Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling at EU level of

Tetrakis (2,6-dimethylphenyl)-m-phenylene biphosphate (PX-200)

EC number: 432-770-2
CAS number: 139189-30-3

ECHA/RAC/CLH-O-0000002526-74-03/F

Adopted

30 November 2012

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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CLH-O-0000002526-74-03/F

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

In accordance with Article 37 (4) of (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: Tetrakis (2,6-dimethylphenyl)-m-phenylene biphosphate (PX-200)

EC number: 432-770-2

CAS number: 139189-30-3

The proposal was submitted by the **United Kingdom** and received by the RAC on **14/05/2012**
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).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Skin Sens 1: H317 Aquatic chronic 4: H413	Xi; R43 R53
Original proposal by dossier submitter for consideration by the RAC	Removal of Aquatic chronic 4 classification	Removal of R53 classification
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Skin Sens 1: H317	Xi; R43

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom 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 **14/05/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **28/06/2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Hans-Christian Stolzenberg**
Co-rapporteur, appointed by the RAC: **Yvonne Mullooly.**

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 **30 November 2012***,* 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 **tetrakis(2,6-dimethylphenyl)-m-phenylene biphosphate (PX-200)** should be classified and labelled as follows:

Classification & Labelling in accordance with CLP:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
015-192-00-1	tetrakis(2,6-dimethylphenyl)-*m*-phnylene biphosphate	432-770-2	139189-30-3	Skin Sens. 1 ~~Aquatic Chronic 4~~	H317 ~~H413~~	GHS07 Wng	H317 ~~H413~~			

Classification & Labelling in accordance with DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
015-192-00-1	tetrakis(2,6-dimethylphenyl)-*m*-phenylene biphosphate	432-770-2	139189-30-3	R43 ~~R53~~	R: 43~~-53~~ S: (2-)24-37~~-61~~		

*Text in the above table which has been struck through indicates the proposed removal of that part of the classification

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by the United Kingdom.

Environmental hazards

Summary of the Dossier submitter's proposal

Tetrakis (2,6-dimethylphenyl)-m-phenylene biphosphate (PX-200) has a harmonised classification as Aquatic Chronic 4, H413 according to CLP Regulation, and R53 according to DSD. This classification was based on its low water solubility, lack of biodegradation and high n-octanol/water partition coefficient (P_{ow}). The dossier submitter (DS) proposes to remove the classification Aquatic Chronic 4, H413 and R53, justified by the absence of ecotoxic effects in all available studies and a mainly QSAR-based re-consideration of PX-200's bioaccumulation potential.

Degradation
Biodegradation of PX-200 was studied in a ready biodegradability test. After 28 days 13.23% biodegradation was observed by test material analysis and no biodegradation was observed by oxygen consumption. Due to the low water solubility no hydrolysis test was performed. Based on the chemical structure, the DS assumed that PX-200 is not degraded by direct photolysis.

Bioaccumulation
A measured and an estimated value of Pow were provided in the CLH report. The measured log P_{OW} of PX-200 was > 6.2 (HPLC method). The QSAR estimate resulted in a log P_{ow} of 11.79 (US EPA KOWWIN v 1.67 of EPI Suite v4). The DS states that for such high values the reliability of the applied methods for log P_{OW} estimates are considered to diminish. Moreover, the DS argues that with increasing log P_{ow} values a decrease of the bioconcentration factor (BCF) can be observed and it has been hypothesized in the literature that in these cases the high log P_{ow} is more an effect of solubility than lipophilicity.
A fish bioaccumulation study (OECD TG 305, *Cyprinus carpio*) on PCX-200 was summarised in the CLH report. The concentration of the test material was of 0.1 mg/l and 1 mg/l. A dispersing agent (3% v/v Tween 80-dimethylformamide) was used and the DS considered it to potentially affect the uptake of the test item to the fish and so reducing the reliability of the result. After 56 days, fish bioconcentration factors (BCFs) of < 0.2 (0.1 mg/l) and < 0.02 (1 mg/l) were determined.
Two QSAR assessments were performed to support the measured BCF. The calculations resulted in BCFs of 8.99 l/kg (EPIWIN -BCFBAF method) and 6 l/kg (CAESAR). The DS considered the results to be suitable for the purpose of a weight of evidence approach. The DS also considered in their assessment of bioaccumulation potential that the uptake of the substance to the test organism was affected by the dispersing agent in the OECD TG 305 study. In a weight-of-evidence approach the DS concludes that the BCF is below the threshold of concern.

