[redacted]

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 PT04
(Food and feed areas disinfectant)

Evaluating Competent Authority: France

November 2017

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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 4 (Food and feed area disinfectants), 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 4.

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 applicant. The evaluating Competent Authority (eCA) accepted the dossier as complete for the purpose of the evaluation on June 2015.

On December 2017, the eCA submitted to ECHA2 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 4, 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.

[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

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.

1.3 Applicant

Name: Laboratoire PAREVA

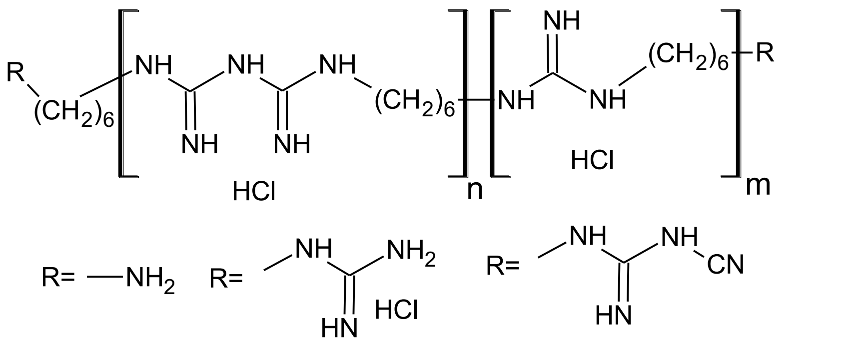
Adress: Zone Industrielle du Bois de Leuze
F-13310 Saint-Martin de Crau
France

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 hydrochloride with a mean number-average molecular weight (Mn) of 1415 and a mean polydispersity (PDI) of 4.7; - Polyhexamethylene biguanide; - 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 document 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 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.".**

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

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

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

Summary of specifications of Pareva PHMB:

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 in this dossier here 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 x 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 of active substance

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 chromatogram 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, eCA considers that if a method could allow the quantification of PHMB in soil, this method could probably not be considered as enforcement method.

- For TP 4, a spray application is proposed, a validated method of determination of PHMB in air 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 in 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 is 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 in food and feeding stuffs or another justification of non-submission of data would be required before active substance approval.

Analytical methods supplied for the analysis of the active substance, PHMB, in the formulated products SANICIL-F2 and PURISAFE-PRO is validated.

Validation data submitted cannot fully support an analytical method on PURISAFE-J due to precision and recovery not tested at actual content of PHMB in PURISAFE-J. Validated method must be submitted at product authorisation stage.

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	**SANICIL-F2**	
Manufacturer´s development code number(s)	None	
Ingredient of preparation	Function	Content %
PHMB	Active substance	20% (w/w) (Range 19.0% – 21.0%)
	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	TK: Technical Concentrate	

Trade name	**PURISAFE-PRO**	
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	AL (Other liquids to applied undiluted)	

Trade name	**PURISAFE-J**	
Manufacturer´s development code number(s)	None	
Ingredient of preparation	Function	Content %
PHMB	Active substance	4% (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	AL (Other liquids to applied undiluted)	

Trade name	**SANICIL-RTU**	
Manufacturer´s development code number(s)	None	
Ingredient of preparation	Function	Content %
PHMB	Active substance	0.016%
	Details of the product composition and information on the co-formulants are confidential	

Physical state of preparation	No data
Nature of preparation	SL: soluble liquid

Trade name	**SANICIL-WIPES**	
Manufacturer´s development code number(s)	None	
Ingredient of preparation	Function	Content %
PHMB	Active substance	0.016% *
	Details of the product composition and information on the co-formulants are confidential	
Physical state of preparation	No data	
Nature of preparation	XX: other	

* content of PHMB in the liquid that is impregnated on the wipes. Data on the content of liquid on wipes or any equivalent data is not available

2.1.2.2 Physico chemical properties of biocidal products

- **SANICIL-F2**

SANICIL-F2 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.

SANICIL-F2 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.

- **PURISAFE-PRO**

PURISAFE-PRO 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.

PURISAFE-PRO 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.

- **PURISAFE-J**

PURISAFE-J 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.

PURISAFE-J 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.

- **SANICIL-RTU and SANICIL-WIPES**

No data were provided for SANICIL-RTU and SANICIL-WIPES were provided. Complete PC properties are needed at product authorisation stage.

2.1.2.3 Methods of analysis

Validated method is available for determination of PHMB in SANICIL-F2 and PURISAFE PRO. Validation data submitted cannot fully support an analytical method on PURISAFE-J due to precision and recovery not tested at actual content of PHMB in PURISAFE-J. Validated method must be submitted at product authorisation stage.

No data were provided for SANICIL-RTU and SANICIL-WIPES. Such data are needed at product authorisation stage.

2.1.3 Intended Uses and Efficacy

2.1.3.1 Field of use envisaged

This Product Type 04 dossier for PHMB is provided to support the following use:

MG01:	Disinfectants
Product Type 04:	*Food and feed area.*
Further specification:	*Equipment, utensils, surfaces, water storage container and pipe network*

2.1.3.2 Function

Biocidal products are used as a disinfectant against bacteria and yeast in food and feed area (PT4) in areas like food, drink and milk industries (FDM), kitchens and canteens, slaughterhouses and butcheries.

The product SANICIL F2 can be used as a disinfectant for the Cleaning-In-Place systems (CIP) and to prepare soaking disinfection solutions.

The products PURISAFE PRO and PURISAFE J are used for the preliminary disinfection of containers and pipe networks of drinking water by pouring (professional users and non-professional users).

Note:
During the commenting period according to article 8(1) of the BPR , the applicant claimed as additional use the general disinfection applications for small scale surface with a ready to use product SANICIL-RTU as trigger spray and product SANICIL WIPE as impregnated wipes , both for professional users.

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.

The contact time is 1 or 5 minutes for a bactericidal activity and 15 minutes for a yeasticidal activity of PHMB depending of the use.

2.1.3.4 Objects to be protected, target organisms

The representative product for the assessment of PHMB in Product type 4 is a general disinfectant used for Food and Feed area disinfection by soaking in disinfection solutions or applied for Cleaning-in-Place (CIP) systems and preliminary disinfection of containers intended for being used as drinking water storage and disinfection of pipes network by pouring.

<u>Note</u>: In the frame of the PT5 PHMB dossier, the applicant intended to use PURISAFE products for:

- *the pre-disinfection of drinking water networks and containers dedicated to the storage of drinking water for animals (professional and non-professional uses)*
- *the direct disinfection of drinking water for animals (only professional uses).*

Intended uses for preliminary disinfection of drinking water networks and containers, are considered relevant for PT4 biocidal product and are therefore assessed in the PT4 PHMB dossier.

Besides, following the commenting period, two additional uses are claimed: general disinfection applications for small scale surface with a ready to use product and impregnated wipes.

The product is also use as a yeasticide against *C. albicans*.

The table below present the efficacy data which support the efficacy of the PHMB in the frame of the active substance dossier. The data are generated from laboratory studies and have to be consolidated at the product authorisation stage related to the actual claims of the products.

Table 2.1-1: Efficacy data which support the efficacy of PHMB

	Application method	Product	In use concentration / contact time (PHMB in the in-use solution)	Activity
Hard surface disinfection Professional use	Soaking Clean in place	SANICIL-F2 (20 % w/w a.s.)	0.016 % w/w a.s., 5 minutes 0.01% w/w a.s., 15 minutes	Bactericide Yeasticidal
Hard surface disinfection small surfaces Professional use	spraying wiping	SANICIL-RTU SANICIL - WIPE	0.016 % w/w a.s., 5 minutes 0.01% w/w a.s., 15 minutes Wipes are impregnated with a solution containing 0.016 % w/w PHMB	Bactericide Yeasticidal
-Preliminary disinfection of containers and pipe networks of drinking water -Disinfection of pipe network Professional use	pouring	PURISAFE PRO (20 % w/w a.s.)	0.036 % w/w a.s., 1 minutes 0.01% w/w a.s., 15 minutes (1 L for 499 L of water to treat)	Bactericidal Yeasticidal
-Preliminary disinfection of containers and pipe networks of drinking water -Disinfection of pipe network Non - Professional use	pouring	PURISAFE J (4 % w/w a.s.)	0.036 % w/w a.s., 1 minutes 0.01% w/w a.s., 15 minutes (10 mL for 990 mL of water to treat)	Bactericidal Yeasticidal

The efficacy data submitted in the dossier demonstrated the innate efficacy of the product at the application rate of 0.016 % w/w PHMB so then no new efficacy data is needed to support this additional claims. As agreed during BPC Working Group III 2017, only ready to use applications were assessed with the claimed doses of 0.016% w/w.

2.1.3.5 Resistance

The evaluation of the literature studies provided does not show particular resistance of fungi, yeasts and bacteria to PHMB.

Nevertheless it is <u>not</u> appropriate to conclude that PHMB resistance is not an issue and that a resistance management strategy is not required. In particular, the description in the literature of cross resistances 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 type 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

SANICIL-F2

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

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

Moreover, 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 SANICIL-TC, a classification STOT RE 1 H372 and Carc. 2 H351 is also needed.

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

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

<u>PURISAFE PRO</u>

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

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

Moreover, 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%), a classification STOT RE 1 H372 and Carc. 2 H351 is also needed.

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

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

PURISAFE J

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

Category	Eye Dam. 1 STOT RE 2 Carc.2 STOT SE 3 Cat 1 Cat 1	Eye damage Category 1 Specific target organ toxicity after repeated exposure category 2 Carcinogenicity Category 2 Specific target organ toxicity after single exposure Category 3 Aquatic Acute Aquatic Chronic
Hazard statement	H318 H373 H351 H335 H400 H410	Cause serious eye damage May cause damage to organs through prolonged or repeated exposure Suspected of causing cancer May cause respiratory irritation Very toxic to aquatic life. Very toxic to aquatic life with long lasting effects.

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

With regard to toxicological data

Classification is determined by calculation according to CLP regulation. The mention EUH 208 'Contains PHMB. May produce an allergic reaction' should appear on the label.

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

SANICIL-RTU and SANICIL WIPES

For SANICIL-RTU product and SANICIL WIPES, no study was provided. The classification is determined by calculation. No classification is needed.

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".

[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

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**

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, eCA 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, eCA 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 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 applicant at a very late stage of the assessment, i.e. during the commenting period.
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 food and feed area disinfectant SANICIL-F2 contains the biocidal active substance PHMB at 20% (active substance as produced). It has to be diluted before used at 0.03% of PHMB. The product is intended to a professional-use only. The product is also available in a ready to use product in the form of a trigger spray or impregnated wipes at the dose of 0.016% PHMB for professional (SANICIL-RTU and S ANICIL WIPES).

Biocidal product PURISAFE is available in "ready-to use" solution for a professional and non-professional use. For professional it is a 200 g/L PHMB concentration which is directly applied in tanks or network to achieve to a concentration of 0.04% PHMB. For non-professional, it is a 40 g/L PHMB concentration.

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 14C-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% is used for concentrate products and a value of 48% is used for dilution at 0.03 and 0.04% of PHMB.

For the exposure to dilution (0.016%), no dermal absorption value covering this dilution is available. In this context, a prorata correction according to the EFSA guidance on dermal absorption (2012) is performed.

A dermal absorption value of 60% is proposed.

Several studies (oral and dermal acute toxicity studies, dermal and ocular irritation and sensitisation) were performed with PHMB 20% aqueous solition (PHMB-P20D). Since SANICIL-F2 and Purisafe are 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)

[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

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.

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:

- 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 SANICIL-F2, 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%).

For purisafe J, classification is determined by calculation according to CLP regulation.
The following classification is need:

- Eye 1 H318
- STOT RE 2 H373: May cause damage to organs through prolonged or repeated exposure
- Carc. 2 H351: Suspected of causing cancer

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

2.2.1.3 Human health risk

- **SANICIL-F2**

The biocidal product SANICIL-F2 is used for the disinfection of food and feed area, disinfection of equipment, containers, consumption utensils or pipework associated with the production, transport, storage or consumption of food, feed or drink (including drinking water) for humans and animals. It can be applied by application on surface, dipping and watering.
SANICIL-F2 can also be used as a disinfectant for the Cleaning-In-Place systems (CIP), to prepare soaking disinfection solutions.

SANICIL-F2 has to be diluted before use by professional.

It is a 200 g/L PHMB concentration which is diluted at 0.15% (i.e. 0.03% PHMB) in water.

Considering the intended uses of the products, different scenarios are assessed for professional users:

- surface disinfection by mopping and/or wiping
- dipping of small object,
- watering ,
- disinfection with CIP system.

- **PURISAFE (PRO and J)**

Biocidal products PURISAFE PROP and PURISAFE J are intended to be used for preliminary disinfection of drinking water containers and pipes network.
It is available at 200 g/L for professional and non-professional and has to achieve a concentration of 0.04% PHMB.

Considering the intended uses of both products, different scenarios are assessed for professional users and non-professional users:

- preliminary disinfection of drinking water containers and pipes network.

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

The oral exposure is not considered as relevant for adult. The main route of exposure for primary exposure is therefore the dermal route.

The dermal absorption of PHMB for use of SANICIL-F2 formulation should be determined according to the PAREVA study "*In vitro* dermal penetration of PHMB across human skin according to OCDE 428 guideline".

In this context, for the exposure to concentrate solution (20% of PHMB), an absorption value of 0.6% will be used. For the exposure to diluted solution (0.04%), an absorption value of 48% will be used and for the exposure to dilution (0.016%), an absorption value of 60% will be used.

For PURISAFE-PRO use, operator will be exposed only to concentrate. A dermal absorption value of 0.6% will be therefore used.

