Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

PHMB (1600; 1.8)

(polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1600 and a mean polydispersity (PDI) of 1.8)

Product type: 2

ECHA/BPC/059/2015

Adopted

17 June 2015

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Opinion of the Biocidal Products Committee

on the application for approval of the active substance PHMB (1600; 1.8) for product type 2

In accordance with Article 89(1) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the approval in product type 2 of the following active substance:

Common name:	PHMB (1600; 1.8) (polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1600 and a mean polydispersity (PDI) of 1.8)
Chemical name:	
	CoPoly(bisiminoimidocarbonyl, hexamethylene hydrochloride), (iminoimidocarbonyl, hexamethylene hydrochloride)
EC No.:	None
CAS No.:	27083-27-8 and 32289-58-0

Existing active substance

This document presents the opinion adopted by the BPC, having regard to the conclusions of the evaluating Competent Authority. The assessment report, as a supporting document to the opinion, contains the detailed grounds for the opinion.

Process for the adoption of BPC opinions

Following the submission of an application by Lonza (previously Arch Chemicals Ltd) on 30 July 2007, the evaluating Competent Authority France submitted an assessment report and the conclusions of its evaluation to the European Chemicals Agency on 8 October 2013. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC and its Working Groups. Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Information on the fulfilment of the conditions for considering the active substance as a candidate for substitution was made publicly available at http://echa.europa.eu/addressing-chemicals-of-concern/biocidal-products-regulation/potential-candidates-for-substitution-previous-consultations on 9 February 2015, in accordance with the requirements of Article 10(3) of Regulation (EU) No 528/2012. Interested third parties were invited to submit relevant information by 10 April 2015.

Adoption of the BPC opinion

Rapporteur: BPC member of France

The BPC opinion on the approval of the active substance PHMB (1600; 1.8) (polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1600 and a mean polydispersity (PDI) of 1.8) in product type 2 was adopted on 17 June 2015.

The BPC opinion takes into account the comments of interested third parties provided in accordance with Article 10(3) of BPR.

The BPC opinion was adopted by consensus.

Detailed BPC opinion and background

1. Overall conclusion

The overall conclusion of the BPC is that the PHMB (1600; 1.8) (polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1600 and a mean polydispersity (PDI) of 1.8) in product type 2 may be approved. The detailed grounds for the overall conclusion are described in the assessment report.

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

a) Presentation of the active substance including the classification and labelling of the active substance

This evaluation covers the use of PHMB (1600; 1.8) (polyhexamethylene biguanide hydrochloride which is identified and characterised with a mean number-average molecular weight (Mn) of 1600 and a mean polydispersity (PDI) of 1.8) in product type 2. PHMB (1600; 1.8) is a polymer that is directly manufactured as an aqueous solution, at a concentration of 20%. Specifications for the reference source are established.

The physico-chemical properties of the active substance as manufactured are deemed acceptable for the appropriate use, storage and transportation of the biocidal product. Not all impurities have been identified or quantified. Validated analytical methods that were required have not been submitted for some impurities and the active substance as well as for the determination of residues in drinking water, body fluids and tissues and food stuff.

A harmonised classification is available and is given below. The current harmonised classification and labelling for PHMB (according to Regulation (EC) No 1272/2008 (CLP Regulation)) is:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox 4; H302 Skin Sens. 1B; H317 Eye Dam. 1; H318 Carc. 2; H351 STOT RE 1; H372 (respiratory tract) (Inhalation) Aquatic Acute 1; H400 Aquatic Chronic 1; H410
Labelling	
Pictograms	GHS07, GHS09, GHS05, GHS08
Signal Word	Dgr
Hazard Statement Codes	H302: Harmful if swallowed. H317: May cause an allergic skin reaction. H318: Causes serious eye damage. H351: Suspected of causing cancer. H372 (respiratory tract) (Inhalation): Causes damage to organs through prolonged or repeated exposure by inhalation. H410: Very toxic to aquatic life with long lasting effects.

