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: 3

ECHA/BPC/060/2015

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 3

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 3 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 July 30th 2007, the evaluating Competent Authority France submitted an assessment report and the conclusions of its evaluation to the European Chemicals Agency on 14 November 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 3 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 3 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 3. PHMB (1600; 1.8) is a polymer that is directly manufactured as an aqueous solution, at a concentration of 20% w/w. 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 treatments in animals housings and veterinary areas (PT 3). A risk assessment was conducted for the following uses:

- Disinfection of equipment (cages equipment, brushes, toys, manure scrapers, trimming/clipping equipment, incubators, etc.) by dipping (professional use);
- Small scale disinfection of veterinary areas by wiping with ready-to-use wipes (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 representative biocidal product (containing 20% w/w of active substance) have demonstrated sufficient efficacy against bacteria (except mycobacteria and bacteria spores) at the concentration of 0.2% w/w of active substance in dirty conditions, for application by dipping, with a contact time of 30 minutes.

Furthermore, the efficacy data in the dossier were suspension laboratory tests (phase 2, step 1) which demonstrate the efficacy of the product by dipping. For surface treatments application (via wiping), it can be considered that these efficacy data could be used for such use. The efficacious dose of 0.2% w/w of active substance (higher than the application rate claimed by the applicant) was used to assess the risk for the application by wiping of surfaces in veterinary 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.

The evaluation of the literature studies provided by the applicant does not show particular resistance to PHMB (1600; 1.8) with bacteria. Nevertheless, cross resistances 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**
Dipping of equipment			
Mixing and loading (filling dipping bath)	*Primary exposure* Manual loading: 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* Manual loading and manual dipping: dermal exposure. • tier 1: without PPE • loading tier 1 and dipping tier 2 as described above • loading tier 2 and dipping tier 2 as described above	Professionals	Acceptable
Dermal contact with residues on equipment	*Secondary exposure* Dermal exposure	Professionals	Not acceptable
Consumption of products of animal origin contaminated with the active substance	*Secondary exposure* Preliminary assessment of indirect exposure via food	General public	-
Wiping in veterinary areas with ready-to-use wipes (*)			
Surface wiping with ready-to-use wipes	*Primary exposure* Handling of wipes: dermal exposure. • without PPE	Professionals	Acceptable

Toddler crawling on surface disinfected with ready-to-use wipes	*Secondary exposure* Dermal and oral exposure	General public: toddler	Not acceptable
Consumption of products of animal origin contaminated with active substance	*Secondary exposure* Preliminary assessment of indirect exposure via food	General public	-

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

The risk is acceptable for the dipping of equipment with the wear of gloves and cotton coverall. Due to the skin sensitisation properties of the active substance, loading of the product into dipping bath shall be done with appropriate personal protective equipment and by professionals only. The risk is considered as acceptable for the use of ready-to-use wipes without personal protective equipment.

Considering secondary exposure, the risk related to dermal contact with residues on equipment (treated by dipping) 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. An acceptable risk for the direct contact with residues on equipment must be demonstrated at product authorisation stage. This may include data to refine the assumptions made for rinsing and the transfer coefficients.

The risk is also unacceptable when considering the exposure of a toddler to treated surfaces (dermal and oral by hand-to mouth transfer). Refinement of the assessment is not possible in absence of appropriate data. However, this situation of a crawling child is not considered as appropriate regarding the location of the application of the product.

The livestock exposure related to the transfer of the active substance from treated equipment and treated surfaces to livestock exceeds the trigger value of 0.004 mg of a.s./kg body weight/day by taking into account a maximalist and draft exposure scenario. Refinement of the assessment of livestock exposure is not possible in the absence of appropriate data.

Additionally, a preliminary assessment of indirect human exposure via food has been performed and confirms the need to refine the assessment for consumers. More data are necessary to demonstrate the relevance and effectiveness of a rinsing step after treatment at product authorisation stage. In absence of these elements and as no guidance is currently avaialble, acceptable risk related to food consumption when disinfection is done in vicinity of food, livestock or any products of animal origins cannot be confirmed.

