Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

COMPETENT AUTHORITY REPORT

Assessment Report

Polyhexamethylene biguanide (Mn = 1415; PDI =4.7) PHMB (1415; 4.7)

Product type PT06
(In-can preservatives)

Evaluating Competent Authority: France

November 2017

Table of Contents

1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 Procedure followed

This assessment report has been established as a result of the evaluation of the active substance polyhexamethylene biguanide hydrochloride (PHMB) as product-type 6 (In-can preservatives), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

PHMB (Not listed on the EINECS inventory because PHMB is a polymer] / CAS no. [32289-58-0 and 1802181-67-4]) was notified as an existing active substance, by Laboratoire PAREVA hereafter referred to as the applicant, in product-type 6.

Commission Regulation (EC) No 1062/2014 of 4 August 2014[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

On July 2007, French competent authorities received a dossier from the Laboratoire PAREVA. The evaluating Competant Authority (eCA) accepted the dossier as complete for the purpose of the evaluation on June 2015.

On December 2016, the eCA submitted to ECHA[2] and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report (CAR). Before submitting the CAR to ECHA, the applicant was given the opportunity to provide written comments in line with Article 8(1) of Regulation (EU) No 528/2012.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2 Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of PHMB for product-type 6, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

[1] COMMISSION DELEGATED REGULATION (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council. OJ L 294, 10.10.2014, p. 1

[2] ECHA : European CHemical Agency

1.3 Applicant

Name: Laboratoire PAREVA

Adress: Zone Industrielle du Bois de Leuze
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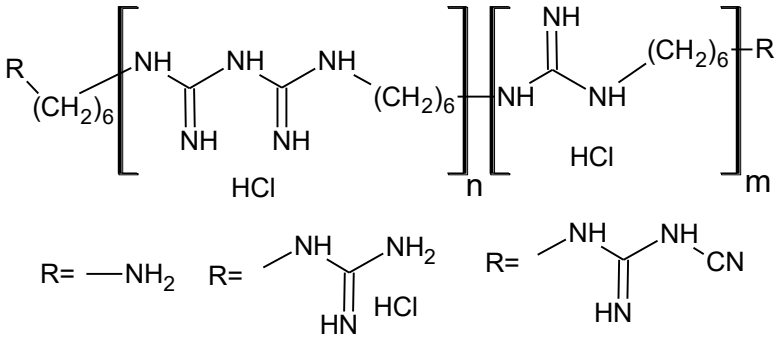
France

2 OVERALL SUMMARY AND CONCLUSIONS

2.1 General substance information / general product information

2.1.1 Identity, Physico-chemical properties & Methods of analysis of the active substance

2.1.1.1 Identity

CAS-No.	32289-58-0 and 1802181-67-4 eCA is of the opinion that second CAS number is more appropriate as it describe more accurately the active substance. However, both CAS number are kept as for historical reasons. It must be noted that CAS number is not based on characterisation data. In case of a different PHMB (for example with a weigh distribution outside of the specification of the PHMB assessed in this report) the CAS number will not be able to differentiate the PHMB.
EINECS-No.	PHMB meets the EU definition of a polymer and is therefore not listed on EINECS
Other No. (CIPAC, ELINCS)	None
IUPAC Name	CoPoly(bisiminoimidocarbonyl,hexamethylene hydrochloride),(iminoimidocarbonyl, hexamethylène hydrochloride)
Common name, synonym	- PHMB (1415; 4.7) i.e. Polyhexamethylene biguanide with a mean number-average molecular weight (Mn) of 1415 and a mean polydispersity (PDI) of 4.7; - Polyhexamethylene biguanide; - PHMB - Poly(hexamethylene biguanide) hydrochloride
Molecular formula	$(C_8H_{18}N_5Cl)_n(C_7H_{16}N_3Cl)m$ with three possible end-chains groups.
Structural formula	
Molecular weight (g/mol)	Weight average molecular weight Mw= 6629; Number average molecular weight Mn= 1415; PolyDispersity Index (Mw/Mn) = 4.67 Monomeric unit of " in-chain biguanides" was calculated for n average= 22.9

	Monomeric unit of " in-chain guanidines" was calculated for m average= 7.6

The active ingredient (a.i.) Poly Hexa Methylene Biguanide (PHMB) is a small size polymer obtained by the polycondensation of two monomers (1,6-hexanemethylenediamine and diamino1,6-hexane, bis(dicyanoamide) salt]

As PHMB is a small size polymer, some side reactions that occurred during the manufacturing process could modify significatively the structure of the polymer. The side reaction to obtain the unit guanidine occurred up to 10% in the process. Therefore, it can be considered that the structure of PHMB is not only composed by repetitive unit of guanidine but it is composed by repetitive unit of guanidine and biguanide.

The active substance as manufactured (TK[3]) is a 20% w/w aqueous solution of PHMB. "Purity" is a difficult concept to apply to PHMB which is a mixture of polymers and related substances. Instead, the applicant refers to the "strength" of the polymer which is defined as "% total solids" or "dried material". The typical PHMB strength is 20 %.

However, eCA considers more appropriate to use the term "% of active substance (% a.s.)" or "active substance content" instead of "strength". The active substance content being defined as the sum of PHMB and its impurities contents, it can be considered identical to the % total solids and thus to the strength. However, the terms strength or dried PHMB are also used in identity and physico chemical sections and refer to the same thing.

As the technical material is the 20 % PHMB solution obtained directly from the manufacturing process (active substance as manufactured or TK), characterisation data were generated from the dried technical material (TC[4]) using the technique of freeze drying.

The content of PHMB can be calculated by subtracting the total content of impurities in the dried technical material (without residual water) to 100. This value cannot be considered as a real purity but is the closest available data.

The minimum content of PHMB TC was demonstrated ≥ 94.3%.

Since the active substance is a copolymer, identity characterisation criteria (based on % solid, content of PHMB in dried material, Mw, Mn and the biguanide/guanide ratio) as well as limits or range for each criterion are proposed by eCA in the confidential of the Competent Authority Report (CAR) to characterise the source of PHMB in order to set reference specifications in case of approval of the active substance and future technical equivalence checks. **It was agreed to rename PHMB considered for approval in this dossier as "Polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1415 and a mean polydispersity (PDI) of 4.7" i.e. "PHMB (1415; 4.7)". For convenience, PHMB (1415; 4.7) is referred to hereafter as "PHMB" or "a.s.".**

There is one relevant impurity, Hexamethylenediamine with a maximal content of 0.1%.

<u>Summary of specifications of Pareva PHMB</u>:

[3] TK: technical concentrate according to GIFAP monograph n°2 nomenclature.

[4] TC: technical material according to GIFAP monograph n°2 nomenclature.

Complete specifications are available in confidential part. The summary is reported here.

Table 2.1-1: Specifications of PHMB (1415; 4.7) - Pareva

Characterisation specification	
Strength	19.9-20.1%
PHMB in dried material	≥ 94.3%
molecular weight by number (Mn)	1218-1613
molecular weight by mass (Mw)	4047-9211
Polydispersity	3.4-5.9
The biguanide / guanide ratio in chain	74.9/25.1 to 81.1/18.9
Total fraction <1000 Da	17.0-20.8%
Impurities	
HMD (relevant impurity)	≤ 0.1%
Other impurities	confidential

Batches available are older than 5 years. QC data to confirm that production was not changed were not submitted. During APCP WG III 2017, it was proposed to use spectral data from toxicological and ecotoxicological studies to demonstrate that the production remains constant. Unfortunately, the comparison of spectral data was not conclusive.

Therefore the demonstration that production was constant since the initial 5 batch analysis should be demonstrated before the approval of the active substance.

- (eco)tox batches: The batches used in the toxicological and ecotoxicological studies cannot be considered identical to batches of productions.
  Applicant proposed to group impurities for the setting of the specifications based on the fact that it is not possible to monitor impurities independently. However, this can only be possible if individual impurities have a similar toxicological/ecotoxicological profile.
  As PHMB is an UVCB, it was proposed at APCP WG III 2017 to compare chromatogram profiles of production batches with those of the (eco)toxicological batches. If the profile would be similar, no more data would be required. However, the comparison of chromatograms profile is not conclusive and the proposed approach cannot be applied. Therefore, demonstration that all impurities have a similar tox/ecotox profile is needed in the form of tox/ecotox QSAR/expert statement to justify the pooling of impurities.

- Criterion data to be used to differentiate PHMB from different origins: All of the presented characterisation data are important to differentiate PHMB assessed and other PHMB. However, some of those criterion could be difficult to control (biguanide / guanide

ratio quantified by NMR) or not selective (strength). eCA is of the opinion that Mn and polydipersity would be the most convenient property for the control of the identity of PHMB used in biocidal products.

2.1.1.2 Physico-chemical properties

The manufacturing process for PHMB produces a 20% aqueous solution as the technical material substance. A sample of purified active substance is prepared by removal of water from the technical material. The appearance of purified PHMB is a white odourless powder. The relative density is 1.237 and has no surface activity. It is thermally unstable above 200°C which is below its melting point. The vapour pressure is below a measurable value ($<1.10^{-6}$ Pa). It is highly soluble in water (401.2 g/L) and so the Henry's Law Constant (being the ratio of vapour pressure to solubility) was calculated as $<1.65 \times 10^{-8}$ (Log H <-7.8), indicating that loss of PHMB by volatilization from water bodies will be negligible. The octanol: water partition coefficient is very low indicating that bioaccumulation is unlikely. PHMB is highly soluble in methanol but only slightly soluble in acetone and n-hexane. It has a dissociation constant of 2.38.

PHMB 20% does not have a self-ignition temperature below 400°C. A theoretical assessment concludes that PHMB is unlikely to have explosive or oxidising properties and the water content of the product makes those risks highly unlikely. The active substance is therefore not classified as highly flammability, explosive or oxidising.

2.1.1.3 Methods of analysis

No method was submitted for determination of PHMB in TC. Furthermore, PHMB is not quantified in the 5 batch analysis.

Determination of impurities in TC was performed with HPLC–MS, HPLC-UV and GPC-UV. However, validations of methods for determination of most of impurities were not submitted.

It was discussed during APCP WG III 2017 that chromatograms fingerprints of all test materials and of the 5-batch analyses shall be provided to the eCA. With these data, similarity is not demonstrated, so fully validated, specific methods are required for impurities.

For polymeric substances it may be difficult to develop an adequate residue analytical method. A limited residue definition in form of a marker will be required if PHMB is proposed for approval.

Residue definition: a proposition of residue definition for drinking water, body fluid and tissues and food and feeding stuff was submitted by the applicant: PHMB quantified by MS part (dimer/trimer/tetramer).

Monitoring methods:

- Based on the bibliography and the nature of the active ingredient, as PHMB is expected to bind irreversibly to soil, determination of PHMB in soil is currently not technically feasible. Moreover, RMS considers that if a method could allow the quantification of PHMB in soil, this method could probably not be considered as enforcement method.

- The non-submission is acceptable for air because occurrence in air is not probable for product types (PT) where no spray application is proposed. When application via spray or aerosol is foreseen, such method is required.

- The non-submission is acceptable for surface water, as eCA considers that the issue is the same than in soil. However, determination of PHMB in drinking water should be technically feasible.

- An ELISA method was submitted in deionised water but not validated on acceptable matrice (drinking water). Therefore, a validated method for determination of PHMB on drinking water would be required before active substance approval.

- For body fluids and tissues, as PHMB is classified as very toxic, applicant submitted methods. However, these methods are still to be validated. Validated method of determination of residue of PHMB in body fluid or an acceptable justification of non-submission is still required before active substance approval. It has to be noted that applicant indicated that ELISA kit is available.

- The justification for non-submission submitted by the applicant is not acceptable for food and feeding stuffs. An analytical method for determination of PHMB for food and feeding stuffs or another justification of non-submission of data would be required before active substance approval.

2.1.2 Identity, physico-chemical properties & methods of analysis of the biocidal product

2.1.2.1 Identification of the biocidal product

Trade name	**PRESERVIL-D2**	
Manufacturer´s development code number(s)	None	
Ingredient of preparation	Function	Content %
PHMB	Active substance	20% (w/w)
	Details of the product composition and information on the co-formulants are confidential	
Physical state of preparation	Limpid to slightly opalescent liquid	
Nature of preparation	SL (Soluble Concentrate)	

2.1.2.2 Physico chemical properties of biocidal products

PRESERVIL-D2 is stable to light and following storage at 54°C for 14 days, showed no loss of

active substance. It is considered to be stable for storage at 54°C for 14 days, no physical changes were observed. It is likely to be stable for two years at room temperature. A study of long-term stability is on-going. A one year shelf life study showed no apparent loss of PHMB. There were no serious reactions with metallic iron and the product did not react with its container material. There were no physical changes on storage at 4°C. The product was found to be stable after storage at low temperature: no change in appearance, and colour was observed after 7 days at 0°C.

PRESERVIL-D2 does not have a self-ignition temperature below 400°C. A theoretical assessment concludes that PHMB is unlikely to have explosive or oxidising properties and the water content of the product makes those risks highly unlikely. The active substance is therefore not classified as highly flammability, explosive or oxidising.

2.1.2.3 Methods of analysis

Validated method is available for determination of PHMB in PRESERVIL-D2.

2.1.3 Intended Uses and Efficacy

2.1.3.1 Field of use envisaged

Main group: 2 – Preservative

Product type 6 – Preservatives for products during storage

2.1.3.2 Function

Polyhexamethylene biguanide (PHMB (1415; 4.7)) is an antimicrobial preservative for aqueous manufactured products in cans, tanks or other closed containers. The preservative must prevent the bio-deterioration of these systems until they are used.

Biocidal product PRESERVIL-D2 is used as a dish detergent preservative (PT6.01) by professional users. The product PRESERVIL-D2 is a 200g PHMB/L formulation and is a ready to use solution. The product has to be directly added into a dish detergent formula to protect it, during its production. The product has to be concentrated at 0.3% PRESERVIL-D2 in the dish detergent (i.e. 0.06% PHMB).

2.1.3.3 Mode of action

The lethal action of PHMB is an irreversible loss of essential cellular components as a direct consequence of cytoplasmic membrane damage. Indeed, the lethal event is believed to be a PHMB-acid phospholipid interaction leading to a phase separation in the outer leaflet of the membrane bi-layer. Such phase separation will lead to instability in the membrane and also loss of membrane-bound enzyme function; resulting in destabilisation which is followed rapidly by a total loss of membrane function owing the phospholipids assuming a hexagonal rather than a bi-layered phase.

2.1.3.4 Objects to be protected, target organisms

The efficacy of PHMB has been achieved against bacteria and yeasts for the application as a preservatives for detergents. The example selected in this dossier is a dish detergent.

The product PRESERVIL D2 (20% w/w PHMB) is active against a variety of bacteria (including but not exclusively: *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus hirae*) and yeasts (*Candida albicans*, *Rhodotorula glutinis*) that could be present within in-can (or tanks or other closed containers) manufactured products. The preservative is added to aqueous based products during their production in the manufacturing plant. The added preservative must prevent the bio-deterioration of these systems until they are used.

Uses against molds have been claimed also but the efficacy demonstrated by the product PRESERVIL D2 has been considered as insufficient in the submitted efficacy test (challenge test).

Table 2.1-2: Intended uses for which efficacy of the active substance PHMB has been proved sufficiently

Uses	a.s rate	Application mode	Effect	Target organisms
Preservatives for detergents.	0.06% w/w	Addition to aqueous manufactured products during their production in the manufacturing plant	Preservative antimicrobial efficacy against potentially harmful and spoilage microorganisms	Bacteria Yeasts

Note: For bacteria the effect is immediate and the product is effective during 28 days. For yeasts, the effect begins 11 days after application and the product is effective until 21 days after application i.e. during 10 days. Efficacy should be demonstrated for each claimed organisms at product authorisation stage.

2.1.3.5 Resistance

The evaluation of the literature studies provided does not show particular resistance of bacteria, fungi and yeasts to PHMB. Nevertheless it is not appropriate to conclude that resistance to PHMB is not an issue and that a resistance management strategy is not required. In particular, the description in the literature of cross resistances and modifications of the expression of genes as a mechanism of tolerance to sublethal concentrations of PHMB should be taken into account in the strategy of resistance management.

Indeed Standard methods of measuring resistance brought about by biocide use are not available and should be developed for all types of biocides (Assessment of the Antibiotic Resistance Effects of Biocides, Scenihr 2009).

2.1.4 Classification and Labelling

2.1.4.1 Proposal for the classification and labelling of the active substance

A harmonised classification according to the Regulation (EC) N° 1272 -2008 (CLP) is available (9th ATP) covering the active substance PHMB with CAS number 32289-58-0:

Category	Carc. 2 Acute Tox. 2 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	Carcinogenicity Category 2 Acute toxicity Category 2 Acute oral toxicity Category 4 Specific target organ toxicity after repeated exposure Category 1 Eye damage Category 1 Skin sensitisation Category 1B Aquatic Acute Aquatic Chronic
Hazard statement	H351 H330 H302 H372 (respiratory tract) (inhalation) H318 H317 H400 H410	Suspected of causing cancer. Fatal if inhaled. Harmful if swallowed. Causes damage to organs through prolonged or repeated exposure by inhalation. Causes serious eye damage. May cause an allergic skin reaction. Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.

Environmental M-Factor for classification of mixtures containing active substance:

- Acute M-Factor: 10
- Chronic M-Factor: 10

2.1.4.2 Proposal for the classification and labelling of the representative product

PRESERVIL-D2 (professional users)

According to the Regulation (EC) N° 1272 -2008 (CLP):

Category	Cat 4	Acute inhalation
	Eye Cat 1	Irreversible effect on the eye
	STOT RE 1	Specific target organ toxicity after repeated exposure
	Carc.2	Carcinogen
	STOT SE 3	Specific target organ toxicity after single exposure
	Cat 1	Aquatic Acute
	Cat 1	Aquatic Chronic
Hazard statement	H332	Harmful if inhaled
	H318	Cause serious eye damage
	H372	Causes damage to organs through prolonged or repeated exposure
	H351	Suspected of causing cancer
	H335	May cause respiratory irritation
	H400	Very toxic to aquatic life.
	H410	Very toxic to aquatic life with long lasting effects.

The mention EUH 208 'Contains PHMB. May produce an allergic reaction' should appear on the label.

With regard to toxicological data

Based on the available studies, a classification category 4 H332 for acute inhalation and category 1 H318 for eyes irritation is necessary.
Based on the concentration of PHMB (20%) in SURFACIL-TC, a classification STOT RE 1 H372 and Carc. 2 H351 is also needed.

Moreover, the applicant proposed to classify the product STOT SE 3 H335: May cause respiratory irritation.

2.2 Summary of the Risk Assessment

2.2.1 Risk characterisation for human health

2.2.1.1 Human health effects of active substance

- **Toxicokinetic**

A limited toxicokinetic/metabolism investigation into urinary polymer-related material from rats given poly(biguanide-1,5-diylhexamethylene hydrochloride) [PHMB] was published in open literature. Gastro-intestinal absorption of PHMB following a single oral dose amounted to only 5.6% of the administered dose. Faeces were the primary route of elimination of the polymer related material which was unmetabolised by gut micro-organisms and from work in bile cannulated rats. There was no biliary component to the excreted PHMB. Expired air was collected but the paper provides no results for any analysis of radiolabel in air. Following repeated administration to rats in diet the temporary tissue concentration reached a maximum of 0.3 µg/g for adipose tissue depots and less than 0.2 µg/g in liver, kidneys and heart. These concentrations rapidly fell away to zero when treated diet was replaced with standard untreated diet. PHMB showed no potential for bioaccumulation in this assay and very limited tissue

distribution.