Specific Concentration limits, M-Factors	M = 10 (acute, chronic)

An opinion of the Risk Assessment Committee (RAC) was adopted in March 2014 for acute toxicity by inhalation:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox 2; H330
Labelling	
Hazard Statement Codes	H330: Fatal if inhaled.

b) Intended use, target species and effectiveness

PHMB (1600; 1.8) is used for the disinfection of equipment and areas (PT2). A risk assessment was conducted for the following uses:

- Disinfection of medical equipment by dipping (professional use);
- Small scale surface disinfection of residential, institutional and industrial areas by wiping with ready-to-use wipes (professional and non-professional use);
- Swimming pool treatment (professional and non-professional use).

The lethal action of PHMB (1600; 1.8) is an irreversible loss of essential cellular components as a direct consequence of cytoplasmic membrane damage. It is concluded that cytoplasmic precipitation is a secondary event to the death of the bacterial cell.

The data on PHMB (1600; 1.8) and the first representative biocidal product (containing 20% w/w of active substance) have demonstrated sufficient efficacy for application by dipping against bacteria at the concentration of 0.02% w/w of active substance and against yeasts at the concentration of 0.04% w/w of active substance, with a contact time of 60 minutes. The assessment covers the dipping of medical equipment outside the scope of the directive 93/42/EEC related to medical devices.

The efficacy data in the dossier were suspension laboratory tests (phase 2, step 1) which demonstrate the efficacy of the product by dipping. For the surface treatments application (via wiping), it can be considered that these efficacy data could be used for such use. The efficacious dose of 0.1% w/w of the active substance (claimed by the applicant) was used to assess the risk for the application by wiping of surfaces in residential, institutional and industrial areas (small scale) with ready-to-use wipes.

It has to be highlighted that the risk assessment for the wiping application is done on the basis of a concentration that is not supported by any appropriate efficacy data. Therefore, the risk assessment does not reflect a dose which has been confirmed by product level efficacy data and has to be confirmed at product authorisation stage.

Furthermore, data on PHMB (1600; 1.8) and the second representative biocidal product (containing 20% w/w of active substance) have demonstrated sufficient efficacy against water-borne bacteria for application by pouring into swimming pools at the concentration of 0.001% w/w of active substance.

The evaluation of the literature studies provided by the applicant does not show particular resistance to PHMB (1600; 1.8) with bacteria. Nevertheless, cross resistance and modifications of the expression of genes as a mechanism of tolerance to subletal concentrations of PHMB (1600; 1.8) are described in the literature and should be taken into account, if needed, in a strategy for resistance management at product authorisation stage.

c) Overall conclusion of the evaluation including need for risk management measures

Human health

PHMB (1600; 1.8) is harmful if inhaled and may cause an allergic skin reaction. By inhalation, it causes damage to organs through repeated exposure and is also suspected of causing cancer. It has no irritant properties and is not genotoxic or reprotoxic.

The table below summarises the exposure scenarios assessed.

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusions**
Private swimming pool treatment			
Pouring into private swimming pool	*Primary exposure* Manual pouring: dermal exposure • tier 1: without personal protective equipment (PPE) • tier 2a: with gloves and normal clothing • tier 2b: with gloves and cotton coverall	Professionals	Acceptable
		Non-professionals (*)	Not acceptable
Swimming into treated private pool	*Secondary exposure* Duration: one hour Dermal and oral exposure	General public (adult, child 3.5 years old, child 1.5 years old)	Not acceptable
Dipping of medical equipment			
Mixing and loading (filling dipping bath)	Primary exposure Manual pouring: dermal exposure • tier 1: without PPE • tier 2: with gloves and cotton coverall	Professionals	Acceptable
Immersion/removal of equipment from the dipping bath	*Primary exposure* Manual dipping: dermal exposure • tier 1: without PPE • tier 2: with gloves and cotton coverall	Professionals	Acceptable
Combined exposure (mixing/loading and dipping)	*Primary exposure* Dermal exposure • tier 1: without PPE • tier 2: with gloves and cotton coverall	Professionals	Acceptable

Dermal contact with residues on treated equipment	*Secondary exposure* Dermal exposure	Professionals	Not acceptable
Wiping of surfaces in residential, institutional and industrial with ready-to-use wipes (**)			
Surface wiping with ready-to-use wipes	*Primary exposure* Handling of wipes: dermal exposure • without PPE	Professionals and non-professionals	Acceptable
Toddler crawling on surface disinfected with ready-to-use wipes	*Secondary exposure* Dermal and oral exposure	General public: toddler	Not acceptable

* PPE are considered according to the Competent Authorities document "*CA-May14 – Doc.5.2.a"*.