Environment

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusions**

Dipping of equipment in livestock farming environment Emission scenario described in the ESD-PT03 (2011) for the disinfection of footwear modified with the volume proposed for the equipment disinfection by dipping (100L) is taken into account.	The solutions are considered to be ultimately discharged *via* two pathways: • *via* the waste water leading to a potential for exposure of both the aquatic (sewage treatment plant (STP), surface water and sediment) and the terrestrial (soil and groundwater) compartments, the latter as a result of contaminated sewage sludge spreading on land. • *via* the manure or slurry leading to a potential for exposure of the terrestrial (soil and groundwater) compartments, following the spreading of contaminated slurry/manure on land.	Not acceptable
Small scale surface disinfection of veterinary areas with ready-to-use wipes (*) Emission scenario for disinfection in industrial premises of the ESD-PT02 is taken into account, as no such scenario is described in ESD-PT03.	The solutions are considered to be ultimately discharged *via* the waste water, leading to a potential for exposure of both the aquatic (STP, 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.

Considering the aquatic compartment (including sediment), the disinfection of equipment by dipping (releases to wastewater) leads to unacceptable risks. Therefore no release to sewage treatment plants shall be allowed. For instance, wastewater should be disposed to manure/slurry instead. When considering the default scenario for surface disinfection by wiping, risks are unacceptable. However, small scale surface disinfection in veterinary areas with ready-to-use wipes leads to acceptable risks, only if small scale treated surface is considered (*i.e.* < 145 m²).

Considering the STP compartment, the disinfection of equipment by dipping and the small scale surface disinfection in veterinary areas with ready-to-use wipe lead to acceptable risks.

Considering the terrestrial compartment, the disinfection of equipment by dipping considering releases via the waste water leads to acceptable risks. However, the disinfection of equipment by dipping considering releases via the manure/slurry spreading on land leads to unacceptable risks for veal calves breeding and for sows in individual pens or in groups, and acceptable risks for others breeding premises. The small scale surface disinfection of veterinary areas with ready-to-use wipes leads to acceptable risks.

Considering the groundwater, the risks are acceptable for all scenarios.

General conclusion

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

Acceptable risk related to food consumption when disinfection is done in vicinity of food, livestock or any products of animal origins cannot be confirmed at this stage

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"[1] and in line with "Further guidance on the application of the substitution criteria set out under Article 10(1) of the BPR"[2] 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

[1] 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).
2 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).

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 3

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:

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, products shall not be authorised for disinfection of equipment via dipping, unless it can be demonstrated that risks can be reduced to an acceptable level. In addition, in case products are authorised, in view of the risk identified for the environment, labels, and where provided, safety data sheets shall indicate that no release to sewage treatment plants shall be allowed, unless it can be demonstrated that risks can be reduced to an acceptable level by other means.

6. In view of the risk identified for human health, labels, and were 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.

7. For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council or Regulation (EC) No 396/2005 of the European Parliament and of the Council shall be verified, and any

appropriate risk mitigation measures shall be taken into account to ensure that the applicable MRLs are not exceeded.

According to Article 28(2) of Regulation (EU) No 528/2012, PHMB (1600; 1.8) gives rise to the following concerns: 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 0.2% w/w of active substance and this concentration 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 (0.1% w/w). 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-resistances and tolerance to sublethal concentrations of the active substance 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 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[3].

5. For the dipping use, Member States shall pay attention to the environmental risk when considering releases via the manure/slurry from the use of products containing PHMB (1600; 1.8). In particular, at this stage, risk for the soil compartment was identified when product is used in veal calves and in sows breeding.

6. For surface disinfection with ready-to-use wipes, safe use for the environment has been identified only for a very limited use: small scale disinfection in veterinary areas, when considering the impregnated solution instead of the wipe itself. No agreed scenario is available:
   - when considering the impregnated solution instead of the wipe itself;
   - when considering the wiping use as PT3.

   Once an agreed scenario is available, a risk assessment has to be provided in dossiers for products authorisation. In particular, data on the transfer rate from the wipe to the treated surface shall be provided by the applicant.

7. The risk assessment for secondary exposure by dermal contact after dipping of 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.

[3] 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.

8. The assessment of human exposure via food consumption is considered not finalised. More data are necessary to demonstrate the relevance and effectiveness of a rinsing step after treatment at product authorisation stage. Member States shall pay attention to risk related to food consumption when relevant.

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.

6. Methods for the determination of PHMB (1600; 1.8) and residues in food and feedstuffs have to be submitted to the Competent Authority (France) as soon as possible but no later than six months before the date of approval.

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