Since no information is available on absorption of PHMB by inhalation, an absorption of 100% is retained.

The absorption of PHMB P100 concentrate (200 g PHMB/L), and aqueous dilutions of it (6.67 g PHMB/L and 0.2 g PHMB/L) through human epidermis was measured in vitro over 24 hours according to OECD 428 Guideline. According to the Guidance of dermal absorption[5], the dermal absorption values were 48%, 6% and 0.6% for 0.2 g/L, 6.67g/L and 200g/L respectively.

- **Acute effects**

The acute oral toxicity study was conducted on solid substance PHMB P100 according to OECD 423 guideline. The acute oral median lethal dose (LD50) of the test item PHMB P100 is higher than 300 mg/kg and lower than 2000 mg/kg. The LD50 cut-off of PHMB may be considered as 500 mg/kg body weight by oral route in the rat. PHMB P100 has to be classified in Category 4 with the hazard statement H302 "Harmful if swallowed".

In a dermal toxicity study, 5 Sprague Dawley rats/sex received a single dermal application of moistened PHMB P 100 at a dose level of 2000 mg/kg bw according to OECD 402 guideline. No death occurred. The acute dermal LD_{50} of PHMB P100 is higher than 2000 mg/kg body weight by dermal route in the rat. The PHMB P100 substance is not classified according to–the Regulation (EC) N° 1272 -2008 (CLP).

The acute inhalation toxicity study was conducted on solid substance PHMB P100 according to OECD 403 guideline. The 4-hour acute inhalation median lethal concentration (LC50) of PHMB in Wistar Crl:(WI) rats is 0.29 mg/L for males and 0.48 mg/L for females.

The LC_{50} for PHMB P100 (0.29 mg/L) is greater than 0.05 mg/L and less than 0.5 mg/L in rats. Therefore it has to be classified in Category 2 with the hazard statement H330 "Fatal if inhaled".

Based on a dermal irritation study in accordance with OECD 404 guideline PHMB P100 PC is not classified as irritant to skin according to the Regulation (EC) N° 1272 -2008 (CLP).

In an eye irritation study in accordance with OECD 405 guideline, the ocular reactions observed during the study have been severe (opacity of the cornea, congestion of the iris and ulceration of the nictitating membrane and the cornea) and not reversible during the 7 days of the test. Taking into account the severity of the reactions at day 7 (maximum ocular irritation index at 83 at day 7) the study was stopped at day 7 in accordance with the principles of animal welfare. PHMB P100 PC has to be classified "Serious eye damage - Category 1" with hazard statement "H318: Causes serious eye damage".

PHMB is considered a skin sensitizer based on animal data and human studies indicate that PHMB is a skin sensitizer in humans, although with a rare frequency of sensitization in the current conditions of consumer uses. Skin sens 1 – H317 for CLP, is therefore warranted. Relatively low incidences from human data support classification as CLP Skin Sens 1B – H317.

- **Repeated toxicity studies**

[5] Guidance on Dermal Absorption, EFSA Panel on Plant Protection Products and their Residues (PPR) European Food Safety Authority (EFSA), Parma, Italy EFSA Journal 2012;10(4):2665

Oral administration via drinking water rats over 28 days with PHMB P100 was conducted in Wistar rats in accordance with OECD 407 guideline. Based on statistical decrease of body weight in males (-58.6%),, the NOAEL of PHMB was established at 1000 mg/L corresponding to 54.9 mg/kg bw/d for males and to 61.3 mg/kg bw/d for females.

A GLP study conducted in compliance with OECD 422 guideline provided information on toxicity effect after repeated administration of PHMB P100. An increase of relative organ weights (spleen, kidney, brain, testes, uterus) was observed at 1500 mg/L. Only one dose (1500 mg/l) was tested during 90 days, the important body weight decrease and relative organ weight increase were considered to be adverse effects. No NOAEL should be derived because only one dose was tested during 90 days in this combined repeated dose toxicity study with the reproduction/developmental toxicity screening test.

In the preliminary study of chronic/carcinogenicity study, test substance related effects such as pigment and haemorrhage were observed in liver of males and females rats at 1500 mg/L after one year of exposure. Based on changes in mean body weight, mean food consumption, toxicity signs exhibited, organ weight changes and histopathological findings in the high dose group (1500 mg/L), the NOAEL of PHMB P100 when administered in the drinking water for 3 months to Wistar rats can be set at 1000 mg/L, corresponding to 95 and 102 mg/kg b.w./day for males and females respectively.

In GLP study, PHMB P100 PC was administered dermally by fully-occluded exposure for six hour per day for four weeks. The application of PHMB at doses up to and including 300 mg/kg/day did not result in any evidence of systemic toxicity. However evidence of local irritancy was evident in females receiving 300 mg/kg/day. Consequently, within the context of this study it was concluded that the No-Observed-Adverse-Effect-Level (NOAEL) for systemic sub-acute dermal toxicity was 300 mg/kg/day, and the NOAEL for local irritancy was 100 mg/kg/day.

A 28-day inhalation study (started in August 2015) is ongoing. A preliminary study of inhalation toxicity in repeated doses was provided by applicant tardily without validation of analytical method. This preliminary study was considered to be unreliable to be considered for risk assessment.

- **Combined chronic/carcinogenicity toxicity study**

In the combined chronic/carcinogenicity study in rats exposed via diet, the long-term NOAEL is 500 mg/L, corresponding to 36 and 43 mg/kg b.w./day for male and female respectively based on changes in mean body weight, mean food consumption, toxicity signs exhibited, organ weight changes, gross and histopathological findings in both intermediate (1000 mg/L equivalent to 69 mg/kg b.w.) and high dose groups (1500 mg/L equivalent to 97 mg/kg b.w.).

This study highlights following neoplastic findings in exposed rats:

- Induction of hepatic hamartoma
- Induction of hepatocellular adenoma. In females, the incidence of this benign tumor is slightly lower than provided historical controls.
- Induction of follicular adenoma in thyroid in males

An increase of this benign tumor is observed with a higher incidence than historical controls at the two higher doses. Observed hamartomas and hepatocellular adenomas support the current classification of PHMB as carcinogenic.

Among others, the most commonly observed neoplasm were pars distalis adenoma of pituitary, fibroadenoma and adenoma of the mammary gland, C-Cell adenoma of thyroid gland, and endometrial stromal polyp of uterus. However, the incidence of these findings was not related to test substance administration.

Hemangioma or hemangiosarcoma are observed in various organs (liver, spleen, mesenteric and mandibular lymph nodes) and different groups. The reported incidence in historical controls confirms that these tumors are very rare. Nevertheless, the very low incidence of vascular tumors observed in this study does not enable to assign clearly to treatment. However, it is noted that a major impact of angiectasis (abnormal dilation of a vessel) is observed in the liver although the dose-response relationship is not linear. Incidence of associated changes like cystic degeneration, hemorrhage, pigment and medial hyperplasia of blood vessels was also increased.

For information, three modes of action were investigated by the applicant:
1) Uptake of iron in sinusoidal lining cells with the release of mitogenic cytokines. The irrelevance of this mode of action to human is not clearly demonstrated by the applicant, no publications are submitted or referenced.
2) Severe stress initially because of dehydration and markedly decreased food intake due to palatability issues with PHMB in the drinking water. However, the relationship between stress and dehydration is not proven and no publications are submitted to robustly justify this.
3) A direct mitogenic effect on the hepatocytes possibly through CAR/PXR. However, RMS considered that the treatment with 1500 mg/L PHMB group in drinking water did not induce an increase in enzyme activity for Cyt2B, Cyt3A or Cyp4A. The expression levels of the PPARα, CAR and PXR responsive genes in the liver tissue of rats, was not affected at 1500 mg/L PHMB. Moreover, centrilobular hypertrophy and increased smooth endoplasmic reticulum were not considered sufficient to demonstrate CAR/PXR-related mode of action.

During the comment period, applicant provided an additional investigation of MOA, suggested by the structural analogy with biguanides.
The role of endothelial cell activation with a release of mitogenic factors cannot be excluded, particularly given the increase in endothelial cell proliferation that occurs within 4 weeks of administration of PHMB and by the ultimate development of ectatic lesions on the liver.
The possible contribution of other mode of actions was not sufficiently excluded. Although genotoxicity is excluded, no other potential mechanisms have been excluded (estrogen receptor (ER), gap junction intercellular communication (GJIC), aryl hydrocarbon receptior (AhR)).

The current harmonised classification of PHMB was based notably on:

- Vascular tumour in mice by oral and dermal route (principally in liver)
- Local tumour by oral routes in mice

To conclude, the results of these studies do not question the carcinogenic effects observed in mice as only rats are tested. They confirm the carcinogenic potential of PHMB in the liver of rats by observing hamartomas and hepatocellular adenomas. They do not identify vascular tumor in rats however vascular lesions (angiectasis) support a concern regarding a PHMB effect on these tissues.

Therefore, these results do not question the relevance of the harmonised classification Carc 2 - H351 of PHMB, currently registered in Annex I of Regulation (EC) 1272/2008.

- **Genotoxicity**

Several *in vitro* studies of genotoxicity were performed with PHMB P20 D (Ames test, gene mutation test y assay in mammalian cells and chromosomal aberration). To conclude, no evidence for genotoxic potential was found in any of the *in-vitro* assays completed in the presence or absence of metabolic activation provided by S-9 mix. No classification for this end point is required.

- **Reprotoxicity**
    - **Teratogenicity**

In an oral Prenatal Developmental toxicity study conducted according to OECD guideline 414, no teratogenic effect of PHMB was observed in the rat. The parameters such as number of corpora lutea, live foetuses, dead foetus, pre and post implantation loss did not vary between the control and the treated group. There was no difference in the mean litter size, mean number of males and females per litter of the control and treated groups. Maternal NOAEL was established to 1000 ppm corresponding to 112.45 mg/ kg bw/d, the highest tested dose in absence of adverse effect. The incidence of external anomalies were comparable in animals of PHMB treated groups and control group. However, increase of foetal and litter incidence of supernumerary lungs lobes was observed from 1000 ppm and foetal incidence of incomplete ossification of the 6th sternebrae from 300 ppm.
Based on the data presented above, foetal NOAEL could be established at 300 ppm based on the increase of lung supernumerary lobe at the LOAEL of 113 mg/kg bw/d. However, it is important to note that the teratogenicity study of Pore (2010) has undergone several amendments between December 2014 and May 2017. Considering all these amendments about the incidence of the effects, it is proposed to have a precautionary approach in the evaluation of the results and to set the developmental NOAEL at 12 mg/kg bw/day, based on lung and skeletal variations observed at higher doses in the previous report.

    - **Fertility**

The GLP study conducted in compliance with OECD 422 guideline provided information on male and female reproductive performance such as gonadal function, mating behavior, conception, development of the concepts and parturition after repeated administration of PHMB P100. Treatment with PHMB in Wistar rats at dose levels of 500, 1000 ppm and 1500 doses. Based on changes observed in the body weights, food and water consumption at the 1500 ppm, a NOAEL for systemic toxicity was considered to be 1000 ppm which was equivalent to 30.64 mg/kg bw/day for males and 154.23 mg/kg bw/day for females. As there were no effects on fertility and reproduction at all the doses tested, the NOAEL for reproductive and developmental toxicity was considered to be 1500 ppm which was equivalent to 50.55 mg/kg bw/day for males and 262.39 mg/kg bw/day for females.

A two generation reproduction toxicity study was conducted to provide general information concerning the effects of the test item PHMB P100 on the integrity and performance of the male and female reproductive systems, according to OECD guideline 416. The test item was weighed and mixed with drinking water and provided to Wistar rats ad libitum at the graduated dose levels of 500, 1000 and 1500 ppm. No effects on general health, body weights, food intake, oestrous cyclicity, pre-coital time, gestation length, pups survivability,

mating, fertility, fecundity or sperm parameters in both the generations were observed. The parental systemic toxicity NOAEL was established at 1000 ppm, (equivalent to 58.21 and 80.05 mg/kg bw/day for males and 145.20 and 167.90 mg/kg bw/day for females for P and F1 generations, respectively.) based on decrease in the ovary, vagina and uterus weight and increase in spleen weight. The NOAEL for the offspring was fixed at 1500 ppm (equivalent to 81.55 and 125.03 mg/kg bw/day for males and 208.82 and 268.03 mg/kg bw/day for females for P and F1 generations, respectively). The NOAEL for reproductive toxicity was also fixed at 1500 ppm.

The results indicated F1 and F2 pups were unaffected by treatment and the NOAEL for offspring effects was established at 1000 ppm, equivalent to 58.21 and 80.05 mg/kg bw/day for males and 145.20 and 167.90 mg/kg bw/day for females for P and F1 generations.

- **Neurotoxicity**

In conclusion, the data indicate that the active substance, PHMB, does not affect the vertebrate nervous system. PHMB is not an organophosphorus substance nor in the family of compounds likely to induce anticholinesterase activity, and as such, neurotoxicity studies were not considered necessary for evaluation of human health risks.

- **Determination of AEL/AEC/ADI/ARfD**

The lowest NOAEL from any oral studies is 12 mg/kg bw/day from the rabbit prenatal developmental toxicity study. This value is based on a precautionary approach in the evaluation of the results setting the developmental NOAEL at 12 mg/kg bw/day, based on lung and skeletal variations observed at higher doses. An explanation for the low value of NOAEL in the teratogenicity study may be the gravid state of exposed animals, involving differences in toxicokinetics and in toxicity. This can however not be established with certainty and the reason of the discrepancy in NOAEL is not known. Therefore, RMS considers that this value cannot be ruled out and the NOAEL from the teratogenicity study is considered relevant for setting of AELs.

NOAEL = 12 mg a.s./kg bw/day.

The percentage of the administered PHMB found to be available for absorption following administration in the diet for females was 5.6%.

Internal NOAEL = 0.67 mg a.s./kg bw/day

The acute, medium-term and long-term AEL is the systemic NOAEL (0.67 mg/kg bw/d) divided by the 100-fold assessment factor (10 for inter-species variation and 10 for intra-species variation).

$$AEL = \frac{Systemic\ NOAEL}{AF} = \frac{0{,}67}{100}\ mg.kg\ bw^{-1}.day^{-1} = 0{,}0067\ mg.kg\ bw^{-1}.day^{-1}$$

An acute, medium-term and long-term AEL of 6.7 x 10-3 mg a.s./kg bw/day is proposed.

The ADI/ARfD is the NOAEL (12 mg/kg bw/d) divided by the 100-fold assessment factor (10 for inter-species variation and 10 for intra-species variation).

$$ADI/ARfD = \frac{NOAEL}{AF} = \frac{12}{100}\ mg.kg\ bw^{-1}.day^{-1} = 0{,}12\ mg.kg\ bw^{-1}.day^{-1}$$

An ADI and an ARfD of 0.12 mg a.s./kg bw/d are proposed.

Table 2.2-1: Summary of the values of the reference values

	AEL
acute, medium and long-term	6.7 µg a.s./kg bw/d
	ADI - ARfD
Chronic and acute	0.12 mg a.s./kg bw/d

Determination of AEC

As no study is available, no AEC for inhalation route can be derived. However, an Ad hoc follow up discussion on the AEC derivation was initiated after the HH WG III 2017. In conclusion, the majority of members who participated to the follow up discussion agreed with the possibility to perform a read across of the data with another PHMB dossier for the AEC for the inhalation route.
If the applicant is able to obtain a Letter of Access to the study, the study could be used without adding additional safety factors
Currently, no letter of access is available. Therefore, no risk assessment can be performed.
The active substance is not volatile. Thus, exposure via inhalation route could occur only for use generating aerosol (application of the product by spraying). At the active substance level, no use generating aerosol was identified by the applicant in the initial dossier, until new uses were proposed by the applicant at a very late stage of the assessment, i.e. during the commenting period of the Competent Authority Report according to article 8(1) of the BPR.
In this context, and in absence of appropriate data to perform the risk assessment, uses generating aerosols are considered as unacceptable. If at the product authorisation stage, applicant wants to claim uses generating aerosols, a local risk assessment via inhalation should be performed. At that time, proper data or a letter of access to the data of the other applicant of PHMB should be provided.

2.2.1.2 Human health effects of products

The preservative PRESERVIL-D2 contains the biocidal active substance PHMB at 200g/kg. The product is intended to a professional use.

Dermal absorption of PHMB was assessed in a study "In vitro dermal penetration of PHMB across Human Skin According to OECD 428 Guideline."

The absorption of PHMB P100 concentrate containing 200 g PHMB/L, and aqueous dilutions of it (6.67 g PHMB/L and 0.2 g PHMB/L) through human epidermis was measured *in vitro* over 24 hours according to OECD 428 Guideline. Absorption of PHMB through the membrane was assessed over the 24 hour experimental period by sampling the receptor fluid at intervals of 2, 4, 6, 8 and 24 hours after application. The *stratum corneum* of each treated skin was removed by tape-stripping, the two first strips were pooled, they corresponded to the excess of the test formulation which was not penetrated (but on the skin) withdrawn by desquamation. At the end of the experiment, the distribution of PHMB in the test system (receptor fluid, skin washes, donor chamber, *stratum corneum* and residual epidermal tissue) was assessed. All samples were analysed by liquid scintillation counting (LSC).

The results showed that the absorbed dose of ^{14}C-PHMB reaching the receptor fluid 24 hours after application was negligible (under the limit of quantification) but a retention of the test compound in the skin (epidermis and dermis) was noted.
Due to the high degree of variability observed in the dermal absorption study, eCA considered for the risk assessment the highest value of absorption of each dilution, as a worst case approach.

According to the Guidance of dermal absorption[6], these values were rounded at 48%, 6% and 0.6% for the PHMB (1415; 4.7) based products at the concentration of 0.2 g/L, 6.67g/L and 200g/L respectively.
In this context, a value of 0.6% will be used for concentrate products, a value of 48% will be used for dilution at 0.06% of PHMB and default value of 75% will be used for dilution inferior to 0.02%.

Several studies (oral and dermal acute toxicity studies, dermal and ocular irritation and sensitisation) were performed with PHMB 20% aqueous solution (PHMB-P20D). Since PRESERVIL-D2 is a dispersal of the active ingredient in a simple carrier, this bridging to the active substance or PHMB 20% toxicity dataset is considered acceptable.

PHMB-P20D was administered to a group of 6 Sprague Dawley rats (3 males and 3 females) at a single dose of 2000 mg/kg bw according to OECD 423. The acute oral LD50 of PHMB *–P20D* was found to be >2000 mg/kg body weight. In this context, no classification is required for this end point.

PHMB-P20D was administered to a group of 10 Sprague Dawley rats (5 males and 5 females) at a single dose of 2000 mg/kg bw according to OECD 402. The acute dermal LD_{50} of PHMB-P20D was found to be >2000 mg/kg bodyweight. In this context, no classification is required for this end point.

PHMB-P20D is considered as non-skin irritant and non-sensitising in Magnusson and Kligman essay. However, it is considered as severely irritant for eyes. A classification in Category 1 H318: Causes serious eye damage is necessary. Moreover, the mention EUH 208 'Contains PHMB. May produce an allergic reaction' should appear on the label.