** The risk assessment for the wiping application is done on the basis of a concentration that is supported only by data on innate activity.

- Swimming pool treatment:

For professionals, the risk is acceptable with the wear of PPE when pouring the product into swimming pools.

For non-professionals, the risk is not acceptable due to local effects when considering pouring the product into swimming pools. The risk would be acceptable only if appropriate PPE were worn and appropriate training were provided. According to the BPR, if, for non-professional users, the wearing of PPE would be the only possible method for reducing exposure to an acceptable level for this population, the product shall normally not be authorised for use by the general public. It shall nevertheless be noted that the discussion took place at the CA meeting and according to the Competent Authorities document "*CA-Sept13-Doc.6.2.a-Final.Rev1"*, it may be considered that under certain circumstances, product may be authorised for the general public even when PPE has to be worn.

The representative product is classified STOT RE 1: thus, the making available on the market for use by the general public is prohibited according to Article 19(4)(b) of Regulation (EU) No 528/2012[1].

The risks related to the exposure of adults and children swimming for 1 hour in treated pools are considered as unacceptable.

The overall conclusion is that products should not be authorised for the treatment of swimming pools.

- Dipping of medical equipment:

For professionals, the risk is considered as acceptable with the wear of PPE when filling the dipping bath.

[1] Amended by Regulation (EU) No 334/2014 of the Eureopean Parliament and of the Council of 11 March 2014 concerning the making available on the market and use of biocidal products, with regard to certain conditions for access to the market. This use should therefore not have been assessed. However, when the assessment was performed and complete, the BPR was not yet amended and thus this use was assessed.

Considering secondary exposure, the risk related to dermal contact with treated medical equipment is considered to be unacceptable. However, the risk assessment is based on a worst case scenario as the secondary exposure could not be refined in absence of appropriate data.

- Small scale disinfection by wiping with ready-to-use wipes:

For professionals and non-professionals, the risk is considered as acceptable when using the ready-to-use wipes.

However, the risk related to secondary exposure (toddlers) is considered as unacceptable. In consequence, the use of ready-to-use wipes containing the active substance should be restricted to areas not accessible to the general public, in order to limit the secondary exposure. Because of this management measure, the non-professional use cannot be allowed.

Environment

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusions**
Private swimming pools treatment		
Scenario covering: - Chronic emission: periodic releases to wastewater due to the cleaning of the filtration system (*e.g.* by backwashing) - Peak emission: annual release to wastewater due to the preparation for overwintering	The assessment is performed considering that the pool water is discharged to drains connected to a sewage treatment plant (STP). As a result of this, there will be potential for exposure of both the aquatic (surface water and sediment) and the terrestrial (soil and groundwater) compartments, the latter as a result of contaminated sewage sludge spreading on land. Two assessments were performed to be representative of the conditions of use throughout EU by considering 550pools/STP in southern countries and 100 pools/STP in northern countries. In addition, two market shares were considered: 0.5 (default value) and 0.005 (realistic value) for PHMB.	Not acceptable
Dipping of medical equipment		
Disinfection of medical equipment by dipping	PHMB will ultimately be discharged to drains and will enter a municipal STP. As a result of this, there will be potential for exposure of both the aquatic (surface water and sediment) and the terrestrial (soil and groundwater) compartments, the latter as a result of contaminated sewage sludge spreading on land.	Not acceptable
Wiping of surfaces in residential, institutional and industrial areas with ready-to-use wipes (*)		

Small scale surface wiping with ready-to-use wipes	PHMB will ultimately be discharged to drains and will enter a municipal STP. As a result of this, there will be potential for exposure of both the aquatic (surface water and sediment) and the terrestrial (soil and groundwater) compartments, the latter as a result of contaminated sewage sludge spreading on land.	Acceptable

* The risk assessment for the wiping application is done on the basis of a concentration that is supported only by data on innate activity.

