Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride or PHMB

EC number: not allocated (polymer)
CAS number: 27083-27-8 or 32289-58-0

CLH-O-0000003799-56-03/F

Adopted

14 March 2014

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CLH-O-0000003799-56-03/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:	**Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride or PHMB**
EC number:	**not allocated (polymer)**
CAS number:	**27083-27-8 or 32289-58-0**

The proposal was submitted by **France** and received by the RAC on **15 May 2013.** All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

France 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 **6 June 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 July 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Agnes Schulte**

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 **14 March 2014** 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 on **PHMB** that 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-factors
					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*	616-207-00-X	Polyhexamethylene biguanide hydrochloride	-	27083-27-8; 32289-58-0	Carc. 2 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H351 H302 H372 (respiratory tract) (inhalation) H318 H317 H400 H410	GHS05 GHS07 GHS08 GHS09 Dgr	H351 H302 H372 (respiratory tract) (inhalation) H318 H317 H410		M=10 M=10
Dossier submitters proposal	616-207-00-X	Polyhexamethylene biguanide hydrochloride	-	27083-27-8; 32289-58-0	**Add:** Acute Tox. 2	**Add:** H330		**Add:** H330		
RAC opinion	616-207-00-X	Polyhexamethylene biguanide hydrochloride	-	27083-27-8; 32289-58-0	**Add:** Acute Tox. 2	**Add:** H330		**Add:** H330		
Resulting Annex VI entry if agreed by COM	616-207-00-X	Polyhexamethylene biguanide hydrochloride	-	27083-27-8; 32289-58-0	Carc. 2 Acute Tox. 2 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H351 H330 H302 H372 (respiratory tract) (inhalation) H318 H317 H400 H410	GHS05 GHS06 GHS08 GHS09 Dgr	H351 H330 H302 H372 (respiratory tract) (inhalation) H318 H317 H410		M=10 M=10

* 5th ATP to CLP Regulation (Commission Regulation (EU) No 944/2013, 2 Oct 2013

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC general comment

On 9 September 2011 RAC adopted an opinion on a harmonised classification and labelling proposal for PHMB as an active substance according to Directive 98/8/EC based on a proposal from the French CA. With regard to the hazard class '*acute toxicity (inhalation)'* RAC agreed in its opinon with the proposed classification of Acute Tox. 1; H330. No provision was made for including this hazard in Annex VI to the CLP Regulation in the proceedings on the adaptation to technical process in October 2013 (see paragraph 7[1] of the 5th ATP), as new data had been made available on acute inhalation toxicity which should be considered by the RAC. The French CA delivered an additional CLH proposal in December 2012 on PHMB that adressed acute inhalation toxicity only.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The dossier submitter submitted information on previously considered studies on acute inhalation toxicity and on repeated dose toxicity, and in addition the results from a recently conducted acute inhalation study (confidential study report, 2012).

The initial conclusion on classification of PHMB for acute inhalation toxicity (Acute Tox 1 – H330) was based on the results from a 28-day inhalation study (Carney, 1976). This study reported the death of all animals after a single exposure to PHMB aerosol and an LC_{50} of less than 0.03 mg/l was estimated for a 4 hour exposure), although interpretation of the study was limited by poor reporting. The validity of the results of this study was however supported by the similar sensitivity in terms of NOAEC and LOAEC to another 28-day study performed according to OECD TG 412 (Noakes, 2006). The highest concentration administered in Noakes (2006) was however only 0.00247 mg/l and no deaths were observed at this concentration. The dossier submitter found this study to be of limited relevance in confirming or contradicting the LC_{50} value observed by Carney (1976).

The dossier submitter referred to the RAC analysis from 2011, which also considered the acute inhalation toxicity study by Kilgour (1999) using a formulation containing 20.6% PHMB. In this study an LC_{50} higher than 0.36 mg/l PHMB was assumed.