For PURISAFE-J, no dermal absorption study is available for a solution of PHMB at 4%. In this context, the dermal absorption of a lowest dilution will be used. Thus absorption of 6% will be used.

- **Additional uses : SANICIL-RTU and SANICIL WIPE**

The biocidal products SANICIL-TU and SANICIL WIPE are used for the disinfection of food and feed small scale areas.

They can be applied by application on surface.

SANICIL-RTU is used as a ready to use product under the form of a trigger spray whereas SANICIL WIPE is used as impregnated wipes.

2.2.1.3.1 Human health risk for professional

2.2.1.3.1.1 Surface disinfection

<u>Initial claimed uses</u>

The disinfection of surface can be performed by wiping and/or mopping. For this use, the representative product is SANICIL-F2 (0.03% PHMB).

In first Tier, a combined estimation of exposure (mopping AND wiping) is performed according to the duration of exposure proposed in the Recommandation 2 of Ad hoc Working Group on Human Exposure: Mopping and wiping time PT2.

In a second Tier, an estimation of exposure during wiping OR mopping alone is performed.

1) **<u>Surface disinfection by mopping and wiping</u>**

Two phases of exposure can be expected:

- Exposure during mixing and loading of product in water;
- Exposure during application of the product by mopping and wiping.

Exposure is determined thanks to surface disinfection model (1 and 3) available in TNsG 2002[7] and reviewed in user guidance[8]. These models take in consideration the phase of mixing and loading.

As mentioned above, the duration of exposure (330 min) is chosen according to Recommandation 2 of Ad hoc Working Group on Human Exposure: Mopping and wiping time PT2.

For dermal absorption, regarding the exposure to the diluted solution (0.03%), an absorption value of 48% is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Surface disinfection by mopping and wiping after dilution of product	Gloves	77.54	**1157%**
		Gloves and coverall	22.03	**329%**

The risk is considered as unacceptable although gloves and coverall are worn.

2) Surface disinfection by wiping

Two phases of exposure can be expected:

- Exposure during mixing and loading of product in water;
- Exposure during application of the product by wiping.

Exposure is determined thanks to surface disinfection model (1 and 3) available in TNsG 2002 and reviewed in user guidance. These models take in consideration the phase of mixing and loading.

As mentioned above, the duration of exposure (220 min) is chosen according to

[7] Technical notes for guidance : human exposure to biocidal products. Guidance on human exposure 2002
[8] Technical notes for guidance : human exposure to biocidal products. Guidance on human exposure 2002. User guidance

Recommandation 2 of Ad hoc Working Group on Human Exposure: Mopping and wiping time PT2.

For dermal absorption, regarding the exposure to the diluted solution (0.03%), an absorption value of 48% is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Surface disinfection by wiping after dilution of product	Gloves	51.69	**772%**
		Gloves and coverall	14.69	**219%**

The risk is considered as unacceptable although gloves and coverall are worn.

3) Surface disinfection by mopping

Two phases of exposure can be expected:

- Exposure during mixing and loading of product in water;
- Exposure during application of the product by mopping.

Exposure is determined thanks to surface disinfection model (1 and 2) available in TNsG 2002 and reviewed in user guidance. These models take in consideration the phase of mixing and loading.

As mentioned above, the duration of exposure (110 min) is chosen according to Recommandation 2 of Ad hoc Working Group on Human Exposure: Mopping and wiping time PT2.

For dermal absorption, regarding the exposure to the diluted solution (0.03%), an absorption value of 48% is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Exposure	%AEL
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Surface disinfection by mopping after dilution of product	Gloves	3.91	58%

The risk is considered as acceptable when gloves are worn.

Additional claimed uses

1) Surface disinfection by trigger spray

Two phases of exposure can be expected:

- Exposure during application of the product by spraying using a trigger spray.
- Exposure via surface disinfection.

Exposure during spraying is determined thanks to consumer spraying and dusting model 2 and exposure during wiping is determined thanks to surface disinfection model 1 reviewed in user guidance. For wiping only exposure to the hands is considered because the product is ever applied on the treated surface and no exposure of the body is expected. Moreover, PHMB is considered non volatile

The duration exposure of 30 min/day is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The systemic risk characterisation is summarised in the following table.

Intended use (MG/PT)	Exposure scenario	PPE	Dermal exposure	%AEL
MG 1 / PT 2.01			Systemic exposure (µg/kg bw/day)	
	Ready to use spraying - **Cumulative**	-	51.7	**771%**
		gloves	1.15	17%

The systemic risk is considered acceptable when gloves are worn.

In absence of appropriate study, no AEC for inhalation route can be derived so no local risk assessment can be performed. For this specific use by trigger spray which generates an

aerosol, exposure via inhalation is a relevant route of exposure. In consequence, as no proper local risk assessment can be performed, this use is considered as unacceptable.
If at the product authorisation stage, applicant claims this use for his products, a local risk assessment via inhalation has to be performed and missing data have to be submitted in the application for product authorisation.

2) <u>Surface disinfection by impregnated wipes</u>

One phase of exposure can be expected:

- Exposure during application of the product by wiping using impregnated wipes.

Exposure is determined thanks to data available in the cleaning fact sheet of consexpo about wet tissues (p63). Considering the low volatility of the active substance, no exposure by inhalation is expected.

For dermal absorption, regarding the exposure to the diluted solution (0.016%), an absorption value of 60% is used.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Dermal exposure**	**%AEL**
MG 1 / PT 2.01			Systemic exposure (µg/kg bw/day)	
	Ready to use wipes	-	7.52E-02	1.1%

The risk is considered acceptable without PPE.

2.2.1.3.1.2 Dipping of small objects

For this use, the representative product is SANICIL-F2 (0.03% PHMB).

Two phases of exposure can be expected:

- Exposure during mixing and loading of product in water;
- Exposure during dipping of objects in the solution.

Exposure is determined thanks to dipping model1 available in TNsG 2002 and reviewed in user guidance. These models take in consideration the phase of mixing and loading.

The duration of exposure of 60 min/day is proposed by eCA considering that dipping of disinfection is longer than for manual dipping of wood (30 min recommended in TNsG 2002).

For dermal absorption, regarding the exposure to the diluted solution (0.03%), an absorption value of 48% is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Dipping of small object	Gloves	29.33	**438%**
		Gloves and coverall	6.26	93%

The risk is considered as acceptable when gloves and coverall are worn.

2.2.1.3.1.3 Watering

For this use, the representative product is SANICIL-F2 (0.03% PHMB).

Two phases of exposure can be expected:

- Exposure during mixing and loading of product in water;
- Exposure during watering.

Exposure is determined thanks to Subsoil treatment model 2 - watering can -of TNsG 2002, reviewed by user guidance page 28. This model takes in consideration the phase of mixing and loading.

The duration of exposure of 120 min/day is proposed according to duration proposed in TNsG 2002 page 62 for Ring main fed hose duration.

For dermal absorption, regarding the exposure to the diluted solution (0.03%), an absorption value of 48% is used.

In first Tier, exposure is estimated without personal protective equipment (PPE). In a second Tier, PPE could be added.

The risk characterisation is summarised in the following table.

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

MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Watering	Gloves	25.06	**374%**
		Gloves and coverall	16.25	**243%**

The risk is considered as unacceptable although gloves and coverall are worn.

2.2.1.3.1.4 Disinfection with CIP system

For this use, the representative product is SANICIL-F2 (0.03% PHMB).

Exposure is expected only during mixing and loading phase. In this context, exposure is estimated thanks to EUROPOEM II database issued from User guidance[9] and HEEG Opinion on the use of available data and models for the assessment of the exposure of operators during the loading of products into vessels or systems in industrial scale, agreed at TM I08.

In this context, the operator is exposed only to the concentrate solution. A dermal absorption value of 0.6% is therefore used.

In a worst case, it is considered that 1000L of diluted solution at 0.03% of PHMB is needed for CIP system. In this context, approximately 0.3 kg of active substance is need.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Disinfection with CIP system	No PPE	2,99E-01	4%

The risk is considered as acceptable without PPE.

2.2.1.3.1.5 Preliminary disinfection of drinking water containers and pipes network

For this use, the representative product is PURISAFE-PRO (0.04% PHMB).

Exposure is expected only during mixing and loading phase. In this context, exposure is

[9] Technical notes for guidance : human exposure to biocidal products. Guidance on human exposure 2002. User guidance

estimated thanks to EUROPOEM II database issued from User guidance and HEEG Opinion on the use of available data and models for the assessment of the exposure of operators during the loading of products into vessels or systems in industrial scale, agreed at TM I08.
In this context, the operator is exposed only to concentrate. A dermal absorption value of 0.6% is therefore used.
In a worst case, it is considered that 1000L of diluted solution at 0.04% of PHMB is needed for disinfection or 0.4 kg of active substance.
The risk characterisation is summarised in the following table:

Intended use (MG/PT)	**Exposure scenario**	**PPE**	**Exposure**	**%AEL**
MG 1 / PT 2.01			Systemic Exposure (µg/kg/day)	
USE				
	Preliminary disinfection of drinking water containers and pipes network	No PPE	3.98E-01	6%

The risk is considered as acceptable without PPE.

2.2.1.3.2 Human health risk for non-professional

Only preliminary disinfection of drinking water containers and pipes network is considered for non-professionals. For this use, the representative product is PURISAFE-J (0.04% PHMB).

Exposure is expected only during mixing and loading phase. In this context, exposure is estimated thanks to mixing and loading model 2 issued from User guidance.

In this context, the non-professional users are exposed only to concentrate. A dermal absorption value of 0.6% is therefore used.

The risk characterisation is summarised in the following table.

Intended use (MG/PT)	**Exposure scenario**	**Exposure**	**%AEL**
MG 1 / PT 4		Systemic Exposure (µg/kg/day)	
	Preliminary disinfection of drinking water containers and pipes network.	6.4 E-02	1%

The risk is considered as acceptable for non-professional users during the mixing and loading phase.

2.2.1.3.3 Human health risk for secondary exposure

Different scenarios of exposure can be considered for secondary exposure:

- Exposure to volatilised residues by inhalation;
- Exposure to residues on disinfected surface by dermal route, Contrary to the uses covered by PT2, exposure of toddler crawling on disinfected surface is not expected for uses covered by PT4 as the surfaces considered for disinfection are mostly in industrial or area not accessible to toddler.
- Exposure to residues in drinks, food, food and products of animal origin by ingestion.

Considering the low vapour pressor of PHMB, the exposure to residues by inhalation is considered as negligible.

For exposure to residues by dermal route, two scenarios can be considered:

- Exposure to wet disinfected surface;
- Exposure to dried disinfected surface.

For each type of surface (wet or dried), a reverse scenario to determine the maximum area that could be rubbed by an adult without risk of systemic effects is performed.

The dose of application proposed by applicant is used for this scenario (10 L of diluted solution for 100 m^2 of floor or 0.1L of diluted solution/m^2).

Dermal absorption values of 48% and 60% are used to determine the exposure to wet surface. No dermal absorption study on the dried residues is available. It was decided at the WG V 2016 to use the same dermal absorption values than the dilutions. Although this approach is conservative, it is in line with the EFSA guidance on dermal absorption.

In order to refine exposure, applicant provided a study to estimate the efficacy of rinse ("Rinse efficacy of treated surface after the used of PHMB solution") and determine the proportion of residues at the surface.

However, this study presents some limitations/deficiencies to be accepted. In this context, this study was not retained and no refinement of the exposure is considered.

Moreover, ingestion of contaminated food or drink is possible, considering a contamination of food and drink in contact with treated utensils, equipment or after disinfection of closed machineries by Cleaning-In-Place (CIP). Consumer exposure can also result from ingestion of food and products of animal origin contaminated with PHMB.

2.2.1.3.3.1 Wet surface

For surface treated by mopping/wiping, dipping, watering and CIP, the maximum area that could be rubbed by an adult is determined from AEL of 6.7 µg/kg/d for an adult of 60kg. Considering a transfer of 100%, an adult can be exposed until a surface of 279 cm^2/d.

This surface is low (lower than hands palms). Therefore, the risk is considered unacceptable.

For surface treated by trigger spray or impregnated wipes, the maximum area that could be rubbed by an adult is determined from AEL of 6.7 µg/kg/d for an adult of 60kg. Considering a transfer of 100%, an adult can be exposed until a surface of 418 cm^2/d.

This surface is low. Therefore, the risk is considered unacceptable.

2.2.1.3.3.2 Dried surface

For surface treated by mopping/wiping, dipping, watering and CIP, the maximum area that could be rubbed by an adult is determined from AEL of 6.7 µg/kg/d for an adult of 60kg. Considering a transfer of 18%, an adult can be exposed until a surface of 0.16 m^2/d.

This surface is low. Therefore, the risk is considered unacceptable for surface disinfection. The risk could be considered acceptable for dipping small objects and disinfection with CIP system.

For small surface treated with trigger spray or impregnated wipes or small object disinfected by dipping , the maximum area that could be rubbed by an adult is determined from AEL of 6.7 µg/kg/d for an adult of 60kg. Considering a transfer of 18%, an adult can be exposed until a surface of 0.23m^2/d.

This surface is low. However, application is limited to the disinfection of small surfaces or small objects. It has to be noted that the dermal adsorption used for the risk assessment related to this use is a very worst case. Therefore, the risk is considered acceptable for small scale surface disinfection.

2.2.1.3.3.3 Consumer exposure via food

To be noted (as discussed at HH WGIII 2017): preliminary assessment of the transfer of biocidal active substance residue into food and feed is performed according to non-agreed guidance and therefore is an eCA proposal.