- Swimming pool treatment:

When considering the lowest emission conditions in the environment (use of PHMB in northern countries swimming pools, combined with the lowest market share), the risk is considered as unacceptable for the aquatic compartment (including sediment), and acceptable for the STP, terrestrial compartment and groundwater.

- Dipping of medical equipment:

The risk is considered as unacceptable for the aquatic compartment (including sediment), and acceptable for the STP, terrestrial compartment and groundwater.

- Small scale disinfection by wiping:

The risk is acceptable for the aquatic compartment (including sediment) only if small scale treatment of surface is considered (*i.e.* < 290 m²). The risk is also acceptable for the STP, terrestrial compartment and groundwater.

General conclusion

A safe use for human health and the environment is identified only for small scale surface disinfection in industrial areas by professional users, by wiping with ready-to-use wipes, in areas not accessible to the general public.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

The table below summarises the relevant information with respect to the assessment of exclusion and substitution criteria:

Property		Conclusions
CMR properties	Carcinogenicity (C)	Carc 2
	Mutagenicity (M)	No classification required
	Toxic for reproduction (R)	No classification required
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	P and vP
	Bioaccumulative (B) or very Bioaccumulative (vB)	not B or vB
	Toxic (T)	T
Endocrine disrupting properties	PHMB (1600; 1.8) is not considered to have endocrine disrupting properties.	

Respiratory sensitisation properties	No classification required.
Concerns linked to critical effects	PHMB (1600; 1.8) does not fulfil criterion (e) of Article 10(1).
Proportion of non-active isomers or impurities	With regard to the proportion of non-active isomers or impurities, PHMB (1600; 1.8) is put on the market as a 20 % aqueous solution of the active substance which has a minimum purity of 95.6% w/w. Given this, PHMB (1600; 1.8) does not fulfil criterion (f) of Article 10(1).

Consequently, the following is concluded:

PHMB (1600; 1.8) does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

PHMB (1600; 1.8) meets the conditions laid down in Article 10(1)(d) of Regulation (EU) No 528/2012, and is therefore considered as a candidate for substitution. PHMB (1600; 1.8) fulfils the P, vP and T criteria.

The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking decisions on the approval of active substances under the BPR"[2] and in line with "Further guidance on the application of the substitution criteria set out under Article 10(1) of the BPR"[3] agreed at the 54th and 58th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

During public consultation, three confidential and eleven non-confidential comments were received from third parties. Comments included information on the availability of alternative active substances, on the essentiality of the active substance PHMB (1600; 1.8) for the control of bacteria, viruses and other pathogens, and on the properties of PHMB (1600; 1.8). There are several other active substances intended for use in the same product type already approved, or currently being reviewed under Regulation (EU) No 528/2012.

2.2.2. POP criteria

PHMB (1600; 1.8) does not fulfil criteria for being a persistent organic pollutant (POP). PHMB (1600; 1.8) does not have potential for long-range transboundary atmospheric transport.

2.3. BPC opinion on the application for approval of the active substance PHMB (1600; 1.8) in product type 2

In view of the conclusions of the evaluation, it is proposed that PHMB (1600; 1.8) shall be approved and be included in the Union list of approved active substances, subject to the following specific conditions:

[2] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc).
3 See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc).

1. The active substance as manufactured is an aqueous solution of 20% w/w of PHMB (1600; 1.8). The dry weight specification (calculated) minimum purity of PHMB (1600; 1.8) is 956 g/kg. The maximum content of the relevant impurity hexamethylene-1,6-diamine hydrochloride is 0.4% (w/w).

2. PHMB (1600; 1.8) is considered a candidate for substitution in accordance with Article 10(1)(d) of Regulation (EU) No 528/2012.

3. The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.

4. For professional users, safe operational procedures, appropriate organisational and technical risk mitigation measures shall be established. Products shall be used with appropriate personal protective equipment where exposure cannot be reduced to an acceptable level by other means.

5. In view of the risk identified for human health and the environment, products shall not be authorised for the treatment of swimming pools, unless it can be demonstrated that risks can be reduced to an acceptable level.

6. In view of the risk identified for human health and the environment, products shall not be authorised for disinfection of medical equipment[4] via dipping, unless it can be demonstrated that risks can be reduced to an acceptable level.

