–10% of the substance was degraded within 28 days and the criterion for rapid degradation (degradation >70% within a 28 days period) is not fulfilled.

Measured BCF values of 0.1–1.5 and 1.4 L/kg would not fulfil the classification criterion of CLP (BCF \geq 500), but the study of Kyushu Chemical Biotesting Center (1986) is not considered to be reliable. The test conditions of the former Japanese standard method (from 1974) are not in accordance with OECD TG 305 in the following aspects:

- (i) the solvent THF (Tetrahydrofuran) is not on the list of acceptable solvents recommended to be used for testing;
- (ii) the selection criteria of the concentration of the test substance given by OECD TG 305 are not fulfilled, as the applied concentrations in this study are not "*within an environmentally relevant range*", but much higher.

One of the QSAR estimates, *i.e.* BCF=101.9 (US EPA T.E.S.T. v4.1: Consensus method, 2014) would not fulfil the classification criterion of CLP (BCF \geq 500), but the reliability of the result was characterised as "*within applicability domain with low confidence*".

Regarding the toxicokinetic evidence demonstrating no bioavailability and no bioaccumulation in rat, the applicability to fish has not been justified.

In conclusion, RAC does not accept the QSAR-based BCFs, even if they are within the model applicability domain but with low confidence, because the log Kow used as the basis for the estimations also carries uncertainties. Furthermore, RAC agrees with the overall conclusion of one MSCA providing comments that 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) has probably no bioaccumulative potential, but does not see this being demonstrated by measured or estimated data, or a well compiled list of convincing evidence supporting the proposal to remove the existing harmonised classification.

2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) does not show acute aquatic toxicity in fish, invertebrates and algae up to its water solubility (LC₅₀ values > water solubility). No chronic aquatic toxicity has been measured in invertebrates and algae up to the water solubility (NOEC values > water solubility). No reliable chronic fish test results are available. RAC does not agree with the DSs' conclusion that a chronic fish test is unnecessary. The already questioned bioaccumulation study did not include data on mortality endpoint, the only information on fish during the 56 days study is "*No abnormal appearance was observed in test fishes*".

Evaluation and comparison with the criteria for safety net classification (Aquatic Chronic 4)

A classification as Aquatic Chronic 4 is assigned to poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility and which are not rapidly degradable and have an experimentally determined BCF \geq 500 (or, if absent, a log Kow > 4), indicating a potential to bioaccumulate. Aquatic Chronic 4 classification is not necessary if in addition to the above criteria other scientific evidence exists showing classification to be unnecessary. Such evidence includes chronic toxicity NOECs > water solubility or > 1 mg/L.

2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)

- (i) is poorly soluble;
- (ii) does not show acute toxicity up to the limit of water solubility;
- (iii) both the experimental BCF study and the QSAR results for BCF estimation represent high uncertainties, in addition the log Kow of 12.7 is also uncertain, thus, the presented overall WoE does not exclude the potential of the substance to bioaccumulate;
- (iv) no chronic fish study is available;

so the classification as Aquatic Chronic 4 is warranted.

In conclusion, RAC does not support the proposal by the DS but recommends to retain the existing harmonised classification as **Aquatic Chronic 4 (H413)**.

ANNEXES:

- Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.
- Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).