Secondary exposure of the general public is possible via ingestion of food or consumption of drinks in contact with remaining residues on the utensils, equipment or surfaces after treatment. Moreover, livestock can be exposed to PHMB via ingestion of contaminated feed and or consumption of contaminated drinks. Therefore, there is also a potential for secondary human exposure arising from consumption of food of animal origin contaminated with residues of PHMB. When livestock exposure is significant, then a secondary exposure to general public via ingestion of food from animal origin has to be assessed. Therefore, in the frame of this assessment, consumer exposure via food including food of animal origin has been evaluated.

To evaluate residue transfer into food and feed, dipping, wiping/mopping and CIP scenarios were considered. For residue transfer into drink, only CIP scenario is used as this is the most representative use for drink and considered as a worst case.

No specific hydrolysis studies were provided. Based on physical-chemical properties of PHMB, the decomposition of PHMB in normal circumstances of use is not expected and only PHMB is considered 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 (HERA, Feb 2005[10]). 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 utensils, equipment or surfaces which may strongly limit the effectiveness of the rinsing. **Therefore, rinsing procedure is only considered for information in this assessment**.

By this way following scenarios are considered for dipping and wiping/mopping 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 surfaces can migrate into food and feed.
- - In a second Tier (informative only), a rinsing procedure is taken into account (only 10% of PHMB remain on surfaces and are available for a transfer into food and feed).

For disinfection of CIP systems, only the first tier is considered as provided rinsing study is not representative of this use. Indeed, CIP systems are usually machines of high complexity and are mainly rinsed by automated cleaning. The model set up and used in rinsing study (described above) did not adequately reflect rinsing conditions for CIP systems.

❖ **Indirect exposure via food (except food of animal origin) and drinks**

o **Results of indirect exposure**

- **Disinfection by dipping:**

As exposure scenario proposed by the applicant is not considered reliable and as no default values and guidance document are available for intended uses, eCA considers more relevant to

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

assess consumer exposure through the migration of substance from residual dishwashing product from utensils into food. It is considered that the utensils and equipment are daily dipped in a 0.03% w/w a.s. solution (the maximal intended concentration covering validated efficacy dose rate). Default values used for this scenario are detailed in table below.

Table 2.2-2: Input values and assessment of indirect oral exposure (dipping scenario)

Use and PT4 specific parameters		**Value**
Duration (HERA, Feb2005)		1 day
Body weight of adult (HERA, Feb2005)		60 kg
Body weight of child (HERA, Feb2005)		10 kg
Area of dishes/eating utensils in daily contact with food (HERA, Feb2005)		5400 cm²
Amount of water left on non-rinsed dinnerware (HERA, Feb2005)		5.5×10^{-4} ml/cm^{2}
Active substance concentration (see efficacy section)	In product	20% a.s. w/w (in water)
	Corresponding effective concentration considered in water	0.03% a.s. w/w (in water)
	PHMB concentration after the dilution of the product for dipping solution	300 mg a.s./L
Residue transfer factor from the utensils, equipment to food	Tier I – no rinsing (all residues remain on treated utensils, equipment)	100%
	Tier II – one effective rinsing (only 10% of residues remains on treated utensils, equipment) (HERA, Feb2005)	10%
Concentration of active substance in food	Tier I – no rinsing (all residues remain on treated utensils/equipment)	0.891 mg a.s./kg food
	Tier II –one effective rinsing (only 10% of residues remains on treated utensils/equipment) (HERA, Feb2005)	0.089 mg a.s./kg food
Exposure	Child/Tier I	8.91×10^{-2} mg a.s/kg b.w./d
	Adult/Tier I	1.49×10^{-2} mg a.s/kg b.w./d
	Child/Tier II	8.91×10^{-3} mg a.s/kg b.w./d
	Adult/Tier II	1.49×10^{-3} mg a.s/kg b.w./d

- **Disinfection <u>by wiping/mopping</u>**

It is considered that SANICIL F2 products containing 0.03% w/w a.s. are daily used as disinfectant in food areas. An amount of 6 mg a.s./m² was determined by considering a film thickness of 20 µm of remaining solution on all treated surfaces (ARTFood/formerly DRAWG)[11].
The results of the exposure assessment are presented in the table below.

Table 2.2-3: Input values and assessment of indirect oral exposure (wiping/mopping scenario)

Use and PT4 specific parameters		**Value**
Duration *(ARTFood/formerly DRAWG)*[12]		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/capita (i.e 0.2 m²/capita)
Water film thickness on treated surfaces *(ARTFood/formerly DRAWG)*		20 µm
Residual solution of SANICIL-F2 on treated surfaces		0.002 mL/cm²
Active substance concentration (see efficacy section)	Corresponding effective concentration considered in water	0.03% a.s. w/w (in water)
	PHMB concentration after product dilution for wiping/mopping use	300 mg a.s./L
Remaining concentration of PHMB on treated surface		6 mg a.s./m²
Residue transfer factor from surfaces to food	Tier I – no rinsing (all residues remain on treated surfaces)	100%
	Tier II – one effective rinsing (only 10% of residues remains on treated surfaces) (HERA, Feb2005)	10%
Concentration of active substance in food	Tier I – no rinsing (all residues remains on treated surfaces)	1.2 mg a.s./kg food
	Tier II –one effective rinsing (only 10% of residues remains on treated surfaces) (HERA, Feb2005)	0.12 mg a.s./kg food
Exposure	Child/Tier I	0.12 mg a.s./kg b.w./d

[11] ARTFood/DRAWG (2014) : Guidance on Estimating Transfer of Biocidal Active Substances into Foods – Professional Uses – 2014 - "Water film thickness on external surface of bottle") – draft not yet published
[12] ARTFood/DRAWG (2014) : Guidance on Estimating Transfer of Biocidal Active Substances into Foods – Professional Uses – 2014 - draft not yet published

Use and PT4 specific parameters		Value
	Adult/Tier I	0.02 mg a.s./kg b.w./d
	Child/Tier II	0.012 mg a.s./kg b.w./d
	Adult/Tier II	0.002 mg a.s./kg b.w./d

- **Disinfection by <u>Cleaning-In-Place systems</u> (CIP) – eCA proposed scenario**

It is considered that closed machineries are daily disinfected by CIP with a 0.03% w/w a.s. solution.

According to the European draft guidance document (2014)[10], in order to develop a model suitable to estimate biocide residues in food or drink for CIP scenario, it is necessary to have internal volumes or internal areas of food producing machinery as well as the amounts of food or drink that come into contact with the remaining residues of disinfectant on surfaces. Corresponding parameters are highly dependent of food or drink, the size of the company and the design of the equipment making it impossible to obtain reliable information or to set standardised values.

The applicant considers that exposure assessment performed for disinfection by dipping covers CIP use. eCA disagrees since no details were provided about the type of closed machinery used. Therefore, a worst case scenario for disinfection of a closed food processing installation (CIP scenario) was proposed by eCA.

Consumer exposure results (for food ingestion and drink consumption) are presented in tables below.

Table 2.2-4: Input values and assessment of indirect oral exposure (Food - CIP scenario)

Use and PT4 specific parameters	Value
Duration *(ARTFood/formerly DRAWG)*[10]	1 day
Body weight of adult *(ARTFood/formerly DRAWG)*	60 kg
Body weight of child *(ARTFood/formerly DRAWG)*	10 kg
Cylinder volume (i.e. pipe) (eCA proposition see details in the CAR)	1 L
Inner diameter of the pipe (eCA proposition see details in the CAR)	1 cm
Cylinder length (eCA calculation see details in the CAR)	1273 cm
Inner surface area of the pipe in contact with food (eCA calculation see details in the CAR)	4000 cm² (i.e 0.4 m²)
Water film thickness on treated surfaces	20 µm

Use and PT4 specific parameters		Value
Remaining SANICIL-F2 volume on treated surfaces (eCA calculation see details in the CAR)		8 mL
Active substance concentration (see efficacy section)	Corresponding effective concentration considered in water	0.03 % a.s. w/w (in water)
	PHMB concentration after product dilution for CIP use	300 mg a.s/L
Remaining concentration of PHMB remaining SANICIL-F2 solution		2.4 mg
Residue transfer factor from the surfaces to food	Tier I – no rinsing (all residues remain on treated surfaces)	100%
Concentration of active substance in food	Tier I – no rinsing (all residues remain on treated surfaces)	2.4 mg a.s./kg food
Exposure	Child/Tier I	0.24 mg a.s./kg b.w./d
	Adult/Tier I	0.04 mg a.s./kg b.w./d

Table 2.2-5: Input values and assessment of indirect oral exposure (Drink - CIP scenario)

Use and PT04 specific parameters		Value
Exposure scenario parameters (duration, body weight, cylinder volume, inner diameter of the pipe, cylinder leigh, inner surface of the pipe in contact with food, water film thickness on treated surfaces) for CIP scenario-Food		See table above
Remaining SANICIL-F2 volume on treated surfaces		8 mL
Active substance concentration (see efficacy section)	Corresponding effective concentration considered in water	0.03% a.s. w/w (in water)
	PHMB concentration after product dilution for CIP use	300 mg a.s/L
Remaining concentration of PHMB remaining SANICIL-F2 solution		2.4 mg

Use and PT04 specific parameters		Value
Residue transfer factor from the surfaces to drink	Tier I – no rinsing (all residues remain on treated surfaces)	100%
Concentration of active substance in drink	Tier I – no rinsing (all residues remain on treated surfaces)	2.4 mg a.s./L drink
Water intake[13]	For a 1 year old child weighting 10 kg	1 L/day
	For an adult	2 L/day
Exposure	Child/Tier I	0.24 mg a.s./kg b.w./d
	Adult/Tier I	0.08 mg a.s./kg b.w./d

- **Results of risk assessment for disinfection by dipping, wiping/mopping and by CIP**

The exposures were calculated for adult and child and were compared to the toxicological reference values (Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD) of 0.12 mg a.s./kg b.w./day). Chronic and acute exposures are respectively expressed in % of ADI and % of ARfD to conclude on the chronic/acute risk acceptability. Results are presented in table below.

Table 2.2-6: Risk characterisation for oral indirect exposure (Dipping, wipping-mopping anc CIP scenarii)

Oral indirect exposure assessment		**Dipping scenario - Food**		**Wiping/mopping scenario - Food**		**CIP scenario – Food and drink**	
General public considered	**Tier**	**Oral exposure** (mg a.s/kg b.w./d)	**Fraction of ADI/ARfD**	**Oral exposure** (mg a.s/kg b.w./d)	**Fraction of ADI/ARfD**	**Oral exposure** (mg a.s/kg b.w./d)	**Fraction of ADI/ARfD**
Child	Tier I- No rinsing	8.91×10^{-2}	74.3 %	0.12	100%	Food: 0.24 Drink:0.24	**Food:200 %** **Drink:200 %**
Adult	Tier I-	1.49 x 10-	12.4 %	0.02	16.7%	Food:	Food:33.3%

[13] EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA); Scientific Opinion on Dietary reference values for water. EFSA Journal 2010; 8(3):1459. doi:10.2903/j.efsa.2010.1459. Available online:www.efsa.europa.eu
EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579. Available online: www.efsa.europa.eu

	No rinsing	2				0.04 Drink:0.08	Drink:66.7%
Child	Tier II-With 1 rinsing step	8.91×10^{-3}	7.4 %	0.012	10%	Not feasible with information/data available at present time	
Adult	Tier II-With 1 rinsing step	1.49×10^{-3}	1.2 %	0.002	1.7%	Not feasible with information/data available at present time	

With CIP scenario, no rinsing step was taken into account because submitted rinsing study protocol is not representative of disinfection by CIP. Exposure is above ADI. Therefore, a reverse scenario is proposed with same default values as stated in calculation for the Tier I:

- Active substance concentration : 0.03% w/w
- Water film thickness on treated surfaces : 20 µm
- Remaining SANICIL-F2 volume on treated surfaces : 8 mL
- Residue transfer factor from the surfaces to food or drink is 100%.

Condition: the risk is acceptable when exposure is below ADI.

For CIP scenario, a rinsing step is necessary to refine exposure and to reach an acceptable risk (i.e dilution factor above 0.24/0.12=2 (reverse calculation))

For dipping scenario, the risk for consumer via food is considered acceptable with and without rinsing.

For wiping/mopping scenario, the default value of 0.2 m^2 for contaminated surface area in contact with food (that represents daily exposure of consumer) used for risk assessment for both adult and child seems not representative and too high for child feeding. Child oral exposure without rinsing is then considered to be below toxicological reference values. Therefore, the risk for consumer via food is considered acceptable with and without rinsing.

For CIP scenario, the risk assessment for indirect exposure via food is not acceptable for child but it is considered as not finalized because adequate data to refine the scenario are missing.. More information on the following points is necessary to refine and properly address the risk assessment and propose reliable restriction measures:

- representative rinsing studies to cover uses at stake (final reports with full analytical validation),
- exhaustive data on treated systems at stake for each use or a demonstration of a sufficiently worst case exposure situation which cover all CIP systems.

❖ **Indirect exposure via food of animal origin**

According to intended uses, feed and drink dedicated to animals may be contaminated with PHMB. Therefore, consumer exposure following the transfer of residues of PHMB into food and products of animal origin was assessed.

The potential for indirect exposure via food may arise from consumption of food of animal origin contaminated with PHMB residues. According to the European draft guidance document (2014)[14]: *"In the stepwise approach, exposure estimates are performed successively in different tiers. If the pre-defined threshold of concern (trigger value = 0.004 mg a.s/kg animal bw/day) is exceeded, exposure estimation moves to the next tier. If the trigger value is not exceeded, no significant residues are expected in food of animal origin and dietary risk assessment is stopped [secondary exposure to the general public is not considered relevant] unless the substance is exceptionally toxic".*

Livestock exposure was estimated according to the methodology and values proposed by ARTFood[8]. No experimental data/studies were provided. Consequently, the daily exposure to PHMB was assessed with worst case scenarios using default values from the ARTFood draft guidance (2014).