For acute toxicity by inhalation route, a study with PHMB at 100% was performed. The 4-hour acute inhalation median lethal concentration (LC50) of PHMB in Wistar Crl:(WI) rats is as follows:

[6] Guidance on Dermal Absorption, EFSA Panel on Plant Protection Products and their Residues (PPR) European Food Safety Authority (EFSA), Parma, Italy EFSA Journal 2012;10(4):2665

- for males: 0.29 mg/L
- for females: 0.48 mg/L.

The corresponding value for a 20%-PHMB solution is:
- for males: LC50 =1.45 mg/L
- for females: LC50 =2.40 mg/L

According to the Regulation (EC) N° 1272 -2008 (CLP), the LC50 for PHMB P100 (0.29 mg/L) is greater than 0.05 mg/L and less than 0.5 mg/L in rats therefore it has to be classified 'Category 2' H330 "Fatal if inhaled". The LC50 for PHMB for 20%-PHMB is estimated at 1.45 mg/L, thus the product has to be classified **Category 4 H332 "Harmful if inhaled"**.

Considering the classification of the active substance PHMB, notably the classification: STOT RE 1 H372 and Carc. 2 H351 and its concentration in PRESERVIL-D2, the following classifications have to be added for the product:

- STOT RE 1 H372: Causes damage to organs through prolonged or repeated exposure
- Carc. 2 H351: Suspected of causing cancer.

For respiratory irritation, specific study is not available. PHMB (100%) is not classified under CLP regulation for this endpoint and no detailed data to justify this classification was provided by applicant.
However, the applicant proposed to classify the product STOT SE 3 H335: May cause respiratory irritation.based on both animal studies conducted by inhalation where laboured respiration and rhonchus were reported and on human incident cases submitted to the EPA Office of Pesticide Programs involving use of PHMB-containing swimming pool products where the most common symptoms for cases of exposure via inhalation were respiratory irritation (75%) and coughing/choking (38%).

2.2.1.3 Human health risk

PRESERVIL-D2 is developed for the protection of dish detergents from spoilage by bacteria and yeasts (PT6). However, in order to have an exhaustive assessment, exposure was estimated for all detergent types.
PRESERVIL-D2 is a 200g PHMB/L formulation and is a ready to use solution for professional. The product has to be directly added into a detergent formula to protect, during its production. The product has to be concentrated at 0.3% PRESERVIL-D2 in detergents (i.e. 0.06% PHMB).

Several scenarios of exposure of PHMB are identified:

1-Exposure during formulation by a professional of detergent product in which PHMB is added.

2-Exposure of professional and general public during use of detergent containing PHMB (hand washed laundry, pre-treatment of clothes, hand dishwashing and cleaning of surface).

Secondary exposure could occur, essentially by dermal route from washed dish, wearing cleaned clothes following contact with cleaned surface and by oral route via ingestion of food containing residues of PHMB.

Considering the lack of aerosol forming during the application coupled with the low vapour pressure (1E-06 Pa) of PHMB, no inhalation exposure is expected.

2.2.1.3.1 Primary exposure

2.2.1.3.1.1 Exposure during formulation of detergent containing PHMB as conservative

The product has to be concentrated at 0.3% PRESERVIL-D2 in the detergent (i.e. 0.06% PHMB).
No specific preparation is needed before use.

Therefore, the main path of exposure is the dermal route.

The mixing and loading tasks involve the removal of the product from its container and introduction to the system and may be conducted by automation or manually. In the automated process, the biocide is added directly into the mixture from a holding tank or other type of bulk container. The manual process involves a worker dispensing (via a tap or by pouring) a measured quantity of product into a jug and manually pouring the product into the sump.

Manual pouring is considered as a worst case scenario compared to the automated transfer. The exposure will be assessed following this scenario.

According to the recommendation by the Human Exposure Expert Group (HEEG), the most relevant model for simple manual loading of liquids is the Model 7, TNsG part.2 (Professional pouring and pumping liquid, and dumping solids into systems, 2002). The TNsG suggests that fluid dilution and/or biocide addition (mixing and loading) occurs 1 time per week and takes 10 minutes per event.

Risk for professional is summarised in the following table:

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Formulation of detergent product: addition of PHMB	Pouring preservil-D2 into formulation of detergent	Without PPE	2,02E-02	**301%**
		With clothes and gloves	2,02E-04	3%

The exposure is superior to AEL when no PPE is worn. However, the exposure becomes inferior when clothes and gloves are worn. In this context, the risk is considered as acceptable during pouring of preservil-D2 into formulation of detergent if clothes and gloves are worn.

2.2.1.3.1.2 Exposure during use of detergent containing PHMB

PHMB is incorporated into detergent at an a.s. concentration of 0.06%.

Exposure to PHMB may occur when individuals use detergent products containing PHMB. It is considered that the following scenario (use of detergent by professional and non-professional), covers other potential scenarios, like machine washing laundry and dishes. Exposure following incidental splash and spillage is assessed by the scenario pre-treatment of clothes.

2.2.1.3.1.3 Use of detergent by professional

- **Exposure during hand washed laundry**

Whereas professionals will more often wash clothes in machine, hand washing is a worst-case scenario for professional laundry washers.

The task is divided in two scenarios:

- Mixing & Loading of detergent (common to machine- or hand-laundry);
- Application (for hand-laundry only).

For the purposes of this assessment, potential exposures to PHMB for professional users were calculated following HEEG opinion 16[7] and using parameters proposed in ConsExpo 4.1[8].

Whereas ConsExpo was developed for non-professional users, the methods and most of the parameters are applicable for professional users. As no specific data and models can be found in TNsG, eCA thinks that this approach is the most appropriate for this assessment, provided that some parameters (from ConsExpo's Cleaning product factsheet, RIVM 2006) are modified as explained for each scenarios.

Mixing and loading:

During this step, dermal exposure could occur, for example due to liquid spills around the opening of the bottle.

A default value of 0.01 mL is proposed in the Consexpo Cleaning Products Factsheet page 23 and will be used for the assessment of exposure.

Washing of laundry:

As suggested in the HEEG opinion 16, the approach described in the Cleaning Products Fact Sheet will be used for the assessment of exposure. It is considered that a thickness of the liquid layer of 0.01 cm is in contact with the skin.
During hand washing of laundry, it is considered that two hands and two forearms are in contact with the diluted solution.

A professional could perform these tasks around 16 times per day.

According to Consexpo, a dilution of the detergent at 1% has to be taken in consideration (page 36). Therefore, the concentration of PHMB in diluted solution is 0.01*0.06%= 0.0006%.

The risk linked to use of detergents is summarised in the following table.

[7] HEEG opinion 16: Biocidal products : model for dipping of hand/forearms in a diluted solution (endorsed at the TM IV 2012 and amended after TMIII 2013 to take into account changed defaults human factors values.
[8] Delmaar JE, Park MVDZ, Van Engelen JGM (2005). ConsExpo 4.0 Consumer Exposure and Uptake Models Program Manual. Report 320104004/2005., RIVM Bilthoven, The Netherlands.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during hand washed laundry	Mixing&Loading (common to machine- or hand-laundry)	No PPE	7,68E-04	11%
	Application (for hand-laundry only)	No PPE	2,34E-02	**349%**
	Combined exposure	No PPE	2,42E-02	**361%**

For hand washing of laundry, the %AEL for mixing and loading is inferior to 100%. However, it is superior for hand laundry (application phase).
It is considered that the use of a refinement factor of 10% for wearing of gloves is not relevant. Indeed, the ability of protection of gloves which will be used in this task is unknown.
In this context, a reverse scenario was performed to determine the minimum protection necessary to have a risk acceptable. The gloves will have to have a protection factor more than 72% and will have to cover hands and forearms to consider the risk as acceptable.
The applicability and reliability of this mitigation measure is doubtful considering that PHMB is present in the product only as conservative. In this context, the risk is considered as unacceptable.

However, the use of washing machine is considered as acceptable as exposure occurs only during the phase of mixing and loading.

- **Exposure during pre-treatment of clothes**

Direct skin contact with PHMB is possible when clothing stains are being removed by spot-treatment with neat liquid (undiluted product). This scenario covers also well the potential exposure following incidental splash and spillage of product, e.g. while pouring the product in a washing-machine.

According to Consexpo Cleaning Products Fact Sheet (page 44), it is assumed that 0.065g of products at 0.06% contacts the skin.

It is considered that a professional could perform these tasks around **16 times per day** (as for hand wash laundry)

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 /			Systemic Exposure (mg/kg/day)	

PT 6				
Exposure during pre treatment of clothes	Spot removers	No PPE	4,99E-03	75%

For spot removers, the %AEL is inferior to 100% although no PPE are worn. Therefore, the risk is considered as acceptable.

- **Exposure during hand dishwashing**

The task is divided in two scenarios assessed separately:

- Mixing&Loading of detergent (common to dishwasher- or hand-dishwashing),
- Application (hand dishwashing)

The exposure during mixing and loading of detergent corresponds to the professional's exposure during the mixing and loading step when considering the dishwasher scenario.

For the purposes of this assessment, potential exposures to PHMB for professional users were calculated following HEEG opinion 16[9] and using parameters proposed in ConsExpo 4.1.

Mixing and loading:

During this step, dermal exposure could occur for example, due to liquid spills around the opening of the bottle.

A default value of 0.01 mL is proposed in the Consexpo Cleaning Products Factsheet page 23 and will be used in the assessment of exposure.

Dishwashing:

As suggested in the HEEG opinion 16, the approach described in the Cleaning Products Fact Sheet will be used for the assessment of exposure. It is considered that a thickness of the liquid layer of 0.01 cm is in contact with the skin.

During hand dishwashing, it is considered that the two hands (palms and backs = 820 cm^2) are in contact with the diluted solution.

It is assumed that a professional could perform these tasks around **24 times per day.**

According to Consexpo, a dilution of the detergent of 714 has to be taken in consideration (page 51). Therefore, the concentration of PHMB in diluted solution is 0.06%/714= 0.00008%.

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL

[9] HEEG opinion 16: Biocidal products : model for dipping of hand/forearms in a diluted solution (endorsed at the TM IV 2012 and amended after TMIII 2013 to take into account changed defaults human factors values.

MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during hand dish washing	Mixing&Loading (common to dishwasher or hand dishwashing)	No PPE	1.15E-03	17%
	Application (for hand-dishwashing only)	No PPE	2.07E-03	31%
	Combined exposure	No PPE	3.22E-03	48%

For hand dishwashing, the %AEL is inferior to 100% for all tasks without PPE. In this context, the risk is considered as acceptable without PPE.

- **Exposure during detergent use on surface by wiping/mopping**

PHMB is used at a maximal concentration of 0,06 % to control the growth of bacteria and fungi in products used for care, floor care, waxes, hard surface cleaners, pre-moistened sponges or mops.

The representative use for this kind of products is wiping or mopping hard surfaces.

The respective exposure can be assessed using the surface disinfection models from the TNsG (models 1 and 3, TNsG (2002) pages 175 and 177, User guidance page 27), according to Recommandation 2 of Ad hoc Working Group on Human Exposure . These models include exposure during diluting and mixing the surfactant in water and wiping surfaces using a wrung cloth or a mop.

Considering that the detergent product is diluted by factor 20[10] in the bucket (page 86 of Consexpo Cleaning factsheet), the concentration of PHMB in diluted solution is 0.003 %.

Both Tier 1 and Tier 2 of the exposure assessment are provided:

- In Tier 1, no personal protective equipment is assumed, excepted gloves already included in the model.
- In Tier 2, professional workers are assumed to wear gloves and coated coveralls.

Clothing penetration is assumed to be 20 % (default value for coated coverall from HEEG opinion default protection factors for protective clothing and gloves agreed in TM I 2010).

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure	Hard surface	Gloves	1.21E-02	**181%**

[10] Default value from ConsExpo Cleaning Products Fact Sheet

during disinfection of surface	disinfection			
		Gloves and coverall	3.44E-03	51%

For surface disinfection, the %AEL is superior to 100% when only gloves are worn. It becomes inferior to 100% if gloves and coverall are worn.
The applicability and reliability of these mitigation measures are doubtful considering that PHMB is present in the product only as conservative. In this context, the risk is considered as unacceptable.

2.2.1.3.1.4 Use of detergent by non-professional

The product in which PHMB has been added as a conservative could be used by general public. In this context, the previous scenarios are also considered for general public.

- **Exposure during hand washed laundry**

The same models of exposure as those used for professionals are considered to determine exposure for non-professional users. However, unlike professionals, it is considered that non-professionals perform this task only 1 time per day.

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during hand washed laundry	Mixing&Loading (common to machine- or hand-laundry)	No PPE	4.80E-05	1%
	Application (for hand-laundry only)	No PPE	1.46E-03	22%
	Combined exposure	No PPE	1.51E-03	23%

For hand washing of laundry, the %AEL for mixing and loading, application and combined exposure is inferior to 100% without PPE. Therefore, the risk is considered as acceptable.

- **Exposure during pre-treatment of clothes**

The same models of exposure as those used for professionals are considered to determine exposure for non-professional users. However, unlike professionals, it is considered that non-professionals perform this task only 1 time per day.

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during pre tratment of clothes	Spot removers	No PPE	3.12E-04	5%

For spot removers, the %AEL is inferior to 100%. Therefore, the risk is considered as acceptable.

- **Exposure during hand dishwashing**

The same models of exposure as those used for professionals are considered to determine exposure for non-professional users. However, unlike professionals, it is considered that non-professionals perform this task only 1 time per day.

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during hand dish washing	Mixing&Loading (common to machine- or hand dishwashing)	No PPE	4.80E-05	1%
	Application (for hand-dishwashing only)	No PPE	8.61E-05	1%
	Combined exposure	No PPE	1.34E-04	2%

For hand dishwashing, the %AEL is inferior to 100% for all tasks. In this context, the risk is considered as acceptable.

- **Exposure during detergent use on surface by wiping/mopping**

The route of exposure will be the same as professional use: dermal route. Indeed, exposure by inhalation and oral routes are considered as not relevant.

Two phases of exposure can be expected:

- Exposure during mixing and loading of product with water

- Exposure during surface disinfection.

Exposure is determined thanks to the Consexpo approach.

For mixing and loading, the default value for dermal exposure during mixing and loading of liquid cleaner proposed in Consexpo Cleaning fact sheet is used.

For application, the approach considering a layer of 0.01 cm on area of hands and forearms proposed in Consexpo Cleaning fact sheet is applied.

The risk linked to use of detergents is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 6			Systemic Exposure (mg/kg/day)	
Exposure during disinfection of surface	Mixing and loading	No PPE	4.80E-05	1%
	Application	No PPE	7.31E-03	**109%**
	Combined exposure	No PPE	7.36E-03	**110%**

For surface disinfection, the %AEL is inferior to 100% for mixing and loading and superior to 100% for application. The risk is therefore considered as unacceptable.

2.2.1.3.2 Secondary exposure

Secondary exposure could occur by dermal contact with washed dish, cleaned clothes and cleaned surface and by oral route by indirect exposure via food

2.2.1.3.2.1 Dermal exposure from washed dish

Starting from AEL, a reverse scenario of exposure has been established. It has allowed calculating the maximum area of utensils that could be rubbed daily without risk of systemic effects. Assuming an amount of water left on dish of 0,000055 ml/cm^2 (according to Consexpo Cleaning factsheet page 51), a scenario of 100% migration from the utensils onto the skin, assuming no rinse-off or drying step and a body weight of 60 kg, the maximum rubbed area without risk of systemic effects would be 162 m^2/day

The situation where a person rubbes 162 m^2 of utensils daily is irrealist. Therefore, the risk for direct contact with residues on utensils is considered to be acceptable.

2.2.1.3.2.2 Dermal exposure from wearing clothes

Exposure to residual PHMB may be possible due to indirect or secondary exposure from clothes cleaned with detergents containing PHMB.

Residues of components of laundry detergents may remain on textiles after washing and could come into contact with the skin via migration from textile to skin.

The quantity of residues migrating to skin can be estimated by ConsExpo, using method and parameters described in the Cleaning Product Fact Sheet.

It is considered that product dries on clothes. No dermal absorption study on the dried residues is available. It was decided at the HH WG V 2016 to use the same dermal absorption value than the dilution. Although this approach is conservative, it is in line with the EFSA guidance on dermal absorption (2012).

The following parameters were used.

	Source	Adult	Child
Body weight		60 kg	15 kg
Dermal absorption value		0.60%	
Product (textile) amount worn per day	Consexpo cleaning fact sheet	1 kg	0,25 kg
Concentration of PHMB in product		0.06%	
Amount of undiluted product used for 5 kg of laundry	Consexpo cleaning fact sheet page 40	115 g	
Percentage of detergent deposited on the fabric	Consexpo cleaning fact sheet page 40	20%	
Total weight of fabric	Consexpo cleaning fact sheet page 40	5 kg	
Percent weight fraction transferred from medium to skin	Consexpo cleaning fact sheet page 40	50%	
Amount of active substance used		0.069 g	0.069 g
Amount of detergent deposited on the fabric		0.0138 g	0.0138 g
Amount of detergent deposited on the fabric		0.00276 g/kg fabric	0.00276 g/kg fabric
Dermal exposure by transfer from fabric to skin		0.00138 g	0.000345 g

The risk linked to exposure of residue is summarized below:

Exposure scenario		**Exposure**	**%AEL**
		Systemic Exposure (mg/kg/day)	
Exposure to residue of PHMB by wearing clothes	Adult	1.73E-02	**257%**
	Child	1.73E-02	**257%**

The %AEL is superior to 100%. Therefore, the risk linked to exposure of residue of PHMB by wearing of clothes is considered as unacceptable for adults and children.

2.2.1.3.2.3 Dermal exposure following contact with cleaned surfaces

Infants could be exposed to residues of preserved liquid detergents on cleaned surfaces, while crawling on these surfaces and ingesting by hand-mouth transfer. Infants could be in contact with wet or dried surfaces.

- **Wet surface**

The following parameters were used to determine exposure:

- A transfer coefficient from floor to skin (worst case) of 100%,
- The detergent product is diluted by a factor 20[11] in the bucket , thus the applied solution contains 0.003 % of PHMB,
- The solution is applied on surface with a film thickness of 0.1 mm (0.01 cm), thus the surface concentration is 0.03 mg/cm^3 x 0.01 cm = 3x10^{-4} mg/cm².
- A 10 kg child is in contact with 6000 cm^2 of cleaned surface area with their bare skin and 30% of the a.s. dislodges to the skin[12],
- From total skin exposure, 10% is transferred in mouth and 90% stay in the skin,

The risk linked to exposure of residue is summarized below:

Exposure scenario	**Exposure**	**%AEL**
	Systemic Exposure (mg/kg/day)	
Exposure to residue of PHMB : infant crawling on cleaned surface	1.23E-01	**1828%**

The %AEL is superior to 100%. Therefore, the risk linked to exposure of residue of PHMB is considered as unacceptable.

- **Dried surface**

The same parameters than wet surface were used, except the transfer coefficient of 18%.

The risk linked to exposure of residue is summarized below:

Exposure scenario	**Exposure**	**%AEL**
	Systemic Exposure (mg/kg/day)	
Exposure to residue of PHMB : infant crawling on cleaned surface	2.21E-02	**329%**

The %AEL is superior to 100%. Therefore, the risk linked to exposure of residue of PHMB is considered as unacceptable.