Aquatic toxicity
Several acute and chronic aquatic toxicity studies were provided in the CLH report but no effects were observed up to the highest test concentrations in any study. Due to the very poor solubility of PX-200 (< 0.1 mg/l), test solutions were difficult to prepare. The highest achievable concentrations varied considerably between studies and were well below 0.1 mg/l.
For fish the 96 h LC_{50} based on the time-weighted mean measured concentration was > 0.027 mg/l. No data on chronic fish toxicity was provided in the CLH report.
The short-term *Daphnia magna* study resulted in a 48 h EC_{50} > 0.032 mg/l based on the time-weighted mean measured concentration of filtered test media.

In a long-term *Daphnia magna* study with PX-200 the 21 d NOEC based on mortality was ≥ 0.00077 mg/l and read across for a related aryl phosphate substance (bisphenol A polyphosphate, EC No: 425-220-8 and CAS No 5945-33-5) gave ≥ 0.0011 mg/l.
Toxicity to algae was examined using only one test concentration and no growth inhibition was observed, resulting in a 72 h growth rate based EC_{50} > 0.031 mg/l and a NOEC of 0.031 mg/l for filtered test media (time-weighted mean measured concentration; the concentrations in the filtered solutions were around 5% of nominal at both the start and the end of the test, suggesting that the organisms were exposed to dissolved concentrations far lower than the nominal concentration of 0.8 mg/l).
Moreover, the DS provides additional information on short- and long-term effects on sediment organisms and terrestrial plants for a related aryl phosphate substance based on read across which shows that no response was seen at the maximum dose of ≥1000 mg/kg soil dw test material.

Comments received during public consultation

Comments were received from five Member States (MS). Four MS agreed with the DS to remove the harmonised classification Aquatic Chronic 4, H413.

One MS did not agree with the DS's conclusion that the substance is not bioaccumulative. The QSAR estimated log P_{OW} of 11.79, which is the basis for the EPIWIN BCF estimation, was not regarded as reliable by the MS because insufficient measured data for log P_{ow} > 9 were within the training dataset of the model. They also criticise the result of the CAESAR estimation because the similarities of the compounds in the CAESAR database were in the range of 0.557-0.76, while similarities above 0.85 are recommended for sufficient reliability.

The experimental BCF was not regarded as reliable by the MS, because the test concentrations in the OECD TG 305 study were higher than the water solubility of the substance and the use of a dispersing agent in stock solution preparation may have resulted in precipitation of the substance in the test vessels, meaning that the reported BCF values may actually be underestimates. The MS concluded that assessment of bioaccumulation should be based on the measured log P_{ow} of > 6.2. Referring to a particular publication (Nendza M & Müller M 2010. *SAR and QSAR in Environmental Research*, 21, 495-512), the MS argued that log P_{OW} > 10 indicate BCFs < 2000, but do not sufficiently indicate that the BCF is < 500. Therefore, according to the MS, relevant bioaccumulation potential cannot be excluded for PX-200.

Responding to these comments, the DS agreed that the available bioaccumulation data and information is of limited reliability. In a weight-of-evidence assessment the DS puts particular emphasis on the observation that substances with log P_{ow} values above 6 often show decreasing bioaccumulation, referring to literature and ECHA guidance documents Chapter R. 11 and Part C. PBT Assessment.

One MS requested clarification on the limit of determination of the test substance in the long-term *Daphnia magna* study. The DS clarified this technicality in the annexed RCOM.

Assessment and comparison with the classification criteria

Classification according to CLP

With the category 'Aquatic Chronic 4' the CLP regulation provides an option to assign a "safety net" for substances not meeting the classification for categories 1, 2, or 3 but still giving some grounds for concern. Chronic 4 is for example triggered if no acute toxicity is recorded at the solubility limit for a poorly soluble substance, which shows a BCF of ≥ 500 (or if absent a log P_{ow} ≥ 4) and is not rapidly degradable, unless other scientific evidence exists showing classification to be unnecessary.

Classification according to DSD

Classification R53 according to the DSD was based on available evidence concerning the persistence, potential to bio-accumulate and predicted or observed environmental fate and behaviour. R53 is for example assigned if a substance is not readily biodegradable and has potential for bioaccumulation as shown by a fish BCF≥ 100 (or if absent a log P_{ow} ≥ 3), unless other scientific evidence exist showing classification to be unnecessary.