In order to estimate animal exposure, first, the concentration of the active substance in feed or drink is calculated. Then, the following parameters have been considered:

- Animal feed and drink consumptions: in the frame of this evaluation, it was considered that animal feed and drink intakes were only constituted by feed and drink contaminated with PHMB.
- Uniform distribution of PHMB in animal tissues,
- Accumulation in livestock tissues of all PHMB consumed day by day over each respective livestock batch period was summed in framework of this evaluation (beside its log Kow<3, there is no other relevant reliable information or parameters available to moderate this assumption: PHMB is a complex charged polymer made of low, mid and high molecular weight fractions and no data about distribution and preferential accumulation in livestock tissues were provided). It has been concluded at HH WGIII 2017 that accumulation potential of the active substance cannot be ruled out.

  - **Livestock and consumer exposures**

- **Livestock exposure**

  - Disinfection of utensils, equipment, pipeworks in food and feed areas:

As describe above, consumer exposure assessment begins with estimation of residues in animal tissues.

To estimate animal exposure, no default values for contaminated surface area in contact with feed (that represents daily exposure of animal) are available. Therefore, the following approaches have been considered to estimate residue transfer into feed for intended uses:

- - Wiping/mopping use: it might be considered that default value of 0.2 m^2 for contaminated surface area in contact with food (default value detailed in section

[14] ARTFood/DRAWG (2014): Dietary Risk Assessment Working Group. « Guidance on estimating livestock exposure to biocidal active substances" – draft not yet published

above) might be used to estimate residue transfer into 1 kg of feed or drink, which is worst case.

- Dipping use is supposed to involve disinfection of small utensils. Without exhaustive details of material really involved at authorization level for this use, surface area in contact with feed after disinfection by dipping is considered lower than 0.2m^2 and consequently covered by wiping/mopping scenario.
- CIP use: the scenario described above (CIP scenario) might be relevant to estimate residue transfer into feed.

For wiping/mopping uses (which covers dipping use – see above), the assessment is performed with and without any rinsing step procedure. For disinfection of CIP systems, only the first tier is considered as provided rinsing study is not representative of this use (see above).

According to this approach, estimation shows that the exposure to PHMB used for the disinfection of primarily cleaned areas used for feed or drink preparation covered by PT4 might be significant (above the trigger value of 0.004 mg as/kg b.w./day as defined in the ARTFood guidance[8]) for the majority of livestock categories with or without rinsing. For products of animal origin (milk, eggs) daily collected, it was considered that all the residues were daily transferred into milk or eggs.

As the trigger value of 0.004 mg a.s./kg b.w./d is exceeded for all species, secondary exposure to general public via ingestion of food and products of animal origin should be assessed.

- Disinfection of drinking water networks for animals and containers dedicated to the storage of drinking water for animals – professional and non-professional uses

PHMB can be used for the pre-disinfection of containers dedicated to the storage of drinking water for animals and for the pre-disinfection of drinking water networks for animals. For PURISAFE products, the effective concentration of PHMB in water is 0.04 % w/w (see efficacy section).
Secondary exposure after ingestion by livestock of water contaminated with PHMB and incidence on the consumer safety following the transfer of residues of PHMB in food and products of animal origin is assessed.

For professional uses, the CIP scenario is considered for the pre-disinfection of drinking water networks to evaluate residue transfer into drinking. The surface of the containers involved to store and in contact with water for animals is considered of lower importance (rectangular parallelepiped shape of large volume vs cylinder of small inner diameter) than water networks scenario. Water network is considered as a worst case.

For non-professional, the main representative use is disinfection of containers and main representative animal species are rabbits and chickens. Therefore, the container scenario was considered for the pre-disinfection of containers dedicated to the storage of drinking water for chickens and rabbits.

Since frequency of use per batch period (animal living) was not available from the applicant, it was decided to proceed gradually and cumulate applications per application until reaching for exposure above toxicological reference values.

The rinsing study detailed previously involves treated surfaces and consequently does not match with the use for network and container disinfection. Therefore, only the first tier is considered.

According to this approach, estimation shows that the exposure to PHMB used for the disinfection of drinking water networks and containers might be significant (above the trigger value of 0.004 mg as/kg b.w./day as defined in the ARTFood guidance[8]) for the majority of livestock categories without rinsing. For products of animal origin (milk, eggs) daily collected, it was considered that all the residues were daily transferred in milk or eggs. As the trigger value of 0.004 mg a.s./ kg b.w./d is exceeded for all species, secondary exposure to general public via ingestion of food and product of animal origin should be assessed.

- **Consumer exposure:**

As the trigger animal exposure value of 0.004 mg a.s./kg b.w./d is exceeded, consumer exposure assessment was considered for:

- Disinfection of surfaces or pipeworks in contact with feed and drinks : **wipping/mopping and CIP scenarios**
- Disinfection of containers and drinking water networks dedicated to animals : **drinking water networks scenario for professional and container scenario for non-professional**

Human exposures were estimated using EU consumption values for food of animal origin (Consumer standard food basket)[15] and are summarized in tables below.

Table 2.2-7: Indirect exposure assessment from standard food basket: <u>wiping/mopping and CIP scenarii</u>

Scenario		Feed - Tier I (no rinsing)		Feed - Tier II (with rinsing)		Drink - Tier I (no rinsing)
		Wiping/mopping*	CIP	Wiping/mopping*	CIP	CIP
Consumer exposure (mg a.s/pers/d)	Meat - Beef cattle	22.30	44.65	2.23	Not feasible with information/data available at present time	111.60
	Eggs - laying hens	0.25	0.50	0.03		0.95
	Milk - dairy cattle	2.56	5.12	0.26		22.63

15 Human exposure was estimated using EU consumption values for food of animal origin (Consumer standard food basket). Volume 8: Notice to applicants and Guideline – Veterinary medicinal products : Establishment of maximum residue limits (MRLs) for residues of veterinary medici,al products in foodstuffs of animal origin

	Sum of daily exposure (meat, eggs and milk)	25.11	50.26	2.52		135.18
Human body weight - adult (kg)		60				
Consumer exposure (mg a.s./kg b.w./d)	**Sum of daily exposure (meat, eggs and milk)**	0.42	0.84	0.04	Not feasible with information/data available at present time	2.25

***** eCA considers that dipping use is covered by wiping/mopping use.

Table 2.2-8: Indirect exposure assessment from standard food basket: professional use - <u>drinking water networks scenario</u>

Scenario		**Tier I**		
		Networks		
Number of disinfection per batch livestock period		**1**	**2**	**5**
Consumer exposure (mg a.s/pers/d)	**Meat - Beef cattle**	0.16	0.32	0.80
	Eggs - laying hens	1.27	1.27	1.27
	Milk - dairy cattle	30.18	30.18	30.18
	Sum of daily exposure (meat, eggs and milk)	31.61	31.77	32.25
Human body weight - adult (kg)		60		
Consumer exposure (mg a.s./kg b.w./d)	**Sum of daily exposure (meat, eggs and milk)**	0.527	0.529	0.537

Table 2.2-9: Indirect exposure assessment from standard food basket – Non-professional use: Container scenario

Scenario	**Tier I (no rinsing)**			
	Container			
Number of disinfection per batch livestock period	**1**	**2**	**5**	**1500**

Consumer exposure (mg a.s/pers/d)	**Meat - Beef cattle**	0.0048	0.0096	0.024	7.2
	Eggs - laying hens	0.019	0.019	0.019	0.019
	Sum of daily exposure (meat, eggs)	0.0238	0.0286	0.043	7.219
Human body weight - adult (kg)		60			
Consumer exposure (mg a.s. /kg b.w./d)	**Sum of daily exposure (meat and eggs)**	$4x10^{-4}$	$4.8x10^{-4}$	$7.2x10^{-4}$	0.12

- **Risk assessment for consumer via food and products of animal origin**

Estimated human exposure is then compared to dietary risk reference values. Actually, European Medicines Agency considers only adult chronic risk assessment. Therefore, only chronic risk calculations were performed in the frame of this dossier. Toxicological reference values (acceptable daily intake (ADI) and acute reference dose (ARfD)) are both established at 0.12 mg/kg b.w./day.

Risks for consumer via food are presented in table below.

Table 2.2-10: Risk assessment with standard food basket - <u>wiping/mopping and CIP scenarii</u>

Risk for consumer via food and products of animal origin					
Scenario	**Feed - Tier I (no rinsing)**		**Feed - Tier II (with rinsing)**		**Drink - Tier I (no rinsing)**
	Wiping/ mopping	**CIP**	**Wiping/ mopping**	**CIP**	**CIP**
Consumer exposure (mg a.s./kg b.w./d)	0.42	0.84	0.04	Not feasible with information/data available at present time	2.25
ADI (mg a.s./kg b.w./d)	0.12				
% of ADI	**350**	**700**	33	Not feasible with information/data available at present time	**1875**

With CIP scenario, no rinsing step was taken into account because submitted rinsing study protocol is not representative of disinfection by CIP. Exposure is above ADI. Therefore, a reverse scenario is proposed with same default values as stated in calculation for the Tier I:

- Active substance concentration : 0.03% w/w
- Water film thickness on treated surfaces : 20 µm
- Remaining SANICIL-F2 volume on treated surfaces : 8 mL
- Residue transfer factor of 100% from the surfaces to the feed

Condition: the risk is acceptable when exposure is below ADI.

For CIP scenario, **a rinsing step is necessary to refine exposure** and to reach an acceptable risk (i.e. dilution factor above to 2.25/0.12 = 19 (reverse calculation)).

For all assessed uses, risk assessment for indirect exposure via food of animal origin is considered as not finalised. More information on the following points is necessary to refine and properly address the risk assessment and propose reliable restriction measures:

- level of residues of PHMB in animal commodities (tissues, milk, eggs)
- representative rinsing studies to cover uses at stake (final reports with full analytical validation)
- exhaustive treated systems at stake for each use or a demonstration of a sufficiently worst case exposure situation which cover all CIP systems.

Table 2.2-11: Risk assessment with standard food basket – Professional use - drinking water networks scenario

Risk for consumer via food and products of animal origin				
Scenario	**Networks – Tier I**			
Number of disinfection per batch livestock period	**1**	**2**	**5**	**…**
Consumer exposure (mg a.s./kg b.w./d)	0.527	0.529	0.537	
ADI (mg a.s./kg b.w./d)	0.12			
% of ADI	**439**	**441**	**448**	

With water network scenario, no rinsing step was taken into account because rinsing study protocol is not representative of disinfection of drinking water networks. Exposure is above ADI. Therefore, a reverse scenario is proposed with same default values as stated in calculation for the Tier I:

- Active substance concentration : 0.04% w/w
- Water film thickness on treated surfaces : 20 µm
- Remaining PURISAFE products volume on treated surfaces : 8 mL
- Residue transfer factor from the surfaces to water is 100%.

Condition: the risk is acceptable when exposure is below ADI.

For drinking water networks scenario and based on only 1 application per batch livestock period, **a rinsing step is necessary to refine exposure** and to reach an acceptable risk (i.e. dilution factor above to 0.527/0.12 = 4.5 (reverse calculation)).

For drinking water networks uses, risk assessment for indirect exposure via food of animal origin is considered as not finalised. More information on the following points is necessary to refine and properly address the risk assessment and propose reliable restriction measures:

- level of residues of PHMB in animal commodities (tissues, milk, eggs)
- representative rinsing studies to cover uses at stake (final reports with full analytical validation)

- detail of drinking water networks installation at stake.

Table 2.2-12: Risk assessment with standard food basket – Non-professional use: Container scenario

Risk for consumer via food and products of animal origin				
Scenario	**Containers – Tier I**			
Number of disinfection per batch livestock period	**1**	**2**	**5**	**1500**
Consumer exposure (mg a.s./kg b.w./d)	$4x10^{-4}$	$4.8x10^{-4}$	$7.2x10^{-4}$	0.12
ADI (mg a.s./kg b.w./d)	0.12			
% of ADI	0.33	0.40	0.60	100

With container scenario, no rinsing step was taken into account because rinsing study protocol is not representative of disinfection of containers. Exposure is below ADI until 1500 disinfections per livestock lifetime. Considering a maximum of 1disinfection of containers per day and a maximum lifetime of 3 years for chickens and rabbits, the maximum number of disinfection will not be reached. Therefore, risk for consumer via food of animal origin is considered acceptable for non-professional use.

❖ **Overall conclusion for indirect exposure via food including food of animal origin and drinks:**

- Disinfection of utensils, equipment, pipeworks in food and feed areas

Overall conclusions are summarized in table below.

Table 2.2-13: Risk assessment conclusions for the consumer

Scenario	Uses	Food	Feed	Drink
Tier I (no rinsing)	**Dipping**	Acceptable	Covered by wiping/mopping	Not applicable
	Wiping/mopping	Acceptable	Not finalized with information/data available at present time	Not applicable
	CIP	Not finalized with information/data available at present time		Not finalized with information/data available at present time
Tier II (with rinsing)	**Dipping**	Acceptable	Covered by wiping/mopping	Not applicable
	Wiping/mopping	Acceptable	Acceptable	Not applicable
	CIP	Not finalized with information/data available at present time		

As a conclusion, risk assessment for the consumer is currently considered as:

- **Acceptable for dipping, and wiping/mopping uses without a rinsing step when considering consumption of food excepting food and products of animal origin.**
- **Not finalized for dipping and wiping/mopping uses when considering consumption of food and products of animal origin**

- **Not finalized for all CIP uses.**

At product authorization stage, Member States shall pay attention to risk related to food, food and products of animal origin and drink consumption, when relevant. Moreover, in case of acceptable risks for all assessed uses, a cumulative consumer risk assessment should be performed taking into account exposure via food, food and products of animal origin and drinks.