The product should be used in zone inaccessible to children.

[11] Default value from ConsExpo Cleaning Products Fact Sheet
[12] Default value from Consexpo Pesticide Products Fact Sheet, p.28.

2.2.1.3.2.4 Indirect exposure via food

To be noted (as discussed at HH WGIII 2017): preliminary assessment of the transfer of biocidal active substance residue into food is performed according to non-agreed guidance and therefore the following assessment is an eCA proposal.
Incidence on consumer safety following the consumption of contaminated products was assessed, considering that consumers can be exposed to residues left on dishware and surfaces treated with product containing preservatives.

No specific hydrolysis studies were provided. Based on physical-chemical properties of PHMB, the decomposition of the PHMB in normal circumstances of use is not expected and only PHMB is considered as a residue for the risk assessment.

One experimental rinsing efficacy study was provided by the applicant. The objective of this study was to measure the remaining quantity of PHMB after a standard wash with tap water of preliminary treated surfaces with solutions containing PHMB (0.03 and 2% w/w in water) tested on 4 surfaces of different material composition (stainless steel, polyvinylchloride (PVC), high density polyethlylene (HDPE) and polyvinylidene difluoride (PVDF)).

As:

- no guideline is available for rinsing efficacy study,

- no glass surface material (material mostly used in food industry) was considered,

- study mass balance was not satisfying,

- and no validation of the analytical methods was available,

the results of this study cannot be fully validated and can only be used as additional and supportive information. A default rinsing factor of 10 % has been derived in guidance document (detailed in HERA TDG, Feb 2005[13]). However, this default value cannot be confirmed by the provided rinsing study (not validated) and does not take into account the likely highly chelating properties of the substance with the treated dishware which may strongly limit the effectiveness of the rinsing. **Therefore, rinsing procedure is only considered for information in this assessment**.

Consequently, the daily exposure to PHMB was assessed with a worst case scenario, using default values from the European guidelines documents[14] (ARTFood, 2014-2015).

By this way following scenarios are considered for dishwashing and surface treatment uses:

In a first tier and conservative approach, the assessment is performed without any rinsing step procedure after the treatment and considering that all the remaining residues on treated dishes and surfaces can migrate into food.

In a second tier (informative only), a rinsing procedure is taken into account (only 10% of PHMB remain on dishes and surfaces and are available for a transfer into food).

It was considered that dishes and surfaces were cleaned with a 0.06% w/w a.s. solution. In addition, as a general approach, preserved products were considered not used pure but

[13] HERA - Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products – guidance Document Methodology – February 2005

[14] ARTfood (formerly DRAWG) : Draft guidance on estimating dietary risk from transfer of biocidal active substances into foods – non-professional uses (ARTFood Project 2) – pilot project published in June 2015 & ARTFood (formerly DRAWG) (2014) : Guidance on Estimating Transfer of Biocidal Active Substances into Foods – Professional Uses – 2014 - draft not yet published

after dilution. A default value of 0.14% (RIVM, 2006)[15] was considered to cover the most common conditions of use for detergents used for dishwashing. To cover the most common condition of use for surfaces detergents, it was considered a dilution of 1/20 (5%) of the pure preserved product. Default values used for these scenarios and risks for consumer are detailed in tables below.

[15] Cleaning products fact sheet to assess the risks for consumer, RIVM report 320104003/2006

Table 2.2-2: Parameters considered in the scenario dishwashing and risk results for consumer

Use and PT6 parameters		**Value**
Duration *(ARTFood/formerly DRAWG)*		1 day
Body weight of adult *(ARTFood/formerly DRAWG)*		60 kg
Body weight of child *(ARTFood/formerly DRAWG)*		10 kg
Area of dishes/eating utensils in daily contact with food *(ARTFood/formerly DRAWG)*		5400 cm²
Amount of water left on non-rinsed dinnerware *(ARTFood/formerly DRAWG)*		5.5×10^{-4} ml/cm^2
Percentage of preservative in preserved product		0.06% i.e. C_1= 600 mg/L = 0.6 mg/mL
Ready to use solution after dilution of the product containing preservative		0.14%
Residue transfer factor from the dishes to food	Tier I – no rinsing (all residues remain on treated dishes)	100%
	Tier II –one effective rinsing (only 10% of residues remains on treated dishes) (HERA, Feb2005)	10%
Exposure	Child/Tier I	2.5×10^{-4} mg a.s./kg b.w./d
	Adult/Tier I	4.2×10^{-5} mg a.s./kg b.w./d
	Child/Tier II	2.5×10^{-5} mg a.s./kg b.w./d
	Adult/Tier II	4.2×10^{-6} mg a.s./kg b.w./d
ADI and ARfD	Adult and child	0.12 mg a.s./kg b.w./d
Risk for consumer (% ADI or ARfD)	Child/Tier I	0.21 %
	Adult/Tier I	0.035 %
	Child/Tier II	0.021 %
	Adult/Tier II	0.0035 %

Table 2.2-3: Parameters considered in the scenario surfaces treatment and risk results for consumer

Use and PT6 specific parameters		**Value**
Duration *(ARTFood/formerly DRAWG)*		1 day
Body weight of adult *(ARTFood/formerly DRAWG)*		60 kg
Body weight of child *(ARTFood/formerly DRAWG)*		10 kg
Area daily in contact with food *(ARTFood/formerly DRAWG)*		2000 cm²
Water film thickness on treated surfaces *(ARTFood/formerly DRAWG)*		20 µm = 0.0020 cm
Percentage of preservative in preserved product		0.06% i.e. C_1= 600 mg/L = 0.6 mg/mL
Ready to use solution after dilution of the product containing preservative		5%
Residue transfer factor from the surfaces to food	Tier I – no rinsing (all residues remain on treated surfaces)	100%
	Tier II – one effective rinsing (only 10% of residues remain on treated surfaces)	10%
Exposure	Child/Tier I	$1.2x10^{-2}$ mg a.s./kg b.w./d
	Adult/Tier I	$2x10^{-3}$ mg a.s./kg b.w./d
	Child/Tier II	$1.2x10^{-3}$ mg a.s./kg b.w./d
	Adult/Tier II	2.10^{-4} mg a.s./kg b.w./d
ADI and ARfD	Adult and child	0.12 mg a.s./kg b.w./d
Risk for consumer (% ADI or ARfD)	Child/Tier I	10%
	Adult/Tier I	1.67%
	Child/Tier II	1%
	Adult/Tier II	0.17%

According to results previously obtained for each scenario, the cumulative exposure of child and adult can be resumed as follow:

Table 2.2-4: Risk characterization for oral indirect exposure (cumulative approach)

Oral indirect exposure assessment		**Cumulative exposure**	
General public considered	**Tier**	**Oral exposure** (mg a.s./kg b.w./d)	**Fraction of ADI/ARfD**
Child	Tier I (no rinsing)	$12.25x10^{-3}$	10.21%
Adult	Tier I (no rinsing)	$2.04x10^{-3}$	1.70%
Child	Tier II (with 1 rinsing step)	$12.25x10^{-4}$	1.02%
Adult	Tier II (with 1 rinsing step)	$2.04x10^{-4}$	0.17%

Cumulated dishwashing and surface exposure scenarios show that exposure to PHMB (used as preservative for detergents) and without any rinsing step would be below the defined ADI and ARfD of 0.12 mg/kg b.w./day (10.21% of the ADI or ARfD for a child and 1.70% for an adult).

These scenarios are considered as covering the non-professional as well as the professional uses of PHMB as in-can preservative (PT6). Consequently, risk for consumer following transfer into food from residues left on treated dishware and surfaces with products containing PHMB as PT6 is considered acceptable.

Conclusion for Indirect exposure via food:

Risk for consumer following transfer into food from residues left on treated dishware and surfaces with products containing PHMB as in-can preservative is considered acceptable.

2.2.2 Risk characterisation for the environment

2.2.2.1 Fate and distribution in the environment

2.2.2.1.1 Abiotic degradation

2.2.2.1.1.1 Hydrolysis as a function of pH

The potential of hydrolysis of the PHMB was assessed with a GLP-study following the OECD guideline 111. The test item was incubated in the dark at 50°C during 5 days. At pH 4, 7 and 9, no degradation occurred in the solutions of the test item.

As a consequence, PHMB should be considered as hydrolytically stable.

2.2.2.1.1.2 Photolysis in water

As PHMB does not absorb visible light, its photo-transformation in water is considered negligible.

2.2.2.1.1.3 Photo-oxidation in air

Estimation of photo-transformation in air of PHMB has been performed with AOPWIN program version 1.92 developed by the US EPA and Syracuse Research Corporation, USA. According to this estimation, considering reaction of PHMB with OH-radicals and ozone, the half-life of PHMB in the atmosphere is 0.213 days (daytime: 24h; 5E+05 OH molecules/cm^3).

2.2.2.1.2 Biodegradation

2.2.2.1.2.1 Ready biodegradation

The ready biodegradability of the active substance PHMB was assessed by performing a GLP-study following the OECD guideline 310. The test item was tested at a nominal concentration of 23 $mg.L^{-1}$ (*i.e.* 10.04 mg $C.L^{-1}$) with an inoculum (4 $mg.L^{-1}$) originated from a domestic waste water treatment plant. The degradation of the test material was determined by following the CO_2 evolution in test vessels.

After 28 days of incubation, no degradation of the active substance PHMB was detected in the test treatment. It was demonstrated in this study that PHMB incubated at a nominal concentration of 23 $mg.L^{-1}$ completely inhibited sodium benzoate degradation throughout the 28-day incubation (*i.e.* 101% reduction in degradation of the sodium benzoate in presence of PHMB in the toxicity control), which induced the absence of PHMB degradation during the test.

The study should be considered as reliable with restrictions, because the concentration of the active substance used for this test induced a complete inhibition of the microorganism activity. Therefore it was not possible to assess the intrinsic property of the active substance to be degraded in the ready biodegradability test conditions.

The ready biodegradability of PHMB was also studied according to standard guideline OECD301D (closed bottle test). Two concentrations were tested, 4 and 8 mg PHMB/L. Non adapted activated sludge microorganisms from a domestic wastewater plant was supplied by a municipal sewage treatment plant. The final concentration of the inoculum in the test medium was $10^{\wedge 4}$ bacteria

per liter. The biodegradation was determined by following the dissolved oxygen in the incubation bottle during exposure.

After 28 days of incubation, no degradation of PHMB was observed for the tested concentrations 4 and 8 mg PHMB/L. As revealed by the toxicity control treatment, the tested concentrations of PHMB significantly inhibited microbial activity for the entire duration of the study.

To conclude, PHMB is considered as not readily biodegradable, and toxic to the aerobic activated sludge microorganisms at the lowest tested concentration of 4 mg PHMB/L.

2.2.2.1.2.2 STP compartment

The elimination and biodegradation of [^{14}C]PHMB in a continuously operated sewage treatment simulation system (Husmann unit) was determined according to the OECD standard guideline 303A.

The final DOC (dissolved organic carbon) concentration of the influent was in the mean 100 mg.L^{-1}.The DOC elimination of the dosed synthetic sewage was regularly measured as an internal control to monitor the biological activity of the sludge. The DOC elimination of 80-97% demonstrated a sufficiently high biological activity of the sludge throughout the test period.

After a settling-in period (10 days) for the stabilization of the test system, the test item was intermittently dosed to the Husmann unit as a mixture of unlabelled and ^{14}C-labeled PHMB. The final target concentration was 0.5 mg.L^{-1} PHMB. The correct dosage of [^{14}C]PHMB was analytically verified by liquid scintillation counting (LSC), showing an acceptable range of 82-128% of the nominal concentration.

During the adaptation period (9 days) and during the following plateau phase (19 days) the total radioactivity was frequently measured by LSC in samples collected from the effluent and from the sludge suspension. The formation of ^{14}CO2 was regularly measured in the discharged air from the air-tight closed Husmann unit.

19% of the applied PHMB was found in the aqueous effluent of the continuous operating sewage treatment simulation system (average of 16 values during plateau phase). This represents a mean elimination rate of 81% of the dosed PHMB.

The dissipation was mainly caused by the adsorption and accumulation of the test item onto the sludge biomass.

The formation of CO_2 was minimal (2-4%), indicating that no relevant ultimate biodegradation of PHMB to CO_2 occurred under the test conditions.

To conclude, PHMB had no significant adverse effect on the activity of the sludge micro-organisms at the tested influent concentration of 0.5 mg/L or due to the test item accumulation in the sludge suspension during the test.

2.2.2.1.2.3 Aquatic compartment

The dissipation of [^{14}C] PHMB in two aquatic systems (river and pond) was investigated at a rate of 50 mg.L^{-1} under aerobic conditions at 20 °C in the dark, in a GLP-study following the OECD standard guideline 308.

Total recoveries of the applied radioactivity (mass balance) averaged 96.6 ± 3.3% and 93.6 ± 3.3% in the river and pond systems, respectively.

Immediately after the application of [^{14}C] PHMB (time 0), >98% of the applied radioactivity was found in the water phase of the river and pond systems. Thereafter, the radioactivity in the water decreased rapidly to levels < 75% by 6 hours, < 65% by day 1 and < 5% by day 9 in both systems. Concurrently, the radioactivity in the sediment increased. Most of the radioactivity in the sediment was non-extractable and exceeded 80% by day 9. The extractable radioactivity was consistently below 5% for both systems throughout the study. Radioactive CO_2 reached 2.9% in both aquatic systems by the end of the study on day 27. Organic volatiles were below 0.1%.

Those results demonstrated that the biodegradation of the PHMB in water/sediment systems should be considered as negligible. Moreover, the rapid dissipation from the water column is mainly due to adsorption to sediment particles with the formation of more than 80% of the applied radioactivity as bound residues, included less than 5% as extractable ones. The identification and quantification of the degradation products has not been investigated by the applicant because of the polymeric nature of the active substance.

It should be raised that the tested concentration (50 mg.L^{-1}) could have toxic effect on the inoculum, with a potential consequence on the biodegradation result of the test. Indeed according to the ready biodegradability tests provided by the applicant, toxic effect on the inoculum was observed from concentration of 4 mg.L^{-1}. No analysis was performed during the present study to check the potential inhibitory effect of the PHMB at 50 mg.L^{-1} during the 27 days of incubation. As a consequence, the potential inhibitory effect on micro-organisms of the PHMB at the concentration of 50 mg.L^{-1} cannot be excluded.

From these results, the applicant calculated dissipation half-life for the water phase and the whole system for both water systems. In accordance with the Focus document (2006)[16] which mentioned that the assessment of the persistence of a substance in the aquatic environment should be based on degradation half-life values, not on dissipation half-life values, the calculated dissipation trigger values were not considered for the environmental risk assessment of the PHMB. Considering that no significant degradation occurred during the test, a default half-life value of 1x10^6 days will be considered for the environmental risk assessment.

2.2.2.1.2.4 Soil

The environmental fate of ^{14}C-PHMB was investigated in four field soils under aerobic conditions in a GLP-study following the OECD standard guideline 307. Fresh soil samples (100 g dry weight) were transferred to 1 liter glass metabolism flasks. The samples were treated with ^{14}C-PHMB at a rate of 200 mg/per kg soil dry weight. PHMB was applied as a mixture of radiolabelled and unlabelled material.

Mean recoveries for all time points were 96.8% ± 1.4% of applied for soil I, 95.6 ± 2.0% for soil II, 94.1 ± 2.2% for soil III and 95.4 ± 2.3% for soil IV.

[16] Guidance Document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration. Final report of the work-group on degradation kinetics of FOCUS. SANCO/10058/2005, version 2.0, June 2006.

Immediately after application of the [^{14}C]PHMB, the majority of the radioactivity was found in the non-extractable fraction. This may lead to the conclusion that the polymer PHMB binds at least initially by physical adsorption to the soil matrix. Overall, the non-extractable radioactivity decreased slightly after time 0 to reach 84.1 – 86.5% by the end of the study on day 60. The slight reduction in non-extractable radioactivity after time 0 coincided with modest formation of radioactive CO_2 from day 7 onwards to reach 3.2 – 3.5% by the end of the study. Considering that less than 5% of mineralisation occurred during the 60 days of incubation, the degradation of the PHMB in the soil is considered negligible.

The radioactive contents of the extracts were below 10% of the applied amounts for all soils and intervals, except for soil I at time 0, were 13.2% of applied was extractable. After time 0, the extractable amounts were relatively stable throughout the study: 8.4 – 9.9% in soil I, 4.9 – 5.1% in soil II, 2.6 – 2.8% in soil III and 3.8-4.8% in soil IV. The extracts are likely to consist of multiple components given that PHMB itself is a mixture of numerous polymers of molecular weights in the range of 500 to 6000 Dalton. While lower molecular weight components and possible degradates of PHMB may have been more available for extraction, the higher molecular weights may have been insoluble in presence of soils colloids and would then constitute the non-extractable fraction of PHMB.

It should be raised that the identification and quantification of the degradation products has not been investigated by the applicant because of the polymeric nature of the active substance.

The decline of PHMB in soil was based on the declining levels of extractable radioactivity measured during the study. Rates of decline of PHMB in the four soils were determined by the applicant in accordance with FOCUS Guidance (2006). However, in accordance with the FOCUS document (2006) which mentioned that the assessment of the persistence of a substance in the soil should be based on degradation half-life values, not on dissipation half-life values, the calculated dissipation trigger values were not considered for the environmental risk assessment of the PHMB. Considering that no degradation (*i.e.* less than 5% of mineralisation after 60 days) occurred during the test, a default half-life value of $1x10^6$ days will be considered for the environmental risk assessment.

2.2.2.1.3 Distribution

The sorption properties of PHMB were studied in four soils and one sewage sludge using the batch equilibrium method in accordance with the OECD standard guideline 106. The test soils included a range of textural classes, with pH values between 4.6 and 7.9 and organic carbon contents between 0.7 and 2.9%. The sewage sludge had an organic carbon content of 44.8%. PHMB was applied as a mixture of radiolabelled and unlabelled material.

Preliminary experiments were conducted to ascertain appropriate solid-to-solution ratios, the time required to achieve equilibrium between PHMB in solution and the methodology to be used. The initial solution concentration of PHMB was 0.5 mg/L in aqueous 0.01M calcium chloride. Solid-to-solution ratios of 1:5, 1:20 and 1:200 w/v were used for the soils, and 1:200 and 1:1000 w/v were used for the sewage sludge. An equilibration time of 4 hours was used for the adsorption and desorption phases. The mass balance was found to be between 103.1% and 135.3%, the last one being clearly an outlier due to the interference in the combustion process

(residue of 110.7%). In conclusion, recovery is acceptable when applying strict protocol of rinsing and using borosilicate glass vessels.

Samples were analysed by liquid scintillation counting to determine the concentrations of radioactivity present in solution and solid during the adsorption and desorption phases. Results indicated a high degree of adsorption (>87% of applied radioactivity) with very little desorption of radioactivity (<4% applied radioactivity). Freundlich adsorption and desorption parameters were not determined. Due to its polymeric and highly charged polymeric structure, PHMB was instantaneously adsorbed to soil particles with little desorption possibility.

Based on screening test conducted with the four soils and sewage sludge, Kd and Koc values was derived considering 4 hours equilibrium time and the arithmetic mean value were used for risk assessment.