Degradation
In a ready biodegradability test PX-200 only degraded by 13.23% in 28 days. Hence, PX-200 does not meet the criteria for being rapidly degradable. Due to limitations of the study method regarding poorly soluble substances no hydrolysis tests have been carried out. Nevertheless, the RAC assumes that PX-200 is not rapidly degraded by hydrolysis. The RAC agrees with the DS that PX-200 is unlikely to undergo direct photolysis, owing to its chemical structure.

In conclusion the RAC considers PX-200 not to meet the criteria for rapid degradability by biotic or abiotic degradation.

Bioaccumulation
The log n-octanol/water partition coefficient has been measured to be > 6.2 using the HPLC method. Since the experimental result is a limit value, a value of 11.79 has been additionally calculated by means of QSAR based on the SMILES-code of the substance. However, in this case the QSAR analysis is subject to some uncertainties as the underlying dataset of the model does not contain sufficient measured data for log P_{ow} values greater than 9. Even if a decrease of the BCF has been observed for substances with a log P_{ow} > 6.2, bioaccumulation cannot be ruled out, especially if the log P_{ow} is not reliable.

One experimental BCF study using common carp determined a BCF < 0.02 based on whole body weight after 56 days. However, the RAC agrees with the DS that this is not reliable due to the use of a dispersing agent and nominal test concentrations are above the reported water solubility in pure water, so the actual dissolved concentration of the test material is unknown.

In addition, the BCF value was calculated using two different QSAR approaches. By means of EPIWIN QSAR a BCF of 8.99 l/kg was estimated while with CAESAR the derived value was 6 l/kg. In the case of the CAESAR QSAR approach, the RAC notes that the chemicals in the datasets used to estimate the BCF show only moderate similarities.

While the experimental and calculated BCFs do not suggest bioaccumulation above the threshold values in the classification criteria (CLP: ≥500, DSD: ≥ 100), the reliability of the methods and results is very limited. Considering the overall deficient information package, the RAC does not see sufficient evidence for disregarding the bioaccumulation potential with a view to the safety net concept of the category Aquatic Chronic 4.

Aquatic Toxicity
Studies are available for both acute and chronic aquatic toxicity. The RAC notes particular uncertainties about real exposure to the test substance, as the measured highest achievable concentrations varied considerably, both across different tests and over test durations.

Acute toxicity
No toxicity was found at the maximum achievable test concentration in the acute tests for fish, daphnids and algae. The RAC does not consider PX-200 acutely toxic for any taxonomic group tested.

Chronic toxicity
No effects were observed at maximum achievable test concentrations in the two available studies with PX-200, one standard algal growth inhibition study and one standard daphnid reprotoxicity study. Data on long-term fish toxicity are not available. The RAC notes that for the related aryl phosphate, i.e. bisphenol A polyphosphate (EC Number: 425-220-8, CAS No: 5945-33-5), one single effect has been found in a daphnid reprotoxicity study at the highest measured test concentration (growth reduction at 1.4 mg/l = LOEC, NOEC = 1.2 mg/l).

Conclusion on classification

PX-200 is considered not rapidly degradable. In addition the RAC does not see sufficient conclusive evidence for absence of bioaccumulation potential, based on the available information on partition coefficient and QSAR-based BCF estimates. However, meaningful test data would only be expected from fish feeding studies, considering the very poor water solubility of PX-200. Overall, the uncertainties associated with all experimental data generated in aquatic test systems are considerable. Moreover, the RAC notes that the DS's approach to read across from related aryl phosphates is rather weakly justified. Preferably, read across from more structurally similar substances should have been attempted, to provide increased confidence in the conclusions.

Two available chronic toxicity studies (for daphnids and algae) show no effects up to the maximum achievable test concentration. The RAC does not expect that in an additional extended or chronic fish study with PX-200 any effects would be seen up to the practical water solubility limit of ~30 µg/l in the test medium (it is noted that although the actual level of exposure is unknown, no toxic effects were observed in the fish bioaccumulation test, and the substance does not show any classifiable chronic toxic effects in other vertebrates). In conclusion the RAC considers the available chronic data as sufficient evidence that a safety net classification in category Aquatic Chronic 4 is not warranted, and agrees with the DS to delete the corresponding entry in Annex VI, table 3.1, of the CLP Regulation.

Regarding DSD criteria, the RAC concludes that the available chronic data sufficiently indicate absence of aquatic toxicity, thus providing evidence for removing the classification R53. Thus, in spite of the very poor solubility, not ready biodegradability, and absence of conclusive evidence on bioaccumulation potential, the RAC agrees with the DS's proposal to delete the corresponding entry in Annex VI, table 3.2, of the CLP Regulation.

ANNEXES:

Annex 1 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 the RAC is contained in RAC boxes.

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