- Disinfection of drinking water networks and containers dedicated to the storage of drinking water for animals

Overall conclusions are summarized in table below.

Table 2.2-14: Risk assessment conclusions for consumer via food – professional use

Scenario	Uses	Conclusion
Tier I	Containers	Covered by drinking water networks
	Drinking water networks	Not finalized with information/data available at present time

Table 2.2-15: Risk evaluation conclusions for consumer via food – non-professional use

Scenario	Uses	Conclusion
Tier I	Containers	Acceptable
	Drinking water networks	Not applicable

The assessment of human exposure via food and products of animal origin after use of PHMB for disinfection of drinking water networks and containers dedicated to the storage of drinking water for animals is considered not finalised for professional uses. Based on non-professional use, risk for consumer is considered acceptable.

At product authorization stage, Member States shall pay attention to risk related to food and products of animal origin for professional uses.

To be noted also that the European commission suggests that for substances which are likely to migrate into food, a limit for residues should be set. Therefore, at product authorization level, for product that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) N° 470/2009 of the European Parliament and of the Council or Regulation (EC) n° 396/2005 of the European Parliament and of the Council shall be verified, and any appropriate risk mitigation measures shall be taken into account to ensure that the applicable MRLs are not exceeded.

2.2.1.3.4 General recommendations

The product is classified for eye irritation, several organizational and technical mitigation measures have to be put in place.

- **For professional users**

Organizational

- Minimise number of staff exposed;
- Management/supervision in place to check that the RMMs in place are being used correctly and OCs followed;
- Training for staff on good practice;
- Good standard of personal hygiene.

Technical

- Containment as appropriate;
- Segregation of the emitting process;
- Effective contaminant extraction;
- Good standard of general ventilation;
- Minimisation of manual phases;
- Regular cleaning of equipment and work area;
- Avoidance of contact with contaminated tools and objects;

Moreover, googles have to be worn.

- **For non-professional users**

- Labelling, instructions for use;
- Child proof closure;
- Packaging eliminating exposure are needed.

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.

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

[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.

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 soluti on 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 4.09×10^{-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 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 is available on 3 taxonomic groups (recommendation from ECHA guidance vol. IV, part B (2015), table 19). Therefore, the $PNEC_{water}$ value used for risk assessment is:

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

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

Guideline / Test method	Endpoint / Type of test	Exposure		Results (mg/kg dry weight)		
		design	Duration	NOEC	EC_{50}	EC_{100}
OECD TG 218	Emergence	Static	28 d	>= 909	ND	ND
	Sex ratio			>= 909	ND	ND
	Development rate			>= 909	ND	ND

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 been 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 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)).

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

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 reliable 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 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 are expected to have higher water solubility than larger oligomers. It can therefore be expected that the smallest oligomers would 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

- **SANICIL-F2 / SANICIL-RTU and SANICIL WIPE**

SANICIL-F2 is the representative product for the PHMB uses as an active substance in PT04. The product is used for the disinfection of food and feed area after dilution, in order to obtain a final concentration of 0.3 $g.L^{-1}$ or 0.16 $g.L^{-1}$ of active substance.

During the commenting period according to article 8(1) of the BPR, the applicant claimed as additional uses, the general disinfection of small scale surfaces by professionals with Ready to Use products:

- The product SANICIL RTU (trigger spray) is used for the spraying on the small surfaces.
- The product SANICIL WIPE (ready to use wet wipes) is used for the wiping of small surfaces.

The initial typical use of the product proposed by the applicant involves disinfection of working areas at the concentration of 0.3 $g.L^{-1}$ (*e.g.* floors, walls etc.) within the food sector, either in food preparation sites*, i.e.* kitchens, or in food production places as well as potential food contact areas (*e.g.* pipelines and mixing and storage tanks associated with production) by dilution of the product with water. For a use on lower surfaces (worktop, shelves, dishes …), the dilution can be done in small containers (plastic bowl…), and applied with a sponge or a cloth. For the disinfection of small size objects, SANICIL-F2 can be used to prepare a soaking solution with the same dosage.

All disinfected equipment is subsequently washed with water before use to ensure food is not contaminated by biocides. For such use conditions the main environmental exposure is via emission to drains, following by releases to municipal sewage treatment plant or directly to the aquatic treatment. Hence, there is potential exposure of both the aquatic (surface and sediment) and the terrestrial (soil and groundwater) compartments, the latter as a result of contaminated sewage sludge spreading on land.

For the environmental risk assessment of PHMB, considering these intended uses, the following emissions scenarios are applied based on the recommendation of the ESD-PT04 (2011)[17]:

- Scenario #1: Releases of disinfectants used in entire plants (*e.g.* breweries, dairies, beverage processing plants) [ESD-PT04 (2011), table 5].

- Scenario #2: Releases of disinfectants used in large scale catering kitchens, canteens, slaughterhouses and butcheries [ESD-PT04 (2011), table 10].

- Scenario #3: Releases of disinfectants used for the disinfection of milking parlour systems [ESD-PT04 (2011), table 11].

- Scenario #4: Refined scenario for RTU small scale applications in large scale kitchen areas (according to draft TAB (2017))

- **PURISAFE**

During the evaluation of the PT05-dossier of the active substance, the intended use for preliminary decontamination of animal drinking water network in a livestock farming

[17] ESD-PT04 (2011). Disinfectants used in food and feed areas

environment has been identified as a PT04-use. This use has been therefore added to the present evaluation with the final concentration of 0.4 g.L^{-1} of active substance.

No specific emission scenario for preliminary decontamination of animal drinking water network in livestock farming environment is described in the ESD for PT04 (2011). The applied scenario is proposed based on the ESD for PT03 (2011)[18], the ESD for PT18 (2006)[19], and the draft proposal guidance on estimating livestock exposure to active substance used in biocidal products (EC, 2010)[20].

The use of PHMB as a disinfectant for preliminary decontamination animal drinking water network and containers is considered to take place mainly in breeding farm. In accordance with the ESD-PT03 (2011), releases to the environment are expected to be:

- *via* the manure or slurry, which induces a potential exposure of the terrestrial compartments (soil and groundwater), following the spreading of contaminated slurry/manure on land,

- *via* the STP for the animal housings such as poultries.

It should be noted that released water from the preliminary decontamination of animal drinking water network is expected to have a low organic load, and is not supposed to be drunk by animals. As a consequence, whatever the type of animal housing, a total release to the STP (*i.e.* Fstp = 1) cannot be excluded. Hence an additional released scenario was taken into account for the environmental risk assessment of PT04-product containing PHMB used for the preliminary decontamination of animal drinking water in livestock environment, considering the complete release *via* the STP. The assessment was carried only for the housing type for which the used water volume was the lowest as a best case (*i.e.* 1600 L for veal calves).

2.2.2.7 Risk characterisation for food and feed area disinfection

To carry out a quantitative risk assessment for the environment when PHMB in SANICIL-F2 is used as PT04 for food and feed areas disinfection, 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] ESD for PT03 : Veterinary hygiene products (2011).
[19] ESD for insecticides for stables and manure storage systems (2006).
[20] EC (2010). Draft Guidance on estimating Livestock Exposure to Active Substances used in biocidal products. CA-Dec10-Doc.6.2.b.

Table 2.2-2-6 - PEC/PNEC ratios for PHMB for use of SANICIL-F2 for food and feed areas disinfection

Emission scenario		STP		Freshwater		Sediment		Soil		Groundwater(*)
		PEC_{STP} [mg.L-1]	PEC / PNEC	$PEC_{freshwater}$ [mg.L-1]	PEC / PNEC	$PEC_{sediment}$ [mg.kg-1wwt]	PEC / PNEC	PEC_{soil} [mg.kg-1wwt]	PEC / PNEC	$PEC_{groundwater}$ [µg.L-1]
Scenario #1	**Releases of disinfectants used in entire plants with off-site STP**	4.98E-02	1.54E-01	3.82E-03	**40.4**	1.67E+01	**44.2**	7.89E+00	**130.5**	<0.001
	Releases of disinfectants used in entire plants with on-site STP	n.r.	-	2.23E-02	**236**	9.77E+01	**258**	n.r.	-	n.r.
Scenario #2	**Releases of disinfectants used in large scale catering kitchens**	2.28E-03	7.06E-03	1.75E-04	**1.85**	7.67E-01	**2.03**	3.62E-01	**6.0**	<0.001
	Releases of disinfectants used in slaughterhouses and butcheries	1.14E-02	3.53E-02	8.75E-04	**9.26**	3.84E+00	**10.2**	1.81E+00	**29.9**	<0.001
Scenario #3	**Releases of disinfectants used for the disinfection of milking parlour systems**	4.99E-03	1.54E-02	3.83E-04	**4.05**	1.68E+00	**4.4**	7.91E-01	**13.1**	<0.001
Scenario #4	**Refined scenario for RTU small scale applications in large scale kitchen areas**	3.04E-05	9.41E-05	2.33E-06	2.47E-02	1.02E-02	0.03	4.82E-03	7.97E-02	<0.001

n.r. - not relevant
(*) – 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 µg.L-1.

2.2.2.7.1 Aquatic compartment (including sediment) and STP

As shown in Table 2.2-26, based on all assessed scenarios, the use of SANICIL-F2 induces PEC/PNEC ratios > 1 for the surface water and the sediment compartment for all the scenarios except for the refined assessment for RTU small scale applications in large scale kitchen areas.

In conclusion, the uses of PHMB as PT04, according to the scenarios for food and feed area disinfection lead to acceptable risks for the aquatic compartment (including sediment) only for RTU small scale applications in large scale kitchen areas.

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 Table 2.2-2, Based on all assessed scenarios, the use of SANICIL-F2 induces PEC/PNEC ratios > 1 for the soil compartment for all the scenarios except for the refined assessment for RTU small scale applications in large scale kitchen areas. The predicted PHMB concentrations in groundwater are all < 0.1 g/L limit set by the EU Groundwater Directive.

In conclusion, the uses of PHMB as PT04, according to the scenarios for food and feed area disinfection lead to acceptable risks for the soil compartment only for RTU small scale applications in large scale kitchen areas.

2.2.2.8 Risk characterisation for preliminary decontamination of animal drinking water network in livestock farming environment (PURISAFE)

2.2.2.8.1 Aquatic compartment and STP

2.2.2.8.1.1 Releases *via* manure/slurry spreading on soil

The PEC and PEC/PNEC ratios for surface water and sediment in the case of an emission standard for nitrogen and land application on grassland or arable land for each housing type are summarized in the Table 2.2-17.

Table 2.2-17 - Summary of the PEC and PEC/PNEC ratios for surface water and sediment due to emissions of PHMB from the preliminary decontamination of animal drinking water network in livestock farming environment *via* the manure/slurry spreading on soil

	Grassland[1]				Arable land			
Housing type	**PIEC10grs-water-N [mg.L^{-1}]**	***PIEC10grs-water-N / PNECwater***	**PIEC10grs-sediment-N [mg.kg$^{-1}_{wwt}$]**	***PIEC10grs-sediment-N / PNECsediment***	**PIEC10ars-water-N [mg.L^{-1}]**	***PIEC10ars-water-N / PNECwater***	**PIEC10ars-sediment-N [mg.kg$^{-1}_{wwt}$]**	***PIEC10ars-sediment-N / PNECsedimen t***
Dairy cow	9.85E-04	**1.04E+01**	4.32E+00	**1.14**	2.45E-04	**2.60E+00**	1.08E+00	**2.86**
Beef cattle	5.04E-04	**5.33E+00**	2.21E+00	0.58	1.25E-04	**1.33E+00**	5.50E-01	**1.46**
Veal calves	2.44E-03	**2.58E+01**	1.07E+01	**2.83**	6.07E-04	**6.43E+00**	2.66E+00	**7.04**
Sows. in individual pens	6.13E-04	**6.48E+00**	2.69E+00	0.71	1.53E-04	**1.62E+00**	6.69E-01	**1.77**
Sows,in groups	6.13E-04	**6.48E+00**	2.69E+00	0.72	1.53E-04	**1.62E+00**	6.69E-01	**1.77**
Fattening pigs	9.54E-04	**1.01E+01**	4.18E+00	**1.11**	2.38E-04	**2.52E+00**	1.04E+00	**2.75**
Laying hens in battery cages without treatment	3.59E-04	**3.80E+00**	1.57E+00	0.42	8.95E-05	9.47E-01	3.92E-01	**1.04**
Laing hens in battery cages with aeration (belt drying)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Laying hens in batters cages with forced drying (deep pit, high rise)	3.56E-04	**3.77E+00**	1.56E+00	0.41	8.88E-05	9.40E-01	3.89E-01	**1.03**
Laying hens in compact battery cages	4.01E-04	**4.24E+00**	1.76E+00	0.47	9.99E-05	**1.06E+00**	4.38E-01	**1.16**
Laying hens in free range with litter floor (partly litter floor, partly slatted)	3.77E-04	**3.99E+00**	1.65E+00	0.44	9.40E-05	9.95E-01	4.12E-01	**1.09**
Broilers in free range - litter floor	4.14E-04	**4.38E+00**	1.81E+00	0.48	1.03E-04	**1.09E+00**	4.52E-01	**1.2**
Laying hens in free range - grating floor	4.24E-04	**4.49E+00**	1.86E+00	0.49	1.06E-04	**1.12E+00**	4.63E-01	**1.22**
Parent broilers in free range - grating floor	2.44E-04	**2.58E+00**	1.07E+00	0.28	6.07E-05	6.42E-01	2.66E-01	0.71
Parent broilers in rearing - grating floor	5.30E-04	**5.61E+00**	2.32E+00	0.61	1.32E-04	**1.40E+00**	5.78E-01	**1.53**
Turkey in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ducks in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Geese in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

[1] According to the ESD-PT03 (2011), the calculation of the PIEC for grassland considered 4 manure applications per year times a year. Considering that PHMB is persistent in soil, no degradation occurs between applications. As a consequence, a worst case should consider a PIECgrs-Nworst-case as 4 * PIECgrs-N for calculations.