	SLUDGE (soil solution ratio 1:1000)	**SOILS (soil:solution ratio 1:200)**			
		Bromsgrove	**Calke**	**Evesham**	**Warsop**
Adsorbed amount (% AR)	73.5	92.5	87.9	96.2	93.6
Amount in aqueous supernatant (% AR)	26.5	7.5	12.1	3.8	6.4
Water volume (mL)	20	200	200	200	200
Soil mass (g)	0.02	1	1	1	1
%OC	44.8	0.7	2.9	2.6	1.4
K_d	**2773**	**2467**	**1453**	**5063**	**2925**
K_{oc}	**6191**	**352381**	**50100**	**194737**	**208929**
Arithmetic Mean K_d: 2977					
Arithmetic Mean K_{oc}: 201537					

2.2.2.1.4 Volatilisation

Considering its polymeric form, PHMB is not considered volatile and is not expected to volatilise to air in significant quantities.

2.2.2.1.5 Accumulation

The active substance PHMB is a polymer which consists of a high number of polymer molecules distributed over a range of molecular weights. HPLC profiles provided by the applicant indicated that at least 85% of molecules exhibit a molecular weight higher than 700 g/mol. PHMB exhibits a number average molecular weight (Mn) of 1415; this high value is considered as an indication of limited bioaccumulation potential. Moreover, in case where a BCF value is not available, Guidance on the Biocidal Products Regulation, Volume IV Environment, Part B Risk Assessment for active substances (ECHA guidance - May 2015)) recommends predicting a BCF for fish from the relationship between Kow and BCF.

Considering that the Kow for PHMB is 4.09 x 10^{-3} (at 22.0°C) [Log Pow = -2.39], and the following equation: Log BCF_{fish} = 0.85 x LogKow – 0.70; the estimation of BCF_{fish} for PHMB is 1.86 x 10^{-3} L/kg

This result indicates that the potential of bioconcentration of PHMB is low.

eCA is of the opinion that this argumentation should be considered relevant for 85% of PHMB (*i.e.* fraction of the PHMB exhibiting a molecular weight higher than 700 g/mol), and not relevant for 15% of the PHMB, *i.e.* fraction of the PHMB exhibiting a molecular weight lower than 700 g/mol, which could penetrate into organisms.

However, given the relationship between water solubility and Kow, a lower solubility would lead to a higher Kow and thus a higher BCF. As the smallest oligomers is expected to have higher water solubility than larger oligomers. It can therefore expect the smallest oligomers to have a lower Kow and thus a lower BCF. Based on this theoretical consideration, bioaccumulation potential of low MW oligomers is not expected. This view is supported by the measured Kow value of the whole PHMB.

As a conclusion, based on its measured Kow, and considering the arguments mentioned above, the PHMB is considered to have a low potential of bioaccumulation.

2.2.2.2 Effects assessment on environmental organisms (active substance)

2.2.2.2.1 Aquatic organisms

Acute and chronic ecotoxicity tests were available for each aquatic trophic level. The results are presented in the table below:

Trophic level	Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg/L)[1]	
				design	duration	NOEC EC10	LC_{50} / EC_{50}
Fish (acute)	OECD TG 203	*Oncorhynchus mykiss*	Mortality	Semi-Static	96 h	-	0.2676
Fish (chronic)	OECD TG 210	*Pimephales promelas*	Hatching success Survival Dry weight/ total length	Flow-through	28 d (post hatch)	4.98E-03 15.3E-03 15.3E-03	>0.153 0.0455 0.0485
Invertebrates (acute)	OECD TG 202	*Daphnia magna*	Immobilisation	Semi-Static	48 h	-	0.11707
Invertebrate (chronic)	OECD TG 211	*Daphnia magna*	Reproduction Growth Mortality	Semi-static	21 d	5.44E-03 14.6E-03 5.44E-03	12.1E-03 - 9.72E-03
Algae	OECD TG 201	*Pseudokirchneriella subcapitata*	Growth inhibition	Static	72 h	**0.945E-03** 2.79E-03	**20.6E-03**

[1] As PHMB, geometric measured concentration

Acute and chronic toxicity data are available for algae, aquatic invertebrates and fish.
On acute basis, the alga is the most sensitive taxonomic group. The acutely most sensitive species have an EC50 value of 20.6E-03 $mg.L^{-1}$.

On chronic basis, the alga is the most sensitive group. The chronic most sensitive has a NOEC value of 9.45E-04 $mg.L^{-1}$.

Therefore PNEC for surface water ($PNEC_{water}$) is based on the algae NOEC using an assessment

factor of 10 considering that chronic toxicity data are available for 3 taxonomic groups (recommendation from ECHA guidance vol. IV, part B (2015), table 19). Therefore, the $PNEC_{water}$ value used for risk assessment is:

$PNEC_{water}$ = 9.45E-05 $mg.L^{-1}$

2.2.2.2.2 Inhibition of aquatic microbial activity

The toxicity to bacteria of PHMB P20 (20.4% of PHMB) was investigated in GLP-compliance according to OECD guideline 209. The results are presented in the table below.

Guideline / Test method	Species / Inoculum	Endpoint / Type of test	Exposure		Results (mg/L)[1]		
			design	duration	NOEC	EC_{50}	EC_{80}
OECD TG 209	Activated sludge from treatment plant treating predominantly domestic sewage	Respiration inhibition	Static	3 h	6.35	32.3	ND

[1] As PHMB, nominal concentration

Several data provided by the applicant can be used to assess the ecotoxicity of the PHMB. By taking into account the corresponding assessment factor described in the table 20 of the ECHA GUIDANCE on BPR VOL IV, part B (2015) for each type of test, several $PNEC_{STP}$ value can be calculated:

Type of test	Value	AF	PNEC (mg/L)
Respiration inhibition test according to OECD TG 209	EC50 = 32.3 $mg.L^{-1}$	100	**0.323**
Ready biodegradability test according to OECD TG 310	Inhibitory effect at the tested concentration (23 $mg.L^{-1}$)	10	n.d.
Ready biodegradability test according to OECD TG 301D	Inhibitory effect at the tested concentrations (4 and 8 $mg.L^{-1}$)		
Simulation test – aerobic sewage treatment – according to OECD TG 303A	No inhibitory effect at the tested concetration (0.5 $mg.L^{-1}$)	1	**0.5**
n.d. – not determined considering that any tested concentration induced no inhibitory effect.			

The lowest $PNEC_{STP}$ was considered for the risk assessment, *i.e.* **$PNEC_{STP}$ = 0.323 $mg.L^{-1}$** which is in accordance with the results observed in biodegradation tests**.**

2.2.2.2.3 Sediment dwelling organisms

A 28-day spiked sediment study performed with sediment dwelling organisms shows no effects at any concentration. Therefore ,a NOEC of 909 mg kg^{-1} dry weight sediment from the 28 day toxicity test on *Chironomus riparius* is derived.

Nevertheless, it should be noted that during the exposure period, the organisms were fed with a fish food suspension. About feeding of the organism during the test, the standard guideline OECD218 mentioned that [§31, p.7]:

"*When testing strongly adsorbing substances (e.g. with log Kow > 5), or substances covalently binding to sedi-ment, the amount of food necessary to ensure survival and natural growth of the organisms may be added to the formulated sediment before the stabilisation period.*".

As a consequence the feeding method applied for the test does not follow the standard guideline, considering the high adsorption properties of the PHMB. The results from this study should actually be taken with caution. Hence, this study was not considered for the PNEC derivation.

A new sediment-water *Lumbriculus* toxicity test using PHMB-spiked sediment was performed in accordance with OECD standard guideline 225 and was provided by the Applicant during the peer review process. It was decided at the WG ENV III-17 to include this new data. This study and the proposed new PNEC were the subject of an adhoc follow up discussion until 14th of July 2017. The NOEC, based on mean measured concentrations, derived from this 28-day spiked sediment study is equal to 174 $mg.kg^{-1}$ dwt sediment of a.s., equivalent to 37.82 $mg.kg^{-1}$ wwt sediment of a.s. on *Lumbriculus variegatus*.

During the adhoc follow up discussion, it was agreed that the new sediment study should be included in the assessment, leading to a NOEC = 174 mg/kg dwt (equivalent to 37.82 mg/kg wwt) and should be used to derive the PNECsediment. This value has not been normalised with organic carbon content since normalisation is not in line with the current guidance on BPR Vol VI Part B (2015) (table 22). An AF of 100 should be applied to derive the PNECsediment, taking into account that only the test on *Lumbriculus variegatus* is considered relevant for PHMB since the Chironomid study is considered unreliable

Thus based on this data, the PNECsediment freshwater for PHMB is 0.378 mg a.s. kg^{-1} wet weight.

2.2.2.2.4 Terrestrial compartment

As mentioned in the section 9.2 of the ECHA GUIDANCE on BPR VOL.IV, PART A (2014), all effect concentrations from earthworms, terrestrial plants and terrestrial micro-organisms should be converted to the standard soil organic matter content (3.4%), or organic carbon (2.0%) before choosing one effect value for derivation of the PNEC. As a consequence, all toxicity thresholds from earthworms, terrestrial plants and terrestrial micro-organisms provided by the applicant were standardized to the standard soil organic matter content (3.4%), according the equation 71 of the ECHA GUIDANCE on BPR VOL.IV, PART B (2015).

Terrestrial organism	Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results (mg/kg dwt)[1]		
				design	duration	$NOEC_{(standard)}$	$LOEC_{(standard)}$	$EC_{50(standard)}$
Micro-organisms	OECD TG 216	*Soil microflora*	Nitrification	Sandy loam (field soil)	28 d	2127.7	ND	> 2127.7
	OECD TG 217	*Soil microflora*	Respiration	Sandy loam (field soil)	28 d	2127.7	ND	> 2127.7
Earthworms	OECD TG 207	*Eisenia fetida*	Mortality	Artificial substrate	14 d	68.34	≥ 68.34	≥ 68.34

[1] Expressed as PHMB active substance (nominal concentration), original data are normalised for standard soil with an organic carbon of 2.0% or organic matter of 3.4%.

In addition, the applicant provided an acute toxicity test to plant, following the OECD standard guideline 208.

The study is considered non acceptable by eCA as the active substance was applied onto soil by spraying. Because of this mode of application, the present study could not be considered in a regulatory purpose for a biocide intended to be used as a disinfectant. In order to be considered, PHMB should have been incorporated into the soil, in order to mimic the expected route of exposure of PHMB used as a disinfectant in PT01 to PT06.

As a consequence, reliable data are available only for terrestrial micro-organisms and earthworms (acute toxicity). Therefore PNEC for soil ($PNEC_{soil}$) is based on the earthworm LC50 using an assessment factor of 1000 (recommendation from ECHA GUIDANCE on BPR VOL IV, part B (2015)).

$PNEC_{soil}$ = 6.83E-02 $mg.kg^{-1}_{dwt}$ = 6.05E-02 $mg.kg^{-1}_{wwt}$

2.2.2.3 Summary of PNEC values

Compartment	PNEC	Basis
Freshwater	9.45E-05 $mg.L^{-1}$	Algae long term NOEC(growth rate) = 9.45E-04 $mg.L^{-1}$, with an assessment factor of 10 (*c.f.* table 19 of ECHA GUIDANCE on BPR VOL IV, part B (2015))
Sediment-	3.78E-01 $mg.kg^{-1}_{wwt}$	*Lumbriculus variegatus* 28d NOEC = 37.82 mg/kg wwt , with an assessment factor of 100 (*c.f.* table 22 of ECHA GUIDANCE on BPR VOL IV, part B (2015))
Terrestrial	6.05E-02 $mg.kg^{-1}_{wwt}$	Normalised with organic carbon content EC50 derived from the acute toxicity on earthworms = 60.47 mg a.s. kg^{-1}_{wwt}, with an assessment factor of 1000 (*c.f.* table 23 of ECHA GUIDANCE on BPR VOL IV, part B (2015))
Microorganisms in a STP	0.323 $mg.L^{-1}$	Inhibition of respiration (OECD209) EC50 = 32.3 $mg.L^{-1}$, with an assessment factor of 100 (*c.f.* table 20 of ECHA GUIDANCE on BPR VOL IV, part B (2015))

2.2.2.4 Environmental effect assessment (product)

No additional data on the environment effects of the biocidal products were submitted. The risk assessment is based on the effect of the active substance PHMB.

2.2.2.5 PBT and POP assessment

According to the annex XIII of the REACH regulation EC/1907/2006, substances are classified as PBT when they fulfill the criteria for all three inherent properties Persistent (P), Bioaccumulable (B), Toxic (T), and/or vPvB when they fulfill the criteria the two inherent properties very Persistent (vP), very Bioaccumulable (vB).

2.2.2.5.1 Persistence criteria

According to the annex XIII of the REACH regulation, criteria for substance to be persistent (and very persistent) are fulfilled when:

- $T_{1/2}$ in marine water > 60 days (60 days for vP criterion) or,
- $T_{1/2}$ in fresh or estuarine water > 40 days (60 days for vP criterion) or,
- $T_{1/2}$ in marine sediment > 180 days or,
- $T_{1/2}$ in freshwater sediment > 120 days (180 days for vP criterion).
- $T_{1/2}$ in soil > 120 days (180 days for vP criterion).

According to study results on biodegradability of active substance PHMB in STP, water/sediment, and soil compartment (c.f. section 2.2.2.1.2), **PHMB fulfills the P and vP criteria**:

- for soil compartment, not extractable residues are > 80% in all tested soils, and mineralization is <5% over the 60 days of incubation. Considering that no degradation occurred during the test, a default half-life value of $1x10^6$ days was considered for the environmental risk assessment.
- for surface water, DT50 in whole system is greater than 6 months at 20°C, non-extractable > 80%, and mineralisation is <3% after 27 days. Considering that no degradation occurred during the test, a default half-life value of $1x10^6$ days was considered for the environmental risk assessment.

2.2.2.5.2 Bioaccumulation criteria

According to the annex XIII of the REACH regulation, criteria for substance to be bioaccumulable are fulfilled when the bioconcentration factor (BCF) exceeds a value of 2000 L/kg. Moreover, a substance is considered to potentially fulfill the B criteria when log Kow exceeds a value of 4.5.

The active substance PHMB is a polymer which consists of a high number of polymer molecules distributed over a range of molecular weights. HPLC profiles provide by the applicant indicated that at least 85% of molecules exhibit a molecular weight higher than 700 g/mol. PHMB exhibits a number average molecular weight (Mn) of 1415; this high value is considered as an indication of limited bioaccumulation potential. Moreover, in case where a BCF value is not available, ECHA GUIDANCE VOL.IV, PART B (2015) recommends predicting a BCF for fish from the relationship between Kow and BCF.

Considering that the Kow for PHMB is 4.09×10^{-3} (at 22.0°C) [Log Pow = -2.39], and the following equation: Log BCF_{fish} = 0.85 x LogKow – 0.70; the estimation of BCF_{fish} for PHMB is 1.86×10^{-3} L/kg:

This result indicates that the potential of bioconcentration of PHMB is low.

eCA is of the opinion that this argumentation should be considered relevant for 85% of PHMB (*i.e.* fraction of the PHMB exhibiting a molecular weight higher than 700 g/mol), and not relevant for 15% of the PHMB, *i.e.* fraction of the PHMB exhibiting a molecular weight lower than 700

g/mol, which could penetrate into organisms.

However, given the relationship between water solubility and Kow, a lower solubility would lead to a higher Kow and thus a higher BCF. As the smallest oligomers are expected to have higher water solubility than larger oligomers. It can therefore be expected that the smallest oligomers wouldo have a lower Kow and thus a lower BCF. Based on this theoretical consideration, bioaccumulation potential of low MW oligomers is not expected. This view is supported by the measured Kow value of the whole PHMB.

As a conclusion, based on its measured Kow, and considering the arguments mentioned above, the PHMB is considered to have a low potential of bioaccumulation, and hence does not fulfill the B and vB criteria.

2.2.2.5.3 Toxicity criteria

According to the annex XIII of the REACH regulation, the toxicity criterion is fulfilled when the chronic NOEC for aquatic organism is less than 0.01 mg/L or when the substance meets the criteria for classification as carcinogenic (1A or 1B), germ cell mutagenic (1A or 1B) or toxic for reproduction (1A, 1B or 2).

Based on ecotoxicity on the most sensitive species *Pseudokirchneriella subcapitata* (i.e. NOEC = 9.45E-04 mg/L of a.s.), **active substance PHMB is considered to fulfill T criteria**.

Therefore, PHMB is not considered to fulfill the PBT nor vPvB criterion. **Anyhow, as PHMB fulfills the criteria of vP and T, PHMB should be considered as a candidate for substitution, according to the article 10 of the Biocides Regulation EU/528/2012.**

2.2.2.5.4 POP assessment

According to the screening criteria described in the Annex D of the Stockholm convention, PHMB is not a POP.

2.2.2.6 Environmental exposure assessment

The active substance, polyhexamethylene biguanide (PHMB), is used as an in-can preservative in a number of products, (PT6). The use pattern for this product type is described in more detail under Section 3.1 above. In accordance with the TAB (2015)[17], intended use of the products corresponds to the following sub-group: product type 6.1. – Washing and cleaning fluids and human hygienic products.

According to the general information provided above, an environmental exposure assessment is required for the "Formulation" and "Use" stages of the preserved product. When possible and relevant, the two available approaches based on consumption data an on tonnage data are applied to conduct the exposure assessment. The tonnage values are given by the applicant as confidential data.

For the formulation phase of preserved products, the tonnage approach only is applied to determine the predicted environmental exposure for the intended uses.

[17] ECHA (2015) - Technical Agreement for Biocides (TAB), September 2015.

For the "use" phase (use and service life of preserved products), the tonnage approach is applied to determine the predicted environmental exposure for the PT6.1 uses. A more targeted assessment based on consumption parameters was also undertaken for the two sub-scenarios. For the product type 6 (In-can preservatives) an ECB Environmental Emission Scenario Document (ESD)[18] is available to address the "Use" stage of preserved products. Due to the wide-ranging uses of In-can preservatives this document is only a framework document and it refers to other ESDs where the use pattern of the product requiring In-can preservation is better described.

The sub-scenarios, for which an assessment based on consumption parameters was made, are:

PT6.1.1 – Washing and cleaning fluids (human hygienic products).

PT6.1.2 – Washing and cleaning fluid (general) and other detergents:

Professional use: To cover at best the professional use of PHMB as in-can preservative for washing and cleaning fluids, emission scenarios based on ESD PT2[19] has been considered for laundry and surface cleaning. The release of disinfectants used for doing biologically contaminated laundry from hospitals was estimated by this emission scenario. Emissions from the preservation of detergents used for professional surface cleaning have been also assessed, in accordance with the conclusion of the WG-V-2015.

Amateur use: To take into account a maximum of PHMB uses as detergents and household products, an assessment based on an average consumption was undertaken for calculating the releases of disinfectants used in human hygiene biocidal products and in washing and cleaning products (Environmental Emission Scenario Document (ESD) [20] for the product type 1). In order to carry out the most exhaustive assessment, the use of different products for human hygiene, and for washing and cleaning surface has been considered. Finally a cumulative assessment of all these uses was proposed. The average consumption of detergent per inhabitant per day has been revised according to the conclusions of the WG IV-2015 and WG-V-2015.