7. In view of the risk identified for human health, ready-to-use wipes shall not be authorised for non-professionals, unless it can be demonstrated that risks can be reduced to an acceptable level.

8. In view of the risk identified for human health, labels, and where provided, safety data sheets, shall indicate that ready-to-use wipes shall be restricted to areas not accessible to general public, unless it can be demonstrated that risks can be reduced to an acceptable level by other means.

According to Article 28(2) of Regulation (EU) No 528/2012, PHMB (1600; 1.8) gives rise to the following concern: it is classified as skin sensitizer (Skin Sens. 1B), carcinogenic of category 2 (Carc. 2), specific target organ toxicant by repeated exposure by inhalation (STOT RE 1), toxic to aquatic life of acute category 1 (Aquatic Acute 1). In addition, it fulfils the substitution criteria vP and T. Therefore inclusion in Annex I of Regulation (EU) No 528/2012 is not acceptable.

2.4. Elements to be taken into account when authorising products

1. The active substance PHMB (1600; 1.8) is considered as a candidate for substitution, and consequently the competent authority shall perform a comparative assessment as part of the evaluation of an application for either national or Union authorisation.

2. The innate activity of the active substance is demonstrated at 0.02% w/w of active substance (bactericide) and 0.04% w/w of active substance (yeasticide). The concentration of 0.1% w/w of active substance, claimed by the applicant, was taken into account when assessing the risk for surface application by wiping. No acceptable data were provided to support efficacy of surface application for the claimed dose. Appropriate efficacy data for surface disinfection have to be submitted at product authorisation stage and risk assessment should be performed on appropriate efficacious dose for surface treatment via wiping.

3. Cross-resistance and tolerance to sublethal concentrations of the active substance

[4] Medical equipment in the scope of the BPR is the equipment not covered by directive 93/42/EEC related to medical devices.

are described in literature. Therefore, Member States should pay attention to possible occurrence of resistance before authorising products.

4. The authorisation of biocidal products containing PHMB (1600; 1.8) at or above the concentration limit triggering classification of the mixture for specific target organ toxicity by repeated exposure category 1 (STOT RE 1) shall be restricted to professionals, in accordance with Article 19(4)(b) of Regulation (EU) No 528/2012[5].

5. It has to be noted that the environmental assessment for swimming pools considered only releases to a sewage treatment plant for permanent pools. If relevant, an environmental assessment should be performed additionally considering above-ground small pools and direct release to soil.

6. For surface disinfection with ready-to-use wipes, safe use for the environment has been identified only for small scale disinfection, when considering the impregnated solution instead of the wipe itself. As no scenario is available for such use, a revised risk assessment will have to be provided at product authorisation stage. In particular, data on the transfer rate from the wipe to the treated surface should be provided by the applicant.

7. The risk assessment for secondary exposure by dermal contact after dipping of medical equipment should be refined at product authorisation stage. This may include the requirement of data to assess the relevance and effectiveness of a rinsing step and determine the transfer coefficient of residues from treated equipment to skin.

2.5. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of PHMB (1600; 1.8). However, further data shall be required as detailed below:

1. Additional information about some impurities, dimers, monomers and the fraction < 1000 Daltons should be provided to the Competent Authority (France) as soon as possible but no later than six months before the date of approval of the active substance.

2. Additional information about (eco)toxicity of some impurities has to be provided to the Competent Authority (France) as soon as possible but no later than six months before the date of approval of the active substance.

3. As PHMB (1600; 1.8) is a polymer, it may be difficult to develop an adequate residue analytical method. A limited residue definition in form of a marker for drinking water, body fluid and tissues has to be provided to the Competent Authority (France) as soon as possible but no later than six months before the date of approval.

4. For drinking water, a validated method for determination of PHMB (1600; 1.8) has to be provided to the Competent Authority (France) as soon as possible no later than six months before the date of approval.

5. An analytical method for determination of PHMB (1600; 1.8) in body fluids and tissues or an acceptable justification of non-submission of data has to be provided to the Competent Authority (France) as soon as possible but no later than six months before the date of approval.

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[5] Amended by Regulation (EU) No 334/2014 of the European Parliament and of the Council of 11 March 2014 concerning the making available on the market and use of biocidal products, with regard to certain conditions for access to the market.