As described in the Table 2.2-17:

- When slurry/manure is spreading on grassland:
    - PIEC/PNEC ratios are above 1 for surface water for all housing types;
    - PIEC/PNEC ratios are above 1 for sediment for dairy caw, veal calves and fattening pigs.
- When slurry/manure is spreading on arable land:
    - PIEC/PNEC ratios are above 1 for surface water except for the housing types:
        - Laying hens in battery cages without treatment;
        - Laying hens in batters cages with forced drying (deep pit, high rise);
        - Laying hens in free range with litter floor (partly litter floor, partly slatted);
        - Parent broilers in free range - grating floor;
    - PIEC/PNEC ratios are above 1 for sediment for all housing types except for parent broilers in free range - grating floor.

2.2.2.8.2 Releases *via* the waste water

The PEC and PEC/PNEC ratios for STP, surface water and sediment for the housing types for which PHMB releases after use as preliminary decontamination of animal drinking water network in livestock farming environment is relevant are summarized in the Table 2.2-18.

Table 2.2-18 - Summary of the PEC and PEC/PNEC ratios for surface water, sediment and STP due to emissions of PHMB from the preliminary decontamination of animal drinking water network in livestock farming environment *via* waste water

Index	i1 Category-subcategory				PEC_{STP} [mg/L]	PEC_{STP} / $PNEC_{STP}$	PEC_{water} [mg/L]	PEC_{water} / $PNEC_{water}$	$PEC_{Sediment}$ [mg/kg$_{wwt}$]	$PEC_{sediment}$ / $PNEC_{sediment}$
1	Cattle	Dairy cattle			n.r.	-	n.r.	-	n.r.	-
2		Beef cattle			n.r.	-	n.r.	-	n.r.	-
3		Veal calves (**)			6.08E-02	0.19	4.67E-03	**49.4**	2.05E+01	**54.2**
4	Pigs	Sow		individual	n.r.	-	n.r.	-	n.r.	-
5		sows		group	n.r.	-	n.r.	-	n.r.	-
6		fattening pigs			n.r.	-	n.r.	-	n.r.	-
7	Poultry	battery	no treatment	laying hens	n.r.	-	n.r.	-	n.r.	-
8			belt trying	laying hens	n.r.	-	n.r.	-	n.r.	-
9			deep pit. high rise	laying hens	n.r.	-	n.r.	-	n.r.	-
10			compact	laying hens	n.r.	-	n.r.	-	n.r.	-
11		free range	litter floor	laying hens	9.50E-03	0.03	7.29E-04	**7.7**	3.20E+00	**8.46**
12		(indoors)	litter floor	broilers	1.90E-02	0.06	1.49E-03	**15.4**	6.39E+00	**16.9**
13			grating floor	laying hens	n.r.	-	n.r.	-	n.r.	-
14			grating floor	parent boilers	n.r.	-	n.r.	-	n.r.	-
15			grating floor	parent boilers in rearing	n.r.	-	n.r.	-	n.r.	-
16			litter floor	turkey	n.d.	-	n.d.	-	n.d.	-
17			litter floor	ducks	n.d.	-	n.d.	-	n.d.	-
18			litter floor	geese	n.d.	-	n.d.	-	n.d.	-

n.r. - not relevant because of no release *via* waste water expected according to the ESD-PT03.
n.d. - not determined
(**) Additional emission scenario taking into account the complete release of the disinfectant solution to the STP for the housing type for which the used water volume is the lowest (*i.e.* 1600 L for veal calves) as a best case.

When emissions are directed to manure or slurry, releases via the waste water are relevant only for free range on litter floor laying hens and broilers. For both housing types, PEC/PNEC ratios are below 1 for STP, and above 1 for surface water and sediment.

When considering a complete release *via* waste water, PEC/PNEC ratios are below 1 for STP, and above 1 for surface water and sediment for the housing type (veal calves) which needed the lowest water volume for the daily animal drinking.

2.2.2.8.3 Atmosphere

No risks are expected, considering that the active substance is not volatile.

2.2.2.8.4 Terrestrial compartment and groundwater

2.2.2.8.4.1 Releases *via* manure/slurry spreading on soil

The initial PEC and PEC/PNEC ratios for soil and PEC for groundwater in the case of an emission standard for nitrogen and land application on arable land or grassland for each housing type are summarized in the Table 2.2-19.

Table 2.2-19 - Summary of the initial PEC and PEC/PNEC ratios for soil due to emissions of PHMB from the preliminary decontamination of animal drinking water network in livestock farming environment *via* the manure/slurry spreading on soil.

Housing type	Grassland[1]			Arable land		
	PIEC10grs-N$_{worst case}$ [mg.kg^{-1}$_{wwt}$]	***PIEC10grs-N$_{worst case}$ / PNECsoil***	**PEC groundwater (*) [µg.L^{-1}]**	**PIEC10ars-N [mg.kg^{-1}$_{wwt}$]**	***PIEC10ars-N / PNECsoil***	**PEC groundwater (*) [µg.L^{-1}]**
Dairy cow	3.50E+01	**5.79E+02**	< 0.001	8.73E+00	**1.44E+02**	< 0.001
Beef cattle	1.79E+01	**2.96E+02**	< 0.001	4.46E+00	**7.38E+01**	< 0.001
Veal calves	8.67E+01	**1.43E+03**	< 0.001	2.16E+01	**3.57E+02**	< 0.001
Sows, in individual pens	2.18E+01	**3.60E+02**	< 0.001	5.43E+00	**8.98E+01**	< 0.001
Sows in groups	2.18E+01	**3.60E+02**	< 0.001	5.43E+00	**8.98E+01**	< 0.001
Fattening pigs	3.39E+01	**5.61E+02**	< 0.001	8.45E+00	**1.40E+02**	< 0.001
Laying hens in battery cages without treatment	1.28E+01	**2.11E+02**	< 0.001	3.18E+00	**5.26E+01**	< 0.001
Laing hens in battery cages with aeration (belt drying)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Laying hens in batters cages with forced drying (deeppit, high rise)	1.27E+01	**2.10E+02**	< 0.001	3.16E+00	**5.22E+01**	< 0.001
Laying hens in compact battery cages	1.43E+01	**2.36E+02**	< 0.001	3.55E+00	**5.87E+01**	< 0.001
Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.34E+01	**2.22E+02**	< 0.001	3.34E+00	**5.53E+01**	< 0.001
Broilers in free range - litter floor	1.47E+01	**2.43E+02**	< 0.001	3.66E+00	**6.06E+01**	< 0.001
Laying hens in free range - grating floor	1.51E+01	**2.49E+02**	< 0.001	3.76E+00	**6.22E+01**	< 0.001
Parent broilers in free range - grating floor	8.66E+00	**1.43E+02**	< 0.001	2.16E+00	**3.57E+01**	< 0.001
Parent broilers in rearing -	1.88E+01	**3.11E+02**	< 0.001	4.69E+00	**7.76E+01**	< 0.001

grating floor						
Turkey in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ducks in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Geese in free range - litter floor	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

[1] According to the ESD-PT03 (2011), the calculation of the PIEC for grassland considered 4 manure applications per year. Considering that PHMB is persistent in soil, no degradation occurs between applications. As a consequence, a worst case should consider a PIECgrs-Nworst-case as 4 * PIECgrs-N for calculations.
(*) – According to 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 µg.L^{-1}.

For all housing types described in the Table 2.2-, PIEC/PNEC ratios are above 1 for soil. With regard to predicted PHMB concentration in groundwater via FOCUS modelling, they do not exceed the 0.1 µg/L limit set by the EU Directive 98/83/EC following the use of PHMB-based product.

2.2.2.8.4.2 Releases *via* waste water

The PEC and PEC/PNEC ratios for soil and PEC for groundwater for housing types for which PHMB releases after use for preliminary decontamination of animal drinking water network in livestock farming environment is relevant are summarized in the Table 2.2-20.

Table 2.2-20 - Summary of the PEC and PEC/PNEC ratios for soil due to emissions of PHMB from the preliminary decontamination of animal drinking water network in livestock farming environment via waste water

Index i1 Category-subcategory					**PEC_{Soil} [mg/kg$_{wwt}$]**	**PEC_{soil} / $PNEC_{soil}$**	**$PEC_{groundwater}$ (*) [µg/L]**
1	Cattle	Dairy cattle			n.r.	-	n.r.
2		Beef cattle			n.r.	-	n.r.
3		Veal calves (**)			9.64E+00	**159**	< 0.001
4	Pigs	Sow		individual	n.r.	-	n.r.
5		sows		group	n.r.	-	n.r.
6		fattening pigs			n.r.	-	n.r.
7	Poultry	battery	no treatment	laying hens	n.r.	-	n.r.
8			belt trying	laying hens	n.r.	-	n.r.
9			deep pit. high rise	laying hens	n.r.	-	n.r.
10			compact	laying hens	n.r.	-	n.r.
11		free range	litter floor	laying hens	1.51E+00	**25**	< 0.001
12		(indoors)	litter floor	broilers	3.01E+00	**50**	< 0.001
13			grating floor	laying hens	n.r.	-	n.r.
14			grating floor	parent boilers	n.r.	-	n.r.
15			grating floor	parent boilers in rearing	n.r.	-	n.r.
16			litter floor	turkey	n.d.	-	n.d.
17			litter floor	ducks	n.d.	-	n.d.
18			litter floor	geese	n.d.	-	n.d.

n.r. - not relevant because of no release *via* waste water expected according to the ESD-PT03.
n.d. - not determined
(*) – 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 µg.L^{-1}.
(**) Additional emission scenario taking into account the complete release of the disinfectant solution to the STP for the housing type for which the used water volume is the lowest (*i.e.* 1600 L for veal calves) as a best case

When emissions are directed to manure and slurry, releases via the waste water are relevant only for free range on litter floor laying hens and broilers. For both housing types, PEC/PNEC ratios are above 1 for the soil compartment.

When considering a complete release *via* waste water, PEC/PNEC ratios is above 1 for soil for the housing type (veal calves) which needed the lowest water volume for the daily animal drinking.

With regard to predicted PHMB concentration in groundwater via FOCUS modelling, they do not exceed the 0.1 µg/L limit set by the EU Directive 98/83/EC following the use of PHMB-based product in free range on litter floor laying hens and broilers, and when considering a complete release *via* waste water for the housing type (veal calves).

2.2.2.8.5 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.

2.2.2.9 Overall conclusion for the environmental risk assessment

2.2.2.9.1 Food and feed area disinfection

The environmental risk assessment of PHMB used for hand disinfection is summarised in the table below.

Scenario	STP	Aquatic compartment (surface water)	Aquatic compartment (sediment)	Terrestrial compartment	Groundwater	Air	Secondary poisoning

Scenario #1	**#1- Releases of disinfectants used in entire plants with off-site STP**	Acceptable	**Unacceptable**	**Unacceptable**	**Unacceptable**	Acceptable	Not relevant
	#2- Releases of disinfectants used in entire plants with on-site STP	Not relevant	**Unacceptable**	**Unacceptable**	Not relevant	Not relevant	Not relevant
Scenario #2	**#3- Releases of disinfectants used in large scale catering kitchens**	Acceptable	**Unacceptable**	**Unacceptable**	**Unacceptable**	Acceptable	Not relevant
	#4- Releases of disinfectants used in slaughterhouses and butcheries	Acceptable	**Unacceptable**	**Unacceptable**	**Unacceptable**	Acceptable	Not relevant
Scenario #3	**Releases of disinfectants used for the disinfection of milking parlour systems**	Acceptable	**Unacceptable**	**Unacceptable**	**Unacceptable**	Acceptable	Not relevant
Scenario #4	**Refined scenario for RTU small scale applications in large scale kitchen areas**	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Not relevant

2.2.2.9.2 Preliminary decontamination of animal drinking water network in livestock farming environment

The environmental risk assessment of PHMB used as PT04 for preliminary decontamination of animal drinking water network in livestock farming environment is summarized in the table below.