2.2.2.7 Risk characterisation

To carry out a quantitative risk assessment for the environment when PHMB is used as PT6.1, the PEC values were compared to the respective PNEC values for the different compartments, resulting in the following PEC/PNEC ratios summarised in the table below.

[18] European Commission, ESD for Biocides used as In-can Preservatives (Product type 6). January 2004.

[19] Supplement to the methodology for risk evaluation of biocides: Environmental Emission Scenarios for Product Type 2: Private and public health area disinfectants and other biocidal products (sanitary and medical sector) - RIVM. March 2001

[20] Environmental Emission Scenarios for biocides used as human hygiene biocidal products (Product type 1) - European Commission DG ENV/RIVM. January 2004.

Table 2.22-4 - PEC/PNEC ratios for PHMB use as PT6.1.

Use	Approach	STP		Surface water		Sediment		Soil		Groundwater
		PEC [$mg.L^{-1}$]	PEC / PNEC	PEC [$mg.L^{-1}$]	PEC / PNEC	PEC [$mg.kg^{-1}_{wwt}$]	PEC / PNEC	PEC [$mg.kg^{-1}_{wwt}$]	PEC / PNEC	PEC [$\mu g.L^{-1}$] (**)
PT6.1 - Formulation	Tonnage	(***)	<1	(***)	<1	(***)	**>1**	(***)	**>1**	<0.001
PT6.1 - Professional uses	Tonnage	(***)	<1	(***)	<1	(***)	<1	(***)	**>1**	<0.001
	Consumption	8.32E-03	2.58E-02	6.39E-04	**6.76E+00**	2.80E+00	**7.4E+00**	1.32E+00	**2.18E+01**	<0.001
PT6.1 - Amateur uses	Tonnage	(***)	<1	(***)	<1	(***)	<1	(***)	<1	<0.001
	Consumption	1.11E-02	3.44E-02	8.54E-04	**9.04E+00**	3.74E+00	**9.9E+00**	1.76E+00	**2.92E+01**	<0.001
PT6.1 - Cumulative emission for Professional and amateurs uses	Consumption	1.94E-02	6.02E-02	1.49E-03	**1.58E+01**	6.54E+00	**1.73E+01**	3.08E+00	**5.10E+01**	<0.001

(**) – According to groundwater concentration modelized by FOCUS PEARL 4.4.4 and compared to the maximum permissible concentration set for drinking water by the Directive 98/83/EC of 0.1 $\mu g.L^{-1}$.
(***) – Confidential.

2.2.2.7.1 Aquatic compartment (including sediment) and STP

As shown in the Table 2.22-4:

- The formulation of products containing PHMB as PT6.1 induces PEC/PNEC ratios < 1 for STP and surface water, and PEC/PNEC ratios > 1 for sediment;
- The professional uses of products containing PHMB as PT6.1 induce:
    - Based on tonnage approach, PEC/PNEC ratio < 1 for STP , surface water and sediment;
    - Based on consumption rate approach, PEC/PNEC ratio < 1 for STP, and PEC/PNEC ratio > 1 for surface water and sediment;
- The amateur uses of products containing PHMB as PT6.1 induce:
    - Based on tonnage approach, PEC/PNEC ratios < 1 for STP, surface water and sediment;
    - Based on consumption rate approach, PEC/PNEC ratio < 1 for STP, and PEC/PNEC ratio > 1 for surface water and sediment;
- Cumulative emission for professional and amateurs uses induces, based on consumption rate approach, PEC/PNEC ratio < 1 for STP, and PEC/PNEC ratio > 1 for surface water and sediment.

In conclusion, the use of PHMB as PT6.1 leads to unacceptable risks for the aquatic compartment.

2.2.2.7.2 Atmosphere

As a polymer, PHMB can be considered as not volatile. Consequently, atmospheric emission resulting from the proposed use will be negligible. It is therefore considered that the resulting level of risk to biota is insignificant and does not give cause for concern.

2.2.2.7.3 Terrestrial compartment and groundwater

As shown in the Table 2.22-4, for the soil compartment:

- The formulation of products containing PHMB as PT6.1 induces PEC/PNEC ratios > 1;
- The professional uses of products containing PHMB as PT6.1 induce:
    - Based on tonnage approach, PEC/PNEC ratio > 1;
    - Based on consumption rate approach, PEC/PNEC ratio > 1;
- The amateur uses of products containing PHMB as PT6.1 induce:
    - Based on tonnage approach, PEC/PNEC ratios < 1;
    - Based on consumption rate approach, PEC/PNEC ratios > 1;

- Cumulative emission for professional and amateurs uses induces, based on consumption rate approach, PEC/PNEC ratio > 1.

Predicted PHMB concentrations in groundwater < 0.1 µg/L limit set by the EU Groundwater Directive for all assessed uses.

In conclusion, the use of PHMB as PT6.1 leads to unacceptable risks for the soil compartment, except for the scenario amateur use of product containing PHMB as PT6.1 based on a tonnage approach.

2.2.2.7.4 Non compartment specific effects relevant to the food chain (secondary poisoning)

There are no indications from the physico-chemical properties of PHMB of positive bioaccumulation potential. In particular:

- It does not have a log Kow of ≥ 3;
- It does not belong to a class of substances known to have potential to accumulate in living organisms;
- There are no indications from structural features. In particular, the high molecular weight of PHMB is likely to result in steric hindrance at passage of gill membranes or cell membranes of respiratory organs, thereby limiting the potential for uptake from the environment.
- It does not concentrate in the food chain.

Therefore it is believed that there is no significant potential for secondary poisoning to occur as a result of the proposed uses of PHMB.

2.2.2.8 Overall conclusion for the environmental risk assessment

The environmental risk assessment of PHMB used as PT6.1 is summarised in the table below.

Use	STP	Aquatic compartment		Terrestrial compartment	Groundwater	Air	Secondary poisoning
		Surface water	Sediment				
PT6.1 - Formulation	Acceptable (1)	Acceptable (1)	Unacceptable (1)	Unacceptable (1)	Acceptable (1)	Not relevant	Not relevant
PT6.1 - Professional use	Acceptable (1;2)	Unacceptable (2)	Unacceptable (2)	Unacceptable (1;2)	Acceptable (1;2)	Not relevant	Not relevant
PT6.1 - Amateur uses	Acceptable (1;2)	Unacceptable (2)	Unacceptable (2)	Unacceptable (2)	Acceptable (1;2)	Not relevant	Not relevant
PT6.1 - Cumulative emission for Professional and amateurs uses	Acceptable (2)	Unacceptable (2)	Unacceptable (2)	Unacceptable (2)	Acceptable (2)	Not relevant	Not relevant

(1) - based on a tonnage approach

(2) - based on a consumption rate approach

In conclusion for all scenarios, as the use of PHMB as PT6.1 leads to unacceptable risks for at least one environmental relevant compartment, the use of PHMB as PT6.1 is considered

unacceptable for the environment.

2.2.3 ED properties

PHMB is not known as an Endocrine Disruptor with regard to the environment. Considering the mode of action of the substance, observed effects on reproduction on fish and daphnia is not expected to be linked to an ED-mode of action.

The effects observed in the repeated toxicity and reprotoxicity studies in mammals are not expected to be related to an ED-mode of action.

Regarding the available data on PHMB, no ED properties have been identified.

2.3 Overall Conclusions of the evaluation

SCENARIO	Human primary exposure		Human secondary exposure		Environment					
	Professional	Non professional	Worker	General public	STP	Aquatic compartment (surface water, sediment)	Terrestrial compartment	Groundwater	Air	Secondary poisoning
Formulation of the biocide in product to be preserved	Acceptable **Erreur ! Source du renvoi introuvable.**	Not relevant	NR	NR	Acceptable	Unacceptable	Unacceptable	Acceptable	NR	Not relevant
PT6.1.3: Preservatives for detergents used in many applications										
Hand wash or machine laundry	Acceptable **Erreur ! Source du renvoi introuvable.**	Acceptable	NR	Unacceptable	Acceptable	Unacceptable	Unacceptable	Acceptable	NR	NR
Pre-treatment of clothes	Acceptable	Acceptable	Acceptable	Unacceptable						
Hand or machine dishwashing	Acceptable	Acceptable	Acceptable	Acceptable						
Surface cleaning (wipping/moping)	Unacceptable	Unacceptable	NR	Unacceptable for children						

NR: Not relevant.

Conditions:

(1) When PPE are worn
Erreur ! Source du renvoi introuvable. When using washing machine

3 PROPOSED DECISION

The outcome of the assessment for PHMB (1415; 47) in product-type 6 is specified in the BPC opinion following discussions at the 2nd meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

3.1 Requirement for further information related to the reference biocidal product

None.

3.2 List of endpoints

The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

4 APPENDICES

Appendix 1 Listing of endpoints

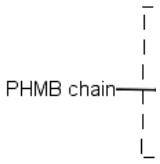
Chapter 1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (Common Name)	PHMB (1415; 4.7)
Function (*e.g.* fungicide)	Bactericide and algaecide
Rapporteur Member State	France

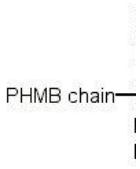
Identity (Annex IIA, point II.)

Chemical name (IUPAC)	CoPoly(bisiminoimidocarbonyl,hexamethylene hydrochloride),(iminoimidocarbonyl, hexamethylène hydrochloride)
Common name, synonym	- Polyhexamethylene biguanidine - PHMB - Poly(hexamethylene biguanide) hydrochloride
CAS No	32289-58-0 and 1802181-67-4
EC No	PHMB meets the EU definition of a polymer and is therefore not listed on EINECS
Other substance No.	None
Minimum purity of the active substance as manufactured (g/kg or g/l)	943 g/kg (TC)
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None.
Molecular formula	$(C_8H_{18}N_5Cl)_n$ with three possible end-chain groups
Molecular mass	Weight average molecular weight Mw= 6629; Number average molecular weight Mn= 1415; PolyDispersity Index (Mw/Mn) = 4.67 Monomeric unit of " in-chain biguanides" was calculated for n average= 22.9 Monomeric unit of " in-chain guanidines" was calculated for m average= 7.6
Structural formula	 The in-chain groups are:

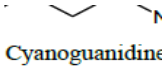
Biguanide hydrochloride group

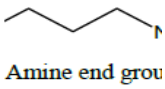


Guanidine hydrochloride group



The 3 possible end-chain groups are:





Physical and chemical properties (Annex IIA, point III., unless otherwise indicated)

Melting point (state purity)	No melting - decomposes starting at 200°C
Boiling point (state purity)	No boiling point at atmospheric pressure - decomposes starting at 200°C
Temperature of decomposition	200°C
Appearance (state purity)	Purified active substance (99.6%) : white solid Technical material (20%) : limpid to slightly opalescent colourless (20% aqueous solution)
Relative density (state purity)	Purified active substance (99.6%) D^{20}_{4} = 1.237
Surface tension	71.5 mN/m (1 g/L solution at 20°C)
Vapour pressure (in Pa, state temperature)	$<1.0 \times 10^{-6}$ Pa at 20°C
Henry's law constant (Pa m^3 mol^{-1})	$<1.65 \times 10^{-8}$ $Pa.m^3.mol^{-1}$ Log H: <-7.8

Solubility in water (g/l or mg/l, state temperature)	pH4: The pKa of PHMB (see IIIA 3.6-01) was determined to 2.38. The solubility is therefore not expected to vary in the pH range of pH5 to pH9. pH7: pH9:
	Pure water: 401.2 g/L at 25 °C
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	acetone: 72 mg/L n-hexane: 184 mg/L methanol: 205.6 g/L All at 25°C
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not applicable because the active substance as manufactured does not include an organic solvent and is not formulated in organic solution in the biocidal product.
Partition coefficient (log P_{OW}) (state temperature)	Log P_{ow} = -2.39 at 22°C
	pH dependency is not considered likely over the pH range 4 to 9
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	pKa: 2.38
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Absorption at pH<2, pH =5.5 and pH >10 within the range from 200nm to 250nm with one peak minimum at 219nm and one local apparent maximal at 234.5nm; no peak maxima at wavelengths ≥ 290 nm can be found. Therefore direct photodegradation of PHMB is not expected.
Flammability	Not flammable, not self-ignition
Explosive properties	Not explosive

Classification and proposed labelling (Annex IIA, point IX.)

with regard to physical/chemical data	None
with regard to toxicological data	Carc. 2 H351 Acute Tox 2 H330 Acute Tox. 4 H302 STOT RE 1 H372 Eye Dam. 1 H318 Skin Sens. 1B H317
with regard to fate and behaviour data	**Harmonised classification (TC):** None **Proposed classification of PHMB 20 % in water (TK):** None

	Proposed classification of SEPTI-HAND (0.4% a.s.) : None
with regard to ecotoxicological data	**Harmonised classification (TC):** Aquatic Acute 1; H400 (M-factor = 10): Very toxic to aquatic life. Aquatic Chronic 1; H410 (M-factor = 10): Very toxic to aquatic life with long lasting effects. **Proposed classification of PHMB 20 % in water (TK)**: Aquatic Acute 1; H400: Very toxic to aquatic life. Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects. **Proposed classification of SEPTI-HAND (0.4% a.s.):** Aquatic chronic2; H411: Toxic to aquatic life, may cause long-term adverse effects in the aquatic environment.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	The content of the active ingredient PHMB in drinking water was determined after complexation with eosin solution by U.V. visible spectrophotometry
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	The determination of three impurities were determined by chromatographic methods: - Gas chromatographic method: Gas chromatograph 6890N -Liquid chromatographic method: Alliance separation module 2695

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	currently not technically feasible
Air (principle of method and LOQ) (Annex IIA, point 4.2)	Not required
Water (principle of method and LOQ) (Annex IIA, point 4.2)	Surface water; currently not technically feasible Drinking water: method required
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	Method required
Food/feed of plant origin (principle of	Method required

method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Method required

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals (Annex IIIA, point 6.2)

Rate and extent of oral absorption:	Gastro-intestinal absorption of PHMB following a single oral dose amounted to only 5.6% of the administered dose.
Rate and extent of dermal absorption:	Dermal absorption : PHMB 20% : PHMB absorbed is 0.6%. PHMB 0.7% : PHMB absorbed is 6% PHMB 0.02% : PHMB absorbed is 48%.
Distribution:	In rats, the radioactivity was distributed within the body of the treated animals at generally low concentration levels. The highest concentrations were detected in adipose tissue depots (0.3µg/g); and less than 0.2µg/g in liver, kidney, heart. Tissue distribution was very limited.
Potential for accumulation:	Tissue concentrations rapidly fell away to zero after treatment was withdrawn. PHMB showed no potential for bioaccumulation in the rat.
Rate and extent of excretion:	The primary route of excretion was elimination of unchanged PHMB in faeces. Gastro-intestinal absorption as measured in urine was only 5.6% of administered dosed. Excretion values for expired air were not available. There was no biliary component to excretion of PHMB.
Toxicologically significant metabolite	No toxicologically significant metabolites were identified.

Acute toxicity (Annex IIIA, point 6.1)

Rat LD_{50} oral	500 mg/kg bw
Rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	Combined LC_{50} =0.37 mg/L Males: 0.29 mg/L Females: 0.48 mg/L
Skin irritation	Non irritant

Eye irritation	Severe persistent irritant
Skin sensitization	Sensitizing

Repeated dose toxicity (Annex IIIA, point 6.3 and 6.4)

Species/ target / critical effect	Rat: minor reductions in food consumption (due to diet palatability) and bodyweight gains
Lowest relevant oral NOAEL / LOAEL	36 mg/kg bw/day based on decrease body weight (rat, combined chronic/carcinogenic oral toxicity)
Lowest relevant dermal NOAEL / LOAEL	Systemic NOAEL : 300 mg/kg/d (no effect) (rat, 28 days) Local NOAEL: 100 mg/kg/d (erythema) (rat, 28 days)
Lowest relevant inhalation NOAEC	On going

Genotoxicity (Annex IIIA, point 6.6)	No genotoxic properties evident in *in vitro* assays with or without metabolic activation.

Carcinogenicity (Annex IIIA, point 6.5 and 6.7)

Species/type of tumour	Rat, oral: hamartomas in liver, Hepatocellular adenomas and follicular adenoma in thyroid. Other types of benign neoplastic lesions in both males and females are also observed.
lowest dose with tumours	Rat, oral: 1000 mg/L

Reproductive toxicity (Annex IIIA, point 6.8)

Species/ Reproduction target / critical effect	Rat
Lowest relevant reproductive NOAEL / LOAEL	NOAEL = 1500 ppm equivalent to approximately 50.55 mg/kg for males in the OECD 422 guideline study
Species/Developmental target / critical effect	Rabbit: No maternal toxicity Increase of foetal and litter incidence of supernumerary lungs lobes and foetal incidence of incomplete ossification of the 6th sternebrae
Lowest relevant developmental NOAEL / LOAEL	Rabbit Maternal: NOAEL = 112mg/kg/d Foetuses: NOAEL = 12mg/kg/d

Neurotoxicity / Delayed neurotoxicity (Annex IIIA, point 6.9)

Species/ target/critical effect	Not applicable
Lowest relevant developmental NOAEL / LOAEL.	Not applicable

Other toxicological studies (Annex IIIA, 6.10)

Data for metabolites	Not applicable.

Medical data (Annex IIIA, point 6.12)

The available data give no indications of special concern in medical records or in relation to any reported medical incidents.

Summary	Value	Study	Safety factor
ADI (if residues in food or feed) (mg/kg bw/day)	0.12 mg/kg/d	Teratogenicity study in rabbits	100
AEL (short-medium and long term) (systemic) (mg/kg bw/day)	0.0067 mg/kg/d	Teratogenicity study in rabbits	100 and correction factor to take into account 5.6% absorption (included in value)
ARfD (acute reference dose)	0.12 mg/kg/d	Teratogenicity study in rabbits	100

Acceptable exposure scenarios (including method of calculation)

Professional users	Formulation of detergent product: addition of PHMB with gloves and clothes Exposure during washed laundry by machine Exposure during pre treatment of clothes Exposure during hand dish washing Exposure during disinfection of surface is acceptable only when gloves and coverall are worn. However, these mitigation measures are doubtful. In this contxet, the risk is considered

	as unacceptable.
Non-professional users	Exposure during hand washed laundry Exposure during pre treatment of clothes Exposure during hand dish washing
Indirect exposure as a result of use	A mitigation measure is need: - The products should be used in zone inaccessible to children **Indirect exposure via food:** Expected contact with food/feed. Exposure estimates based on "worst" case and cumulative assumptions with dishwashing and surface cleaning scenarios, regarding magnitude of residues, transfer to food and consumption do not indicate a concern for human health. Concerning the secondary and cumulative exposure via ingestion of food placed on dishware and surfaces previously contaminated by a product containing PHMB as PT6, without considering any rinsing step, the fraction of ADI or ARfD is below 100% for adult and child. Risk for consumer following transfer into food from residues left on treated dishware and surfaces with products containing PHMB as PT6 is considered acceptable.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)		PHMB is stable in aqueous solutions between pH 4 and pH 9.
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites		No photolysis study in water was performed as PHMB does not absorb visible light.
Readily biodegradable (yes/no)		No.
Biodegradation in seawater		No data
Degradation in water/sediment (2 systems)	- DT_{50} water - DT_{90} water	No $DT50_{total\ system}$ determined.
	- DT_{50} whole system - DT_{90} whole system	No $DT50_{total\ system}$ determined.
Distribution in water / sediment systems (active substance)		Maximum of non-extractables: 87.1%

Distribution in water / sediment systems (metabolites)	Not determined

Route and rate of degradation in soil (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

Mineralization (aerobic)	Less than 5% mineralization after 60 d at 20°C
Laboratory studies (range or median, with number of measurements, with regression coefficient)	One study conducted in four soils according to OECD Guideline 307 DT50lab (25ºC, aerobic)- not calculated as <5% mineralisation observed.
	DT_{50lab} (20°C, pF 2, anaerobic): Not applicable.
Field studies (state location, range or median with number of measurements)	Not applicable.
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Anaerobic degradation	Soil exposure is negligible and therefore no studies have been performed.
Soil photolysis	The substance does not absorb light and therefore no studies have been performed.
Non-extractable residues	Max 86.5% after 60 days
Relevant metabolites – name and/or code, % of applied a.i. (range and maximum)	Not investigated
Soil accumulation and plateau concentration	Not required

Adsorption/desorption (Annex IIA, point XII.7.7 ; Annex IIIA, point XII.1.2)

a) Active substance

K_{oc} / K`oc / $K_d$ / K`	The sorption properties of PHMB have been investigated during a study conducted according to OECD guideline 106, in four soils and sewage sludge. Koc (soils): 50100 – 352381 (n=4). Mean: 201537 L/kg Kd (sludge): 2773 L/kg
pH dependence (yes / no) (if yes type of dependence)	No

Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

Direct photolysis in air	Not applicable.
Quantum yield of direct photolysis	Not applicable.
Photo-oxidative degradation in air	Estimated half-life (day time 24 hrs): 0.213 d

	(AOPWIN)
Volatilization	PHMB is not volatile

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study)	No monitoring data has been reported.
Surface water (indicate location and type of study)	No monitoring data has been reported.
Ground water (indicate location and type of study)	No monitoring data has been reported.
Air (indicate location and type of study)	No monitoring data has been reported.