In 2011 RAC came to the following conclusion:

> *"RAC cannot explain with certainty the dissimilar results of both tests. Possible reasons could be the use of different rat strains, different vehicles and the generally few animals used in these studies.*
>
> *For this reason and in line with the CLP guidance, RAC is of the opinion that the lowest value should be the basis for classification and therefore concludes that a*

[1] 5th Adaptation to Technical Progress (ATP) to the CLP Regulation, Commission Regulation (EU) No. 944/2013, (Paragraph (7)). With regard to the substance polyhexamethylene biguanide hydrochloride (CAS number 27083-27-8 or 32289-58-0), new scientific data has been made available for the hazard class 'acute toxicity (inhalation)', which suggests that the classification for this hazard class as recommended in the RAC opinion, which is based on older data, might not be appropriate. Therefore, this hazard class should not be included in Annex VI to Regulation (EC) No 1272/2008 until RAC has had the opportunity to deliver an opinion on the new information, while all other hazard classes covered by the earlier RAC opinion should be included.

classification Acute Tox 1– H330 (CLP), and T+; R26 (DSD) is warranted based on the results from the study by Carney (1976).”

The dossier submitter stated that the new study available (confidential study report, 2012) was of good quality (GLP and according to the OECD guideline) and reported an LC_{50} of 0.29 mg/l in male rats. The study was performed with an aqueous vehicle, but according to the dossier submitter, differences in the vehicle could not explain the difference in the LC_{50} results between this new study and Carney (1976). Differences in the vehicle were also hypothesised to explain the difference between the results in the studies of Carney (1976) and Kilgour (1999).

The dossier submitter stated that differences in rat strains used in the various studies exist but that they were unlikely to explain a difference in sensitivity of a factor of 10. It was also noted that although a small number of animals was used in the different studies, which was likely to have contributed to the degree of variability, the numbers were in line with guidelines, apart from a slight deviation from the guideline in Carney (1976) where 4 animals/sex/concentration were used instead of 5.

In the absence of information on whether the actual exposure concentrations had been controlled in the study by Carney (1976), the dossier submitter considered that the results obtained in the more recent studies raised doubts regarding the exact concentrations to which animals were exposed (in the Carney study).

Taking into account all the currently available data and based on the weight of the evidence, the dossier submitter considered that the new 2012 study should be used as the relevant study for classification of PHMB for acute inhalation toxicity. The critical LC_{50} was therefore 0.29 mg/l for male rats.

On this basis, classification as Acute Tox 2 – H330 (CLP), was warranted.

Comments received during public consultation

Two member states supported the proposed classification as Acute Tox. 2, H330. A third member state requested more information on study details (purity of the test substance, concentration tested) and asked for explanations on the differences between previously considered studies and the new study.

Assessment and comparison with the classification criteria

In a recently submitted acute inhalation toxicity study (confidential study report, 2012), rats were exposed at concentrations of 0.1, 0.3 or 0.5 mg/l to an aerosol of PHMB (99.6%) in aqueous solution with particles with an MMAD range of 1.49-2.2 µm (GSD of ±1.84-2.29 µm). Clinical signs (laboured respiration, decreased activity, hunched posture, transient body weight loss on Day 1) were observed in male and female rats at all tested concentrations and the severity/incidence/duration of effects increased with the test concentration. Mortalities were observed at 0.3 mg/l and above. In this study, the LC_{50} values were determined to be 0.29 mg/l for males, 0.48 mg/l for females and 0.37 mg/l for males and females combined. These values are in the range of concentrations that justify classification for acute toxicity Category 2 for inhalation exposure to dust/mist (0.05 mg/l < Category 2 ≤ 0.5 mg/l).

RAC agrees with the assessment of the dossier submitter. The committee finds the new study robust, based on its compliance with OECD TG 403 and on its detailed description of clinical and lethality information.

RAC gives more weight to this study than to the less reliable single exposure study of Kilgour (1999) or to the repeated dose studies (Carney, 1976, Noakes, 2006). It is noted that differences in calculated LC_{50} values among all available studies could still not be fully explained. The previous RAC opinion was mainly based on the acute mortalities in the repeated dose studies due to the lack of robust single exposure studies. The discrepancies in the LC_{50} values among the less valid studies and the new study were not considered to be important, since more weight was given to the new study which was consistent with the guideline (OECD TG 403).

In its previous opinion from September 2011, RAC recommended to classify PHMB with Acute Tox. 1; H330 (inhalation). Based on the new information, classification as Acute Tox. 2; H330 (inhalation), as suggested by the dossier submitter, is supported by RAC.

No other hazard endpoints were addressed for classification purposes.

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 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)