Scenario (housing type)	STP	Aquatic compartment (surface water)	Aquatic compartment (sediment)	Terrestrial compartment	Groundwater	Air	Secondary poisoning

1	Dairy cow	Not relevant	**Unacceptable**	**Unacceptable** (1) (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
2	Beef cattle	Not relevant	**Acceptable** (1) (2)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
3	Veal calves (**)	Acceptable (4)	**Unacceptable** (1) (2) (4)	**Unacceptable** (1) (2) (4)	**Unacceptable** (1) (2) (4)	Acceptable	Not relevant
4	Sows, in individual pens	Not relevant	**Unacceptable** (1) (2)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
5	Sows in groups	Not relevant	**Unacceptable** (1) (2)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
6	Fattening pigs	Not relevant	**Unacceptable** (1) (2)	**Unacceptable** (1) (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
7	Laying hens in battery cages without treatment	Not relevant	**Unacceptable** (1)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
8	Laing hens in battery cages with aeration (belt drying)	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined
9	Laying hens in batters cages with forced drying (deeppit, high rise)	Not relevant	**Unacceptable** (1)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
10	Laying hens in compact battery cages	Not relevant	**Unacceptable** (1) (2)	**Unacceptable** (2)	**Unacceptable** (1) (2)	Acceptable	Not relevant
11	Laying hens in	Acceptable	**Unacceptable**	**Unacceptable**	**Unacceptable**	Acceptable	Not relevant

	free range with litter floor (partly litter floor, partly slatted)	(3)	(1)(3)	(2) (3)	(1) (2) (3)		
12	Broilers in free range - litter floor	Acceptable (3)	**Unacceptable** **(1) (2)**(3)	**Unacceptable** **(2) (3)**	**Unacceptable** **(1) (2) (3)**	Acceptable	Not relevant
13	Laying hens in free range - grating floor	Not relevant	**Unacceptable** **(1)**	**Unacceptable** **(2)**	**Unacceptable** **(1) (2)**	Acceptable	Not relevant
14	Parent broilers in free range - grating floor	Not relevant	**Unacceptable** **(1) (2)**	**Acceptable**	**Unacceptable** **(1) (2)**	Acceptable	Not relevant
15	Parent broilers in rearing - grating floor	Not relevant	**Uncceptable** **(1) (2)**	**Unacceptable** **(2)**	**Unacceptable** **(1) (2)**	Acceptable	Not relevant
16	Turkey in free range - litter floor	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined
17	Ducks in free range - litter floor	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined
18	Geese in free range - litter floor	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined

[1] – Considering relevant releases *via* the slurry/manure spreading on grassland.
[2] – Considering relevant releases *via* the slurry/manure spreading on arable land.
[3] – Considering relevant releases *via* waste water.
[4] – Considering complete releases *via* waste water.
(**) Additional emission scenario taking into account the complete release of the disinfectant solution to the STP for the

housing type for which the used water volume is the lowest (*i.e.* 1600 L for veal calves) as a best case

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**	**Terrestrial compartment**	**Groundwater**	**Air**	**Secondary poisoning**
Surface disinfection										
wipping 0.03 % w/w a.s.	Not acceptable	NR	NR	Not acceptable	Acceptable	Not acceptable	Unacceptable	Acceptable	NR	NR
Mopping 0.03 % w/w a.s.	Acceptable (1)	NR	NR	Not acceptable	Acceptable	Not acceptable	Unacceptable	Acceptable	NR	NR
RTU small scale applications: trigger spray 0.016 % w/w a.s.	Acceptable (1)	NR	NR	Not acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
RTU small scale applications: impregnated wipes 0.016 % w/w a.s.	Acceptable	NR	NR	Acceptable (4)	Acceptable	Acceptable	Acceptable	Acceptable	NR	NR
Dipping of small objects										
Dipping 0.03 % w/w a.s.	Acceptable (2)	NR	NR	Acceptable (4)	Acceptable	Not acceptable	Not acceptable	Acceptable	NR	NR
Watering										

0.03 % w/w a.s.	Unacceptable	NR	NR	Unacceptable	Acceptable	Not acceptable	Not acceptable	Acceptable	NR	NR
Disinfection with CIP system										
0.03 % w/w a.s.	Acceptable	NR	NR	Acceptable	Acceptable	Not acceptable	Not acceptable	Acceptable	NR	NR
Preliminary disinfection of drinking water containers and pipes network										
0.04 w/w a.s.	Acceptable	Acceptable	NR	Acceptable	Acceptable	Not acceptable (3)	Not acceptable	Acceptable	NR	NR

NR: Not relevant.

Conditions:

(1) Only if gloves are worn

(2) Only if the PPE are worn

(3) Except for certain types of livestock

(4) Only when surface are totally dried

3 PROPOSED DECISION

The outcome of the assessment for PHMB (1415; 47) in product-type 4 is specified in the BPC opinion following discussions at the 22nd 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

No data on physical-chemical properties and methods of analysis were provided for SANICIL-RTU and SANICIL-WIPES. These data are needed at product authorisation stage.

The local risk assessment for inhalation exposure is necessary for uses generating aerosol. However, this assessment could not be performed due to missing data for the derivation of an AEC inhalation. A read across with the AEC inhalation value from the dossier on PHMB (1600; 1.8), submitted by another applicant (Lonza), was agreed during the WG III 2017 HH.
Due to the lack of a letter of access to this value, the risk assessment could not be performed at the active substance level. Therefore, the risk assessment for applications generating aerosol by trigger spray could not be finalised and a quantitative local risk assessment has to be provided at the product authorization level.

3.2 List of endpoints

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

4 APPENDICES

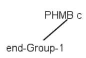
Appendix 1 Listing of endpoints

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

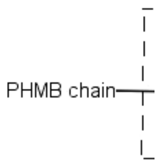
Active substance (Common Name)	PHMB (1415; 4.7)
Function (*e.g.* fungicide)	Bactericide and algaecide

Rapporteur Member State	France

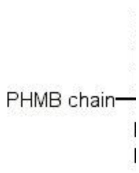
Identity (Annex IIA, point II.)

Chemical name (IUPAC)	Poly(iminoimidocarbonyl)iminoimido-carbonyliminohexamethylene 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:

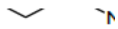
Biguanide hydrochloride group



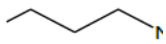
Guanidine hydrochloride group



The 3 possible end-chain groups are:



Cyanoguanidine



Amine end grou

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 x 10^{-6} Pa at 20°C

Henry's law constant (Pa m^3 mol^{-1})	<1.65 x 10^{-8} $Pa.m^3.mol^{-1}$ Log H: <-7.8
Solubility in water (g/l or mg/l, state temperature)	pH4: pH7: pH9: 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.
	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 SANICIL-F2 (20% 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 SANICIL-F2 (20% a.s.)**: Aquatic Acute 1; H400: Very toxic to aquatic life. Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects.

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 <u>not technically feasible</u>
Air (principle of method and LOQ) (Annex IIA, point 4.2)	Method is required if a use via spraying is claimed
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 and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Method required
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	Surface disinfection: only by mopping with gloves

	Dipping: with gloves and coverall Disinfection with CIP: without PPE Preliminary disinfection of drinking water containers and pipes network
Non-professional users	Preliminary disinfection of drinking water containers and pipes network
Indirect exposure as a result of use	A mitigation measure is necessary: The surface has not to be touched until it is totally dried. **Indirect exposure via food:** For the treatment of utensils, equipment and pipeworks in food and feed areas, risk assessment for the consumer is currently considered as: - Acceptable for dipping, and wiping/mopping uses without a rinsing step only for food excepting food and products of animal origin. - Not finalized for dipping and wiping/mopping uses for food and products of animal origin - Not finalized for all CIP uses. For the treatment of drinking water networks and containers dedicated to the storage of drinking water for any livestock intended for human consumption, risk assessment for consumer is considered as not finalized for professional uses and acceptable for non-professional uses. More data are necessary to perform a refined risk assessment and Member States shall pay attention to risk related to food consumption when relevant. Moreover, in case of acceptable risks for all assessed uses, a cumulative consumer risk assessment should be realized taking into account exposure via food, food and products of animal origin and drinks.

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 - DT_{50} water - DT_{90} water	No $DT50_{total\ system}$ determined.

(2 systems) - 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* (Annex IIIA, point XIII.3.2)	14-day LC_{50} > 201 mg a.s./kg soil dry weight 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

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment	Remarks
			Type	Conc [% PHMB]	Method	Number	Interval		
Hard surface disinfection	SANICIL-F2 (20 % w/w a.s.)	Bacteria Yeasts	SL	20 % w/w	Soaking clean in place	1	One application. Before re-use of equipment	0.03 % w/v active substance	Professional use only.
Drinking water storage disinfection Pipe network disinfection	PURISAFE PRO (20 % w/w a.s.) PURISAFE PRO J (4 % w/w a.s.)	Bacteria Yeasts	SL	20 % w/w 4 % w/w	pouring	1	One application. Before re-use of equipment	0.03 % w/v active substance	Professional use only.
Hard surface disinfection	SANICIL RTU (0.016 % w/w a.s.) SANICIL WIPE (Impregnated 0.016 % w/w a.s.)	Bacteria Yeasts		0.016 % w/w a.s.	Spraying wiping wiping	1	One application. Before re-use of equipment	0.016 % w/w active substance	Professional only

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.	N	Public
Anonymous	5.4	2007	Mode of action of PHMB. Avecia technical service document, Non-GLP/Published.	N	Public
ANSM	4.2	2013	Evaluation de la conformité aux bonnes pratiques de laboratoire	Y	Laboratoire PAREVA
[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)	Y	[redacted]
[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)	Y	[redacted]
[redacted]	6.10.4	2015	Early Proliferative Effects of PHMB on the Liver Tissue of Male Wistar Han Rats (study No 342)	Y	[redacted]
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	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA

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	N	Public
Birnschein K.	3.11	2008	Flammability (solids) of PHMB P100 PC	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA
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)	N	Published
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.	N	Public
[redacted]	7.4.3.2	2013	PHMB Fish Early Life Stage Toxicity Test for Fathead Minnow	Y	[redacted]
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	N	Published

Chen J.	6.18_03	2003	PHMB - 2nd Report of the Hazard Identification Assessment Review Committee.	N	Published
Cohen S.M. and Creppy E.E.	6.10.5	2015	Evaluation of PHMB-induced Rodent Tumors and Assessment of Human Relevance (Position Paper)	Y	Laboratoire PAREVA
[redacted]	6.1.2	2012	Evaluation of acute dermal toxicity in rats	Y	[redacted]
Creppy E.E.	6.10.1b	2012	Etude in vitro des possibles propriétés Epigénétiques du PHMB	Y	Laboratoire PAREVA
Creppy E.E. et al.	6.10.1a	2014	Study of Epigenetic Properties of Poly(HexaMethylene Biguanide) Hydrochloride (PHMB)	N	Published
Cros D.	2.1	2013	Formulation composition statement of trades names	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 PC	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 SP	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 TX	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P2056	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMBG	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 D	Y	Laboratoire PAREVA
Cros D.	2.1	2013	MATERIAL SAFETY DATA SHEET OF REVACIL	Y	Laboratoire PAREVA
Cros D.	2.4.1	2007 2012 (updated)	Laboratoire PAREVA: active subtance Polyhexamethylene biguanidine (PHMB) Information about CAS number	Y	Laboratoire PAREVA
Cros D.	2.5.1	2007 2012 (updated)	Laboratoire PAREVA: active subtance Polyhexamethylene biguanidine (PHMB) Information about CAS number	Y	Laboratoire PAREVA

Cros D.	2.5.2	2012	Synthesis of PHMB radiolabelled with 14C ([14C]PHMB). Technical data on the final product obtained	Y	Laboratoire PAREVA
Cros D.	2.6	2013	Description of the manufacturing process of the active substance PHMB followed by Laboratoire PAREVA	Y	Laboratoire PAREVA
Cros D.	2.7	2012	Synthesis of PHMB radiolabelled with 14C ([14C]PHMB). Technical data on the final product obtained	Y	Laboratoire PAREVA
Cros D.	2.8	2014	Summary of the batch references used in Toxicological and ecotoxicological studies	Y	Laboratoire PAREVA
Cros D.	4.1	2014	Reference DCI document. Request for additional information. Point No 5	Y	Laboratoire PAREVA
Cros D.	4.2	2014	Reference DCI document. Request for additional information. Point No 8	Y	Laboratoire PAREVA
Cros D.	4.2	2014	Reference DCI document. Request for additional information. Point No 8	Y	Laboratoire PAREVA
Curl M.G	7.3.1	2007	Computer modelled properties of PHMB using EPI Suite ™	Y	Laboratoire PAREVA
Curl M.G.	3.15	2007a	Expert statement on the explosive properties of poly(hexamethylenebiguanide) hydrochloride (PHMB)	Y	Laboratoire PAREVA
Curl M.G.	3.16	2007b	Expert statement on the oxidizing properties of poly(hexamethylenebiguanide) hydrochloride (PHMB)	Y	Laboratoire PAREVA
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	N	Public
Dawson, M.W., Brown, T., Till, D.	5.10	1983	The effect of Baquacil on pathogenic free-living amoebae (PFLA) 1. In axenic conditions New Zealand Journal of Marine and Freshwater Research, 1983, Vol. 17, p. 305 - 311 Non-GLP/Published	N	Public

DeMatteo V.	2.1	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.2	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.5.1	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.5.2	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.5.3	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.7	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	2.8	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
DeMatteo V.	4.1	2010	Preliminary Analysis of Polyhexamethylene Biguanide (PHMB) Solid	Y	Laboratoire PAREVA
[redacted]	7.4.1.1	2013	PHMB: Acute Toxicity to Rainbow Trout	Y	[redacted]
Dickinson R.A.	7.4.1.2	2013	PHMB: Acute Toxicity to Daphnia Magna	Y	Laboratoire PAREVA
Dickinson R.A.	7.4.1.3	2013	PHMB Algal Growth Inhibition Assay	Y	Laboratoire PAREVA
Dickinson R.A.	7.4.3.4	2013	PHMB: Daphnia Magna Reproduction Toxicity Test	Y	Laboratoire PAREVA
Eckenstein H.	7.5.1.1-01	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Effects on Soil Microflora Activity	Y	Laboratoire PAREVA
Eckenstein H.	7.5.1.1-02	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Effects on Soil Microflora Activity	Y	Laboratoire PAREVA
Eisner G.	7.1.2.1.1	2013	Poly HexaMethylene Biguanide, hydrochloride (PHMB): Elimination and Primary Biodegradation in an Activated Sludge Simulation Test	Y	Laboratoire PAREVA
Feil N.	7.1.1.2.1	2009 (revised date 2014)	Ready Biodegradability of PHMB P100 PC in a CO2 headspace Test	Y	Laboratoire PAREVA
Ferte C.	6.12.3		Study on PolyHexaMethylène Biguanidine impact (PHMB) and/or its manufacturing process impact on the workshop staff	Y	Laboratoire PAREVA