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)
(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	Endpoint	Toxicity
Fish			
Oncorhynchus mykiss	96 hours	LC_{50}	0.2676 mg a.s./L
Pimephales promelas	28 days post-hatch	NOEC	4.98E-03 mg a.s./L
Invertebrates			
Daphnia magna	48 hours	EC_{50}	0.11707 mg a.s./L
Daphnia magna	21 days	NOEC	5.44E-03 mg a.s./L
Algae			
Pseudokirchneriella subcapitata	72 hours	E_rC50 E_rC10 NOEC	2.06E-02 mg a.s./L 2.79E-03 mg a.s./L 9.45E-04 mg a.s./L
Microorganisms			
Activated sludge	3 hours	EC50 NOEC	32.3 mg a.s./L 6.35 mg a.s./L
Sediment dwelling organisms			
Lumbriculus variegatus	28 days	NOEC	174 mg a.s./kg dry sediment 37.82 mg a.s./kg wet sediment

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia foetida*	14-day LC_{50} > 201 mg a.s./kg soil dry weight

(Annex IIIA, point XIII.3.2)	After normalization at 3.4% of organic matter: 14-d LC_{50_std}: 68.34 mg a.s./kg soil dry weight

Effects on soil micro-organisms (Annex IIA, point 7.4)

Nitrogen mineralization	LC_{50}: > 1000 mg a.s./kg soil dry weight NOEC = 1000 mg a.s./kg soil dry weight After normalization at 3.4% of organic matter: LC_{50_std}: > 2127.7 mg a.s./kg soil dry weight $NOEC_{std}$ = 2127.7 mg a.s./kg soil dry weight
Carbon mineralization	LC_{50}: > 1000 mg a.s./kg soil dry weight NOEC = 1000 mg a.s./kg soil dry weight After normalization at 3.4% of organic matter: LC_{50_std}: > 2127.7 mg a.s./kg soil dry weight $NOEC_{std}$ = 2127.7 mg a.s./kg soil dry weight

Effects on terrestrial plants (Annex IIIA, point XIII.3.2)

Seedling emergence	No reliable study available
Vegetative vigour	No reliable study available

Effects on terrestrial vertebrates

Acute toxicity to mammals (Annex IIIA, point XIII.3.3)	Rat oral > 2000 mg/kg bw
Acute toxicity to birds (Annex IIIA, point XIII.1.1)	No data presented (no exposure)
Dietary toxicity to birds (Annex IIIA, point XIII.1.2)	No data presented (no exposure)
Reproductive toxicity to birds (Annex IIIA, point XIII.1.3)	No data presented (no exposure)

Effects on honeybees (Annex IIIA, point XIII.3.1)

Acute oral toxicity	Not required
Acute contact toxicity	Not required

Effects on other beneficial arthropods (Annex IIIA, point XIII.3.1)

Acute toxicity	Not required

Acute toxicity	Not required

Bioconcentration (Annex IIA, point 7.5)

Bioconcentration factor (BCF)	1.86 x 10^{-3} L/kg (calculation based on log Kow of -2.39)
Depuration time (DT_{50}) (DT_{90})	Not applicable as no bioaccumulation expected.
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable as no bioaccumulation expected.

Chapter 6: Other End Points

Not applicable.

Appendix 2 Summary of intended uses

Summary of intended uses

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment	Remarks
			Type	Conc [% PHMB]	Method	Number	Interval		
Preservatives for detergents.	PRESERVIL D2	Bacteria yeasts	SL	20 % w/w	Manual	1	One application. by incorporation at the time of manufacture	0.06% w/v active substance	Industrial use only The activity has been demonstrated on a dish detergent.

Appendix 3 List of studies by author

List of studies for the active substance

Author	Section No	Year	Title	Data protection claimed	Owner of data
Anonymous	5.4	2007	Mode of action of PHMB. ICI technical service document, Non-GLP/Published.	Public	N
Anonymous	5.4	2007	Mode of action of PHMB. Avecia technical service document, Non-GLP/Published.	Public	N
ANSM	4.2	2013	Evaluation de la conformité aux bonnes pratiques de laboratoire	Laboratoire PAREVA	Y
[redacted]	6.10.2	2015	Assessment of the Bioavailability and Distribution of PHMB in the Rat and Its Effects on Oxidative Stress, Cytotoxicity, Mitogenicity, and Histologic Alterations in the Rat Liver. Assessment of the Bioavailability of PHMB in Blood, Urine, and Tissues Using [14C]PHMB – (Studies No 338 and 338A)	[redacted]	Y
[redacted]	6.10.3	2015	Evaluation of the Proliferative Effects of Chronic Treatment with PHMB in the Liver Tissue of Wistar Han Rats (Study No 339)	[redacted]	Y
[redacted]	6.10.4	2015	Early Proliferative Effects of PHMB on the Liver Tissue of Male Wistar Han Rats (study No 342)	[redacted]	Y
Baltussen I.	2.8	2008	Determination of the content of Hexamethylene diamine, hexamethylene diammonium salt of bis-dicyanamide and Sodium dicyanamide in PHMB P20 D	Laboratoire PAREVA	Y
Baltussen I.	4.1	2008	Determination of the content of Hexamethylene diamine, hexamethylene diammonium salt of bis-dicyanamide and Sodium dicyanamide in PHMB P20 D	Laboratoire PAREVA	Y

Barker, J., Brown, M. R. W., Gilbert, B., Collier, P.J., Farrell, I.D.	5.10	1993	The Physiological Status of Legionella pneumophila and Its Susceptibility to Chemical Inactivation, in Legionella: Current Status and Emerging Perspectives, ed. Barbaree, J.M., Breiman, R.F. and Dufour, A.P., pages 259 – 260. Non-GLP/Published	Public	N
Birnschein K.	3.11	2008	Flammability (solids) of PHMB P100 PC	Laboratoire PAREVA	Y
Birnschein K.	3.17	2008	Reactivity of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride) towards the Container Material after Accelerated Storage at 54°C for 2 Weeks	Laboratoire PAREVA	Y
Bratt, H., Hathway, D.E.	6.2	1976	Characterisation of the urinary polymer-related material from rats given poly(biguanide-1,5-diylhexamethylene hydrochloride). Imperial Chemical Industries Linited report. Makromol. Chem. 177, 2591-2605 (1976)	Published	N
Broxton, P., Woodcock, P.M., Gilber, P.	5.10	1983	A study of the antibacterial activity of some polyhexamethylene biguanides towards Escherichia coli ATCC 8739 Journal of Applied Bacteriology, 1983, 54, p. 345 – 353. Non-GLP/Published.	Public	N
[redacted]	7.4.3.2	2013	PHMB Fish Early Life Stage Toxicity Test for Fathead Minnow	[redacted]	Y
Button S.G.	7.2.3.1	2013	PHMB Adsorption/Desorption in five Soils	Laboratoire PAREVA	
Caron C.	3.5	1995	Series 63, Physical and chemical characteristics - 63.8. Solubility of pure PHMB	MAREVA	
Caron C.	3.7	1995	Series 63, Physical and chemical characteristics - 63.8. Solubility of pure PHMB	MAREVA	

Chen J.	6.12.1	2004	Report on Health Effects of PHMB in Humans - U.S. EPA Office of Pesticide Programs, Antimicrobials Division	Published	N
Chen J.	6.18_03	2003	PHMB - 2nd Report of the Hazard Identification Assessment Review Committee.	Published	N
Cohen S.M. and Creppy E.E.	6.10.5	2015	Evaluation of PHMB-induced Rodent Tumors and Assessment of Human Relevance (Position Paper)	Laboratoire PAREVA	Y
[redacted]	6.1.2	2012	Evaluation of acute dermal toxicity in rats	[redacted]	Y
Creppy E.E.	6.10.1b	2012	Etude in vitro des possibles propriétés Epigénétiques du PHMB	Laboratoire PAREVA	Y
Creppy E.E. et al.	6.10.1a	2014	Study of Epigenetic Properties of Poly(HexaMethylene Biguanide) Hydrochloride (PHMB)	Published	N
Cros D.	2.1	2013	Formulation composition statement of trades names	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 PC	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 SP	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 TX	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P2056	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMBG	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 D	Laboratoire PAREVA	Y
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF REVACIL	Laboratoire PAREVA	Y

Cros D.	2.4.1	2007 2012 (updated)	Laboratoire PAREVA: active subtance Polyhexamethylene biguanidine (PHMB) Information about CAS number	Laboratoire PAREVA	Y
Cros D.	2.5.1	2007 2012 (updated)	Laboratoire PAREVA: active subtance Polyhexamethylene biguanidine (PHMB) Information about CAS number	Laboratoire PAREVA	Y
Cros D.	2.5.2	2012	Synthesis of PHMB radiolabelled with 14C ([14C]PHMB). Technical data on the final product obtained	Laboratoire PAREVA	Y
Cros D.	2.6	2013	Description of the manufacturing process of the active substance PHMB followed by Laboratoire PAREVA	Laboratoire PAREVA	Y
Cros D.	2.7	2012	Synthesis of PHMB radiolabelled with 14C ([14C]PHMB). Technical data on the final product obtained	Laboratoire PAREVA	Y
Cros D.	2.8	2014	Summary of the batch references used in Toxicological and ecotoxicological studies	Laboratoire PAREVA	Y
Cros D.	4.1	2014	Reference DCI document. Request for additional information. Point No 5	Laboratoire PAREVA	Y
Cros D.	4.2	2014	Reference DCI document. Request for additional information. Point No 8	Laboratoire PAREVA	Y
Cros D.	4.2	2014	Reference DCI document. Request for additional information. Point No 8	Laboratoire PAREVA	Y
Curl M.G	7.3.1	2007	Computer modelled properties of PHMB using EPI Suite ™	Laboratoire PAREVA	Y
Curl M.G.	3.15	2007a	Expert statement on the explosive properties of poly(hexamethylenebiguanide) hydrochloride (PHMB)	Laboratoire PAREVA	Y
Curl M.G.	3.16	2007b	Expert statement on the oxidizing properties of poly(hexamethylenebiguanide) hydrochloride (PHMB)	Laboratoire PAREVA	Y

Davies, A., Field, B.S.	5.10	1969	Action of Biguanides, Phenols and Detergents on Escherichia coli and its spheroplasts. J. appl. Bact., 1969, 32, p. 233 – 243. Non-GLP/Published	Public	N
DeMatteo V.	2.1	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.2	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.5.1	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.5.2	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.5.3	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.7	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
DeMatteo V.	2.8	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Laboratoire PAREVA	Y
[redacted]	7.4.1.1	2013	PHMB: Acute Toxicity to Rainbow Trout	[redacted]	Y
Dickinson R.A.	7.4.1.2	2013	PHMB: Acute Toxicity to Daphnia Magna	Laboratoire PAREVA	Y
Dickinson R.A.	7.4.1.3	2013	PHMB Algal Growth Inhibition Assay	Laboratoire PAREVA	Y
Dickinson R.A.	7.4.3.4	2013	PHMB: Daphnia Magna Reproduction Toxicity Test	Laboratoire PAREVA	Y
Eckenstein H.	7.5.1.1-01	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Effects on Soil Microflora Activity	Laboratoire PAREVA	Y
Eckenstein H.	7.5.1.1-02	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Effects on Soil Microflora Activity	Laboratoire PAREVA	Y
Eisner G.	7.1.2.1.1	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Elimination and Primary Biodegradation in an Activated Sludge Simulation Test	Laboratoire PAREVA	Y

Feil N.	7.1.1.2.1	2009 (revised date 2014)	Ready Biodegradability of PHMB P100 PC in a CO2 headspace Test	Laboratoire PAREVA	Y
Ferte C.	6.12.3		Study on PolyHexaMethylène Biguanidine impact (PHMB) and/or its manufacturing process impact on the workshop staff	Laboratoire PAREVA	Y
Ferte C.	6.12.6		Study on PolyHexaMethylène Biguanidine impact (PHMB) and/or its manufacturing process impact on the workshop staff	Laboratoire PAREVA	Y
Gaylarde, C.C., Johnston, J.M.	5.10	1984	Some recommendations for sulphate-reducing bacteria biocide tests. JOCCA, 1984 (12), p. 305 – 309. Non-GLP/Published.	Public	N
Gilbert, P., Pemberton, D., Wilkinson, D.	5.10	1990	Synergism within the polyhexamethylene biguanide biocide formulations. Journal of Applied Bacteriology 1990, 69, p. 593 – 598. Non-GLP/Published.	Public	N
Gilbert, P., Pemberton, D., Wilkinson, D.	5.10	1990	Barrier properties of the Gram-negative cell envelope towards high molecular weight polyhexamethylene biguanides. Journal of Applied Bacteriology 1990, 69, p. 585 – 592. Non-GLP/Published.	Public	N
Giordanengo A.	4.2	2014	Validation of an ELISA method for the quantification of PHMB in water	Laboratoire PAREVA	Y
Goeres D.M, Palys T., Sandel B.B, Geiger J.	5.10	2004	Evaluation of disinfectant efficacy against biofilm and suspended bacteria in a laboratory swimming pool model	Public	N

[redacted]	6.3.3_01	2013	PHMB: Dose Range Finding Inhalation Toxicity Study (Nose-Only) in the rat	[redacted]	Y
[redacted]	6.3.3_02	2013	PHMB: 28-Day Inhalation Toxicity Study (Nose-Only) in the rat	[redacted]	
[redacted]	6.1.3	2012	Acute Inhalation Toxicity Study (Nose-only) in the Rat according to OECD 403 guideline	[redacted]	Y
Harmand, M.F.	6.6.1	2002	Reverse Mutation Assay on Salmonella typhimurium his and Escherichia coli,	Laboratoire PAREVA	Y
[redacted]	6.6.2	2002	In-vitro mammalian chromosome aberration test using Chinese Hamster Ovary Cells (CHO)	[redacted]	Y
Harmand, M.F.	6.6.2	2002-2012	Historical Controls	Laboratoire PAREVA	N
Harmand, M.F.	6.6.3	2002	In-vitro mammalian cell gene mutation test	Laboratoire PAREVA	Y
Ismael, N., Furr, J.R., Russell, A.D.	5.10	1987	Inhibitory and lethal effects of chlorhexidine and a polymeric biguanide on some strains of Providencia stuartii. Letters in Applied Microbiology, 1987, 5, p. 23 – 26. Non-GLP/Published Journal of Applied Bacteriology 1990, 69, p. 585 – 592. Non-GLP/Published.	Public	N
L'Haridon J.	7.1.1.2.1	2002b	PHMB P20 D: Determination of Ready Biodegradability Closed Bottle test (study 23441 ECS)	Laboratoire PAREVA	Y
Laboratoire PAREVA	2.7	2011	PHMB from Laboratoire PAREVA: Summary of the available data	Laboratoire PAREVA	Y
Laboratoire PAREVA	2.7	2014	Answer to additional information: Point No. 1 Content in PHMB < 1000 Da	Laboratoire PAREVA	Y
Laboratoire PAREVA	2.7	2014	Answer to additional information: Point No. 2 Certified range values of active substance and impurities	Laboratoire PAREVA	Y

Laboratoire PAREVA	8	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 D According to Annex I of Regulation 453/2010	Laboratoire PAREVA	Y
L'Haridon J.	7.4.1.4	2002	Activated Sludge, Respiration Inhibition Test	Laboratoire PAREVA	Y
Lonza	2.1	2012	MATERIAL SAFETY DATA SHEET OF LONZABAC™ PC	Laboratoire PAREVA	Y
Lonza	2.1	2012	MATERIAL SAFETY DATA SHEET OF LONZABAC™ BG	Laboratoire PAREVA	Y
Maher M.	3.4.3	2012	PHMB Batch Characterisation (Bx 111077)	Laboratoire PAREVA	Y
Maher M.	3.11	2013	PHMB P100 Analysis – Relative Self-Ignition Temperature of a Solid According to EC Physico-Chemical Test A16	Laboratoire PAREVA	Y
[redacted]	6.8.2_02	2015	PolyHexaMethylene Biguanide hydrochloride (PHMB): Two Generation Reproduction Toxicity Study by Oral route (Through Drinking Water) in Wistar Rats. Advinus Therapeutics Ltd., Study No. G8974.	[redacted]	Y
[redacted]	6.3.1_02	2014	PolyHexaMethylene Biguanide hydrochloride (PHMB): Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test by Oral Route (Through Drinking Water) in Wistar Rats. Advinus Therapeutics Ltd., Study No. G8973. 20 November 2014 (unpublished).	[redacted]	Y
[redacted]	6.4.1_02	2014	PolyHexaMethylene Biguanide hydrochloride (PHMB): Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test by Oral Route (Through Drinking Water) in Wistar Rats. Advinus Therapeutics Ltd., Study No. G8973. 20 November 2014 (unpublished).	[redacted]	Y