Ferte C.	6.12.6		Study on PolyHexaMethylène Biguanidine impact (PHMB) and/or its manufacturing process impact on the workshop staff	Y	Laboratoire PAREVA
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.	N	Public
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.	N	Public
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.	N	Public
Giordanengo A.	4.2	2014	Validation of an ELISA method for the quantification of PHMB in water	Y	Laboratoire PAREVA
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	N	Public
[redacted]	6.3.3_01	2013	PHMB: Dose Range Finding Inhalation Toxicity Study (Nose-Only) in the rat	Y	[redacted]
[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	Y	[redacted]

Harmand, M.F.	6.6.1	2002	Reverse Mutation Assay on Salmonella typhimurium his and Escherichia coli,	Y	Laboratoire PAREVA
[redacted]	6.6.2	2002	In-vitro mammalian chromosome aberration test using Chinese Hamster Ovary Cells (CHO)	Y	[redacted]
Harmand, M.F.	6.6.2	2002-2012	Historical Controls	N	Laboratoire PAREVA
Harmand, M.F.	6.6.3	2002	In-vitro mammalian cell gene mutation test	Y	Laboratoire PAREVA
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.	N	Public
Kusnetsov, J.M., Tulkki, A.I., Ahonen, H.E., Martikainen, P.J.	5.10	1977	Efficacy of three prevention stages against legionella in cooling water systems Journal of Applied Microbiology 1997, 82, p. 763 – 768 Non-GLP/Published	N	Public
L'Haridon J.	7.1.1.2.1	2002b	PHMB P20 D: Determination of Ready Biodegradability Closed Bottle test (study 23441 ECS)	Y	Laboratoire PAREVA
Laboratoire MAREVA	8	2007	Guide d'utilisation du Revacil - Piscines publiques	Y	Laboratoire PAREVA
Laboratoire PAREVA	2.7	2011	PHMB from Laboratoire PAREVA: Summary of the available data	Y	Laboratoire PAREVA
Laboratoire PAREVA	2.7	2014	Answer to additional information: Point No. 1 Content in PHMB < 1000 Da	Y	Laboratoire PAREVA
Laboratoire PAREVA	2.7	2014	Answer to additional information: Point No. 2 Certified range values of active substance and impurities	Y	Laboratoire PAREVA

Laboratoire PAREVA	8	2013	MATERIAL SAFETY DATA SHEET OF PHMB P20 D According to Annex I of Regulation 453/2010	Y	Laboratoire PAREVA
L'Haridon J.	7.4.1.4	2002	Activated Sludge, Respiration Inhibition Test	Y	Laboratoire PAREVA
Lonza	2.1	2012	MATERIAL SAFETY DATA SHEET OF LONZABAC™ PC	Y	Laboratoire PAREVA
Lonza	2.1	2012	MATERIAL SAFETY DATA SHEET OF LONZABAC™ BG	Y	Laboratoire PAREVA
Maher M.	3.11	2013	PHMB P100 Analysis – Relative Self-Ignition Temperature of a Solid According to EC Physico-Chemical Test A16	Y	Laboratoire PAREVA
Maher M.	3.4.3	2012	PHMB Batch Characterisation (Bx 111077)	Y	Laboratoire PAREVA
[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.	Y	[redacted]
[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).	Y	[redacted]
[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).	Y	[redacted]
[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).	Y	[redacted]

[redacted]	6.7_04a	2014	Evaluation of Liver and Thyroid Proliferative Lesions from the Pareva PHMB P100 Two-Year Rat Study	Y	[redacted]
Ministère du redressement productif	4.2	2013	Certificat de conformité aux bonnes pratiques de laboratoire	Y	Laboratoire PAREVA
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	N	Public
[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"	Y	[redacted]
N/A	2.10	2015	EUSES files	Y	Laboratoire PAREVA
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.	N	Public
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	Y	Laboratoire PAREVA
[redacted]	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): Analysis in rat faeces	Y	[redacted]

[redacted]	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): Analysis in rat urines	Y	[redacted]
Padel L.	4.2	2014	Poly(HexaMethylene Biguanide), hydrochloride (PHMB): analysis in serums.	Y	Laboratoire PAREVA
Pawsey B.	7.4.3.5.1	2015	PHMB: Toxicity to the Sediment-Dwelling Phase of the Midge Chironomus riparius	Y	Laboratoire PAREVA
[redacted]	6.8.1_02	2010	Prenatal Developmental Toxicity study of PHMB [Poly (HexaMethyleneBiguanide), hydrochloride] in New Zealand White Rabbit	Y	[redacted]
[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).	Y	[redacted]
[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).	Y	[redacted]
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Graph, 2013 03 20	Y	Laboratoire PAREVA
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Excel Spreadsheet list	Y	Laboratoire PAREVA
Quotient Bioresearch	7.4.2	2013	High Performance Liquid Chromatogram, Batch CFQ41501, Excel Spreadsheet list	Y	Laboratoire PAREVA
[redacted]	6.7_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats	Y	[redacted]
[redacted]	6.4.1_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats.	Y	[redacted]
[redacted]	6.5_01	2012	Combined Chronic Toxicity/Carcinogenicity Study with PHMB P100 in Wistar rats.	Y	[redacted]
[redacted]	6.1.1	2011	Evaluation of acute oral toxicity in rats: Acute toxic class method.	Y	[redacted]
[redacted]	6.1.4_01	2008	Skin irritation test in the rabbit	Y	[redacted]
Richeux F.	6.1.4_01	2008	Assessment of Acute Dermal Irritation - Study Plan	Y	Laboratoire PAREVA

[redacted]	6.1.4_02	2008	Eye irritation test in the rabbit	Y	[redacted]
[redacted]	6.1.5	2011	Assessment of sensitive properties on albino guinea pigs: Maximisation test according to Magnusson and Kligman	Y	[redacted]
Shamim, A.N	6.15.3	2003	RED Chapter: PHMB Dietary Exposure Assessments for he Reregistration Eligibility Decision (OPPTS 248.3000) USA, EPA review.	N	Published
Smeykal H.	3.1.1	2007a	PHMB P100 PC Batch No.: 5519 MELTING POINT (A.1.) OECD 102	Y	Laboratoire PAREVA
Smeykal H.	3.1.2	2007b	PHMB P100 PC Batch No.: 5519 BOILING POINT (A.2.) OECD 103	Y	Laboratoire PAREVA
Smeykal H.	3.10	2007	Thermal Stability (OECD 113) of PHMB P100 PC Batch N°5519	Y	Laboratoire PAREVA
Smeykal H.	3.2	2007c	PHMB P100 PC Batch No.: 5519 VAPOUR PRESSURE (A.4.) OECD 104	Y	Laboratoire PAREVA
Stabler D.	7.5.1.2	2007	Acute Toxicity of PHMB P20 D on Earthworms, Eisenia fetida Using an Artificial Soil Test	Y	Laboratoire PAREVA
[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	Y	[redacted]
[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	Y	[redacted]
[redacted]	6.3.1	2009	PHMB P100: 28-day drinking water administration toxicity study in Wistar Rats	Y	[redacted]
Thery F.	5.10	2009	Determination de l’activité bactericide de base selon la norme NF EN 1040 .	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA
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)	Y	Laboratoire PAREVA

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	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA
Thom M.	3.1.3	2007a	Relative density of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.13	2007c	Surface Tension of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.3.1	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.3.2	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.3.3	2007b	Physical State, Colour and Odour of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.4.1	2008	UV/VIS Absorption Spectrum and Infrared Absorption-Spectrum of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
Thom M.	3.4.2	2008	UV/VIS Absorption Spectrum and Infrared Absorption-Spectrum of PHMB P100 PC (Poly(HexaMethyleneBiguanide), hydrochloride)	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA

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	Y	Laboratoire PAREVA
THOR	2.1	2007	ACTICIDE® PHB 20 Product Information	Y	Laboratoire PAREVA
THOR GmbH	2.1	2007	Material Safety Data Sheet ACTICIDE PHB 20	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA
Truslove N.	2.5.2	2011	5-Batch Analysis Proton NMR Spectra	Y	Laboratoire PAREVA
Truslove N.	2.5.2	2011	PHMB 5-Batch Characterisation-UV/Visible Spectra	Y	Laboratoire PAREVA
Truslove N.	3.4.3	2011	PHMB 5-Batch Characterisation - Proton NMR Spectra	Y	Laboratoire PAREVA
Ulbert O.	7.1.1.1.1	2013	PHMB: Determination of the Hydrolysis as a Function of pH (Preliminary Test)	Y	Laboratoire PAREVA
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	N	Public
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	Y	Laboratoire PAREVA
Walther D.	7.2.1	2013b	PolyHexaMethylene Biguanide (PHMB): degradation and metabolism in four soils of [14C]PHMB incubated under aerobic conditions	Y	Laboratoire PAREVA
Walther D.	7.2.2.1	2013b	PolyHexaMethylene Biguanide (PHMB): degradation and metabolism in four soils of [14C]PHMB incubated under aerobic conditions	Y	Laboratoire PAREVA
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	Y	Laboratoire PAREVA

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	Y	Laboratoire PAREVA
Witte A.	3.4.4	2008	Developement of an analytical method for determination of PHMB in water and soil	Y	Laboratoire PAREVA
Witte A.	4.2	2008	Developement of an analytical method for determination of PHMB in water and soil	Y	Laboratoire PAREVA
	6.18_01	2004	POLYHEXAMETHYLENE BIGUANIDE (PHMB) RED DOCUMENT	N	Published
	6.18_02	2002	Polyhexamethylene biguanide (PHMB): Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document	N	Published

List of studies for the reference product

Author	Section No	Year	Title	Owner of data	Data protection claimed
Cros D.	2.1	2013	Formulation composition statement	Laboratoire PAREVA	Y
Cros D.	2.2	2013	Formulation composition statement	Laboratoire PAREVA	Y
Cros D.	2.2	2013	MATERIAL SAFETY DATA SHEET OF SANICIL-F2	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
Panaiva L.	3.10	2010	DETERMINATION OF THE CINEMATIC VISCOSITY OF PHMB P20 D: 5-BATCH ANALYSIS	Laboratoire PAREVA	Y
Mazzei N.	3.11	2014	Surface Tension on the sample PHMB P20 D(Poly(HexaMethyleneBiguanide), hydrochloride at 20%)	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
Tremain S.	3.4	2007	PHMB P20 D: POLY(HEXAMETHYLENE BIGUANIDE), HYDROCHLORIDE DETERMINATION OF AUTO-IGNITION TEMPERATURE (LIQUIDS and GASES)	Laboratoire PAREVA	Y
Cros D.	3.5	2013	Certificate of analysis	Laboratoire PAREVA	Y
Laboratoire PAREVA	3.5	2007	Analytical method - pH	Laboratoire PAREVA	Y
Cros D.	3.6	2013	Certificate of analysis	Laboratoire PAREVA	Y
Laboratoire PAREVA	3.6	2007	Analytical method - density	Laboratoire PAREVA	Y
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
Cros D.	3.7	2014	Long Term Stability of 20%-PHMB solutions.	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
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
Rondon C., Tiedje M.H.	3.7	1995	Corrosion Characteristics of Polyhexamethylene Biguanide Hydrochloride (PHMB)	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
Tiedje M.H.	3.7	1995	Stability of Polyhexamethylene Biguanide Hydrochloride (PHMB)	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
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
Witte A.	4.2	2008	Developement of an analytical method for determination of PHMB in water and soil	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	2011	Détermination de l'activité bactéricide du produit « PHMB P20 D »selon la norme NF EN 1276 (Mars 2010) - Activité bactéricide pour usages généraux - 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
Thery F.	5.10	2011	Détermination de l'activité bactéricide du produit « PHMB P20 D » selon la norme NF EN 1656 (Mars 2010) - Activité bactéricide pour usages généraux - - Conditions obligatoires	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
[redacted]	6.1.3_01	2012	Acute Inhalation Toxicity Study (Nose-only) in the Rat according to OECD 403 guideline	[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	2002	Assessment of sensitising properties on albino guinea pig: Maximisation test according to Magnusson & Kligman	[redacted]	Y
Lopez B.	6.4	2013	In vitro derma penetration of PHMB across human skin according to OECD 428 Guideline	Laboratoire PAREVA	Y

ECHA	6.6_01	2013	GUIDANCE ON INFORMATION REQUIREMENTS (DRAFT) SCIENTIFIC GUIDANCE TO REGULATION (EU) No 528/2012 CONCERNING THE MAKING AVAILABLE ON THE MARKET AND USE OF BIOCIDAL PRODUCTS (BPR)	Public	N
Laboratoire PAREVA	6.6_01	2013	SANICIL-F2 Technical Concentrate for Food & Feed area disinfection Technical Data Sheet	Laboratoire PAREVA	Y
RIVM - CONSEXPO	6.6_01	2006	Cleaning Products Fact Sheet To assess the risks for the consumer	Public	N
Tessier V.	6.6_02	2014	Determination of the residual PHMB after simple rinsing operation of treated surface	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
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
L'Haridon J.	7.7.1.1_04	2002	PHMB P20 D: Activated sludge, respiration inhibition test	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
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
AVANTOR	2.2	2012	MATERIAL SAFETY DATA SHEET OF HYDROCHLORIC ACID	Laboratoire PAREVA	Y
Laboratoire PAREVA	8	2013	MATERIAL SAFETY DATA SHEET OF SANICIL-F2- According to Annex I of Regulation 453/2010	Laboratoire PAREVA	Y