[redacted]	6.8.2_01	2014	PolyHexaMethylene Biguanide hydrochloride (PHMB): Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test by Oral Route (Through Drinking Water) in Wistar Rats. Advinus Therapeutics Ltd., Study No. G8973. 20 November 2014 (unpublished).	[redacted]	Y
[redacted]	6.7_04a	2014	Evaluation of Liver and Thyroid Proliferative Lesions from the Pareva PHMB P100 Two-Year Rat Study	[redacted]	Y
Ministère du redressement productif	4.2	2013	Certificat de conformité aux bonnes pratiques de laboratoire	Laboratoire PAREVA	Y
Morpeth, F.	5.10	1993	Polyhexanide Revisited. SPC March 1993, p. 37 – 39. Non-GLP/Published Polyhexanide Revisited. SPC March 1993, p. 37 – 39. Non-GLP/Published Polyhexanide Revisited. SPC March 1993, p. 37 – 39. Non-GLP/Published	Public	N
[redacted]	6.7_04b	2014	Pathology Peer review & Expert Opinion Consensus of the "Combined Chronic Toxicity and Carcinogenicity Study with PHMB P100 in Wistar Rats"	[redacted]	Y
N/A	2.10	2015	EUSES files	Laboratoire PAREVA	Y
Naik, V., Varde, S., Hindley, P., Yeates, T., Kundu, S.	5.10	2003	Study of a biocide (Vantocil-IB) for aerial and surface disinfection Asian Jr. of Microbiol. Biotech. Env. Sc., Vol. 5, No. 4, p. 483 – 486. Non-GLP/Published.	Public	N

O'Connor B.J., Wolley S.M.	3.9	2007	PHMB P20D Poly(HexaMethylene Biguanide), hydrochloride: DETERMINATION OF NUCLEAR MAGNETIC RESONANCE SPECTRA AND PARTITION COEFFICIENT	Laboratoire PAREVA	Y
[redacted]	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): Analysis in rat faeces	[redacted]	Y
[redacted]	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): Analysis in rat urines	[redacted]	Y
Padel L.	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): analysis in serums.	Laboratoire PAREVA	Y
Pawsey B.	7.4.3.5.1	2015	PHMB: Toxicity to the Sediment-Dwelling Phase of the Midge Chironomus riparius	Laboratoire PAREVA	Y
[redacted]	6.8.1_02	2010	Prenatal Developmental Toxicity study of PHMB [Poly (HexaMethyleneBiguanide), hydrochloride] in New Zealand White Rabbit	[redacted]	Y
[redacted]	6.7_02	2012	Certificate of Toxicological Evaluation regarding the Combined chronic Toxicity and Carcinogenicity study with PHMB P100 in Wistar Rat (OECD 453).	[redacted]	Y
[redacted]	6.5_02	2012	Certificate of Toxicological Evaluation regarding the Combined chronic Toxicity and Carcinogenicity study with PHMB P100 in Wistar Rat (OECD 453).	[redacted]	Y
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Graph, 2013 03 20	Laboratoire PAREVA	Y
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Excel Spreadsheet list	Laboratoire PAREVA	Y
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Excel Spreadsheet list	Laboratoire PAREVA	Y
[redacted]	6.7_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats	[redacted]	Y
[redacted]	6.4.1_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats.	[redacted]	Y

[redacted]	6.5_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats.	[redacted]	Y
[redacted]	6.1.1	2011	Evaluation of acute oral toxicity in rats: Acute toxic class method.	[redacted]	Y
[redacted]	6.1.4_01	2008	Skin irritation test in the rabbit	[redacted]	Y
Richeux F.	6.1.4_01	2008	Assessment of Acute Dermal Irritation - Study Plan	Laboratoire PAREVA	Y
[redacted]	6.1.4_02	2008	Eye irritation test in the rabbit	[redacted]	Y
[redacted]	6.1.5	2011	Assessment of sensitive properties on albino guinea pigs: Maximisation test according to Magnusson and Kligman	[redacted]	Y
Shamim, A.N	6.15.3	2003	RED Chapter: PHMB Dietary Exposure Assessments for he Reregistration Eligibility Decision (OPPTS 248.3000) USA, EPA review.	Published	N
Smeykal H.	3.1.1	2007a	PHMB P100 PC Batch No.: 5519 MELTING POINT (A.1.) OECD 102	Laboratoire PAREVA	Y
Smeykal H.	3.1.2	2007b	PHMB P100 PC Batch No.: 5519 BOILING POINT (A.2.) OECD 103	Laboratoire PAREVA	Y
Smeykal H.	3.2	2007c	PHMB P100 PC Batch No.: 5519 VAPOUR PRESSURE (A.4.) OECD 104	Laboratoire PAREVA	Y
Smeykal H.	3.10	2007	Thermal Stability (OECD 113) of PHMB P100 PC Batch N°5519	Laboratoire PAREVA	Y
Stabler D.	7.5.1.2	2007	Acute Toxicity of PHMB P20 D on Earthworms, Eisenia fetida Using an Artificial Soil Test	Laboratoire PAREVA	Y
[redacted]	6.3.2_01	2013	Preliminary Toxicity Study by Dermal Administration to Sprague-Dawley Rats for 2 Weeks; Huntingdon Life Sciences, Study number SSF0007, 18 December 2013	[redacted]	Y
[redacted]	6.3.2_02	2014	PHMB: Toxicity Study by Dermal Administration to Sprague-Dawley Rats for 4 Weeks; Huntingdon Life Sciences, Study number SSF0008, 27 March 2014	[redacted]	Y

[redacted]	6.3.1	2009	PHMB P100: 28-day drinking water administration toxicity study in Wistar Rats	[redacted]	Y
Thery F.	5.10	2009	Determination de l'activité bactericide de base selon la norme NF EN 1040 .	Laboratoire PAREVA	Y
Thery F.	5.10	2009	Evaluation de l'activité fongicide du produit « PHMB » selon la norme NF EN 1275 (Avril 2006) – Méthode par filtration sur membrane	Laboratoire PAREVA	Y
Thery F.	5.10	2009	Evaluation de l'activité fongicide du produit « PHMB » selon la méthodologue décrite dans la norme NF EN 1275 (Avril 2006)	Laboratoire PAREVA	Y
Thom M.	2.1	2007	Determination of PHMB (Poly(HexaMethyleneBiguanide), hydrochloride) in Five Batches of PHMB P20 D Eurofins-GAB GmbH Study code: 20071197/01-PC5B GLP/Unpublished	Laboratoire PAREVA	Y
Thom M.	2.3	2007	Determination of PHMB (Poly(HexaMethyleneBiguanide), hydrochloride) in Five Batches of PHMB P20 D Eurofins-GAB GmbH Study code: 20071197/01-PC5B GLP/Unpublished	Laboratoire PAREVA	Y
Thom M.	3.1.3	2007a	Relative density of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	3.3.1	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	3.3.2	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	3.3.3	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	3.4.1	2008	UV/VIS Absorption Spectrum and Infrared Absorption-Spectrum of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	3.4.2	2008	UV/VIS Absorption Spectrum and Infrared Absorption-Spectrum of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y

Thom M.	3.13	2007c	Surface Tension of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Laboratoire PAREVA	Y
Thom M.	4.1	2007	Validation of Analytical Method for the determination of PHMB (Poly(HexaMethyleneBiguanide), hydrochloride) in drinking water "EOSIN Method", Eurofins-GAB GmbH Study code: 20071121/01-PCVE, GLP/Unpublished	Laboratoire PAREVA	Y
Thom M.	4.1	2007	Determination of PHMB (Poly(HexaMethyleneBiguanide), hydrochloride) in Five Batches of PHMB P20 D Eurofins-GAB GmbH Study code: 20071197/01-PC5B GLP/Unpublished	Laboratoire PAREVA	Y
THOR	2.1	2007	ACTICIDE® PHB 20 Product Information	Laboratoire PAREVA	Y
THOR GmbH	2.1	2007	Material Safety Data Sheet ACTICIDE PHB 20	Laboratoire PAREVA	Y
Tiedje M.H.	3.6	1995	Dissociation Constant(s) of PolyHexaMethylene Biguanide hydrochloride (PHMB)	MAREVA	
Truslove N.	2.5.2	2011	PHMB 5-Batch Characterisation-FTIR Spectra	Laboratoire PAREVA	Y
Truslove N.	2.5.2	2011	5-Batch Analysis Proton NMR Spectra	Laboratoire PAREVA	Y
Truslove N.	2.5.2	2011	PHMB 5-Batch Characterisation-UV/Visible Spectra	Laboratoire PAREVA	Y
Truslove N.	3.4.3	2011	PHMB 5-Batch Characterisation - Proton NMR Spectra	Laboratoire PAREVA	Y
Ulbert O.	7.1.1.1.1	2013	PHMB: Determination of the Hydrolysis as a Function of pH (Preliminary Test)	Laboratoire PAREVA	Y
Wallace, M	5.10	2001	Testing the Efficacy of Polyhexamethylene Biguanide as an Antimicrobial Treatment for Cotton Fabric. AATCC Review, Novemer 2001, p. 18 – 20. Non-GLP/Published	Public	N

Walther D.	7.1.2.2.2	2013a	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Route and Rate of Degradation of [14C]PHMB in Aerobic Aquatic Sediment Systems	Laboratoire PAREVA	Y
Walther D.	7.2.1	2013b	PolyHexaMethylene Biguanide (PHMB): degradation and metabolism in four soils of [14C]PHMB incubated under aerobic conditions	Laboratoire PAREVA	Y
Walther D.	7.2.2.1	2013b	PolyHexaMethylene Biguanide (PHMB): degradation and metabolism in four soils of [14C]PHMB incubated under aerobic conditions	Laboratoire PAREVA	Y
Wedemeyer N.	7.5.1.3	2008	Seedling Emergence Limit Test for Non-Target Plants Following one Application of PHMB on Six Species of Plants	Laboratoire PAREVA	Y
Wedemeyer N.	7.5.1.3	2008	Vegetative Vigour Limit Test for Non-Target Plants Following One Application of PHMB on Six Species of Plants	Laboratoire PAREVA	Y
Witte A.	3.4.4	2008	Developement of an analytical method for determination of PHMB in water and soil	Laboratoire PAREVA	Y
Witte A.	4.2	2008	Developement of an analytical method for determination of PHMB in water and soil	Laboratoire PAREVA	Y
	6.18_01	2004	POLYHEXAMETHYLENE BIGUANIDE (PHMB) RED DOCUMENT	Published	N
	6.18_02	2002	Polyhexamethylene biguanide (PHMB): Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document	Published	N

List of studies for the biocidal product

Author	Section No	Year	Title	Owner of data	Data protection claimed
CARON C.	3.7	1995	63.12.pH of the End Used Product, Révacil	Laboratoire PAREVA	Y
CARRARA M.	3.7	2014	Accelerated stability study at 54°C for 14 days on the test item PHMB P20D (polyhexamethylene biguanide, hydrochloride at 20%)	Laboratoire PAREVA	Y
Carrara S.	4.1	2014	Set up and validation of an HPLC/MS method for the identification and quantification of active ingredient polyhemathylene biguanide hydrochloride (PHMB) in the test item PHMB P20D (polyhexamethylene biguanide, hydrochloride at 20%)	Laboratoire PAREVA	Y
Corre J.	5.10	2013	Determination des concentrations minimales inhibitrices du produit "PHMB P20D" vis-à-vis de différensts microorganismes	Laboratoire PAREVA	Y
Cros D.	2.1	2013	Formulation composition statement	Laboratoire PAREVA	Y
Cros D.	2.2	2013	MATERIAL SAFETY DATA SHEET OF HYDROCHLORIC ACID	Laboratoire PAREVA	Y
Cros D.	2.2	2013	MATERIAL SAFETY DATA SHEET OF PRESERVIL-D2	Laboratoire PAREVA	Y
Cros D.	2.3	2013	Certificate of analysis	Laboratoire PAREVA	Y
Cros D.	3.1	2013	Certificate of analysis	Laboratoire PAREVA	Y
Cros D.	3.5	2013	Certificate of analysis	Laboratoire PAREVA	Y
Cros D.	3.6	2013	Certificate of analysis	Laboratoire PAREVA	Y
Cros D.	3.7	2014	Long Term Stability of 20%-PHMB solutions.	Laboratoire PAREVA	Y
Cros D.	6.6_01	2013	PRESERVIL-D2 : Preservative Concentrate for dish detergent protection - Technical Data Sheet	Laboratoire PAREVA	Y
Cros D.	8	2013	MATERIAL SAFETY DATA SHEET OF PRESERVIL-D2 According to Annex I of Regulation 453/2010	Laboratoire PAREVA	Y
Curl M.G	3.2	2007	Expert statement on the explosive properties of poly(hexamethylene biguanide) hydrochloride PHMB Point 3.11	Laboratoire PAREVA	Y

Curl M.G	3.3	2007	Expert statement on the oxidising properties of poly(hexamethylene biguanide) hydrochloride PHMB Point 3.12	Laboratoire PAREVA	Y
Curl M.G.	3.4	2007	Expert statement on the flammability of poly(hexamethylenebiguanide) hydrochloride (PHMB) Point 3.9	Laboratoire PAREVA	Y
De Castro J.	3.7	2014	Accelerated Stability study for 1 week at 0°C on the test item PHMB P20D (PolyHexaMethylene Biguanide Hydrochloride at 20%)	Laboratoire PAREVA	Y
De Castro J.	3.8	2014	Persistent Foaming Analysis on Five sample batches containing different amounts of Polyhexamethylene Biguanide Hydrochloride (PHMB) according to CIPAC MT 47.1 and 47.2 Methods	Laboratoire PAREVA	Y
Grabbe R.	5.10	2011	ACTICIDE PHB 20. Examination of microbial efficacy for Product Type 6 (Definition in Annex V of 98/8/EC).	Laboratoire THOR GmBH	Y
[redacted]	6.1.3_01	2012	Acute Inhalation Toxicity Study (Nose-only) in the Rat according to OECD 403 guideline	[redacted]	Y
IBRG International Biodeterioration Research Group	5.10	2000	A method for Evaluating the Resistance of Water-based Paints to Bacterial Growth in the Wet-State-Draft (9),	Laboratoire THOR GmBH	Y
L'Haridon J.	7.7.1.1_04	2002	PHMB P20 D: Activated sludge, respiration inhibition test	Laboratoire PAREVA	Y
Laboratoire PAREVA	3.5	2007	Analytical method - pH	Laboratoire PAREVA	Y
Laboratoire PAREVA	3.6	2007	Analytical method - Density	Laboratoire PAREVA	Y
Laboratoire THOR GmBH	5.10	2009	THOR MICORBIOLOGICAL TEST METHOD D 730 - Wet state Fungal Resistance Test	Laboratoire THOR GmBH	Y
Laboratoire THOR GmBH	5.10	2009	THOR MICORBIOLOGICAL TEST METHOD D 740 Wet-state Yeast Resistance Test	Laboratoire THOR GmBH	Y

Laboratoire THOR GmbH	5.10	2002	THOR MICORBIOLOGICAL TEST METHOD D 720-Wet-state Bacterial Resistance Test	Laboratoire THOR GmbH	Y
Lanata M.	3.7	2015	Shelf life stability study at 25°C/60°C RH for 24 months on the test item "PHMB P20D (Polyhexamethylene biguanide, hydrochloride at 20%)	Laboratoire PAREVA	Y
Lopez B.	6.4_01	2013	In vitro derma penetration of PHMB across human skin according to OECD 428 Guideline	Laboratoire PAREVA	Y
Martelle I.	7.7.1.1_01	2002a	Acute toxicity in freshwater fish (96 hours) – 0.1, 1 and 10 mg/L Oncorhynchus mykiss	Laboratoire PAREVA	Y
Martelle I.	7.7.1.1_02	2002b	Acute toxicity in Daphnia 48 hours – 1, 10, 100 mg/L Daphnia magna	Laboratoire PAREVA	Y
Mazzei N.	3.11	2014	Surface Tension on the sample PHMB P20 D(Poly(HexaMethyleneBiguanide), hydrochloride at 20%)	Laboratoire PAREVA	Y
Panaiva L.	3.10	2010	DETERMINATION OF THE CINEMATIC VISCOSITY OF PHMB P20 D: 5-BATCH ANALYSIS	Laboratoire PAREVA	Y
Paradis B.	7.7.1.1_03	2002	Algal inhibition test (72 hours) – 0.01, 0.05, 0.1 mg/L Selenastrum capricornutum	Laboratoire PAREVA	Y
[redacted]	6.1.1	2002	Assessment of acute oral toxicity in rats: Acute toxic class method.	[redacted]	Y
[redacted]	6.1.2	2002	Assessment of acute dermal toxicity in rats.	[redacted]	Y
Richeux F.	6.2_01	2002	Assessment of acute irritant/corrosive effect on the skin.	Laboratoire PAREVA	Y
Richeux F.	6.2_02	2002	Assessment of acute irritant/corrosive effect on the eyes.	Laboratoire PAREVA	Y
[redacted]	6.3_01	2002	Assessment of sensitising properties on albino guinea pig: Maximisation test according to Magnusson & Kligman	[redacted]	Y
Rondon C., Tiedje M.H.	3.7	1995	Corrosion Characteristics of Polyhexamethylene Biguanide Hydrochloride (PHMB)	Laboratoire PAREVA	Y
Rueb B.	5.10	2011	Certificate	Laboratoire PAREVA	Y
Stabler D.	7.8.4	2007	Acute toxicity of PHMB P20 D on Earthworms, Eisenia fetida Using an Artificial soil test	Laboratoire PAREVA	Y

Tessier V.	6.6-02	2014	Determination of the residual PHMB after simple rinsing operation of treated surface	Laboratoire PAREVA	Y
Thery F.	5.10	2011	Détermination de l 'activité bactéricide de base du produit « PHMB P20 D » selon la norme NF EN 1040 (Avri l 2006) - Conditions obligatoires -	Laboratoire PAREVA	Y
Thery F.	5.10	2011	Détermination de l 'activité levuricide de base du produit « PHMB P20 D » selon la norme NF EN 1275 (Avril 2006) - Conditions obligatoires -	Laboratoire PAREVA	Y
Thery F.	5.10	2012	Détermination de l 'activité levuricide du produit « PHMB P20 D » selon la norme NF EN 1650 (Octobre 2008) - Activité bactéricide pour usages généraux - - Conditions obligatoires -	Laboratoire PAREVA	Y
Thom M.	3.7	2007	Storage Stability of PHMB P20 D (Poly(HexamethyleneBiguanide), hydrochloride) at 4°C for 7 days	Laboratoire PAREVA	Y
Thom M.	4.1	2007	Determination of PHMB (Poly(HexaMethyleneBiguanide), hydrochloride) in Five Batches of PHMB P20 D Eurofins-GAB GmbH Study code: 20071197/01-PC5B GLP/Unpublished	Laboratoire PAREVA	Y
Thom M.	4.1	2007	Validation of Analytical Method for the determination of PHMB	Laboratoire PAREVA	Y
Tiedje M.H.	3.7	1995	Stability of Polyhexamethylene Biguanide Hydrochloride (PHMB)	Laboratoire PAREVA	Y
Tremain S.	3.4	2007	PHMB P20 D: POLY(HEXAMETHYLENE BIGUANIDE), HYDROCHLORIDE DETERMINATION OF AUTO-IGNITION TEMPERATURE (LIQUIDS and GASES)	Laboratoire PAREVA	Y
Wedemeyer N.	7.8.6	2008	Seedling Emergence Limit Test for Non - Target Plants Following One Application of PHMB on Six Species of Plants	Laboratoire PAREVA	Y

Wedemeyer N.	7.8.6	2008	Vegetative Vigour Limit Test for Non - Target Plants Following One Application of PHMB on Six Species of Plants	Laboratoire PAREVA	Y
Witte A.	4.2	2008	Developement of an analytical method for determination of PHMB in water and soil	Laboratoire PAREVA	Y