Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

Piperonyl Butoxide

Product type: 18

ECHA/BPC/118/2016

Adopted

16 June 2016

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Opinion of the Biocidal Products Committee

on the application for approval of the active substance Piperonyl Butoxide for product type 18

In accordance with Article 89(1) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the approval in product type 18 of the following active substance:

Common name:	**Piperonyl Butoxide**
Chemical name(s):	**5-{[2-(2-butoxyethoxy)ethoxy]methyl}-6-propyl-1,3-benzodioxole**
EC No.:	**200-076-7**
CAS No.:	**51-03-6**
Existing active substance	

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

Process for the adoption of BPC opinions

Following the submission of an application by Endura S.p.A. in 2007, the evaluating Competent Authority Hellas (EL) submitted an assessment report and the conclusions of its evaluation to the Agency on 29 May 2015. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations *via* the BPC and its Working Groups. Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Adoption of the BPC opinion

Rapporteur: Greece

The BPC opinion on the approval of the active substance Piperonyl Butoxide in product type 18 was adopted on 16 June 2016.

The BPC opinion was adopted by simple majority of the members present having the right to vote. The minority positions including their grounds are published on the ECHA webpage at: http://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval.

Detailed BPC opinion and background

1. Overall conclusion

The overall conclusion of the BPC is that the Piperonyl Butoxide in product type 18 may be approved. The detailed grounds for the overall conclusion are described in the assessment report.

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

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

This evaluation covers the use of Piperonyl Butoxide in product type 18. Pyperonyl Butoxide is applied in amenity areas and woodlands (outdoor) against adult mosquitoes and public buildings (indoor) against flying insects (adult mosquitoes and houseflies). Specifications for the reference source are established.

Piperonyl Butoxide is always used in insecticidal formulations in combination with other insecticides mainly belonging to pyrethrins and synthetic pyrethroids. In the Working Group Efficacy the status of Piperonyl Butoxide was discussed and whether it may be considered as an active substance or a synergist. Studies are available demonstrating the innate efficacy against dust mites and house flies where it was shown that Piperonyl Butoxide has its own effect against these target organisms. Therefore it was concluded that Piperonyl Butoxide should be regarded as an active substance. This was confirmed by the BPC in the meeting of 2 - 5 December 2014.

The physico-chemical properties of the active substance and biocidal product have been evaluated and are deemed acceptable for the appropriate use, storage and transportation of the active substance and biocidal product.

Validated analytical methods are available for the active substance as manufactured and for the significant impurities. For two relevant impurities validation data are required. Validated analytical methods are available for soil, water and air. No analytical methods for food and feed of animal origin is available.

No harmonised classification for Piperonyl Butoxide is available. The CLH dossier is currently prepared and will be submitted to ECHA as soon as possible.

The eCA proposal for classification and labelling for Piperonyl Butoxide according to Regulation (EC) No 1272/2008 (CLP Regulation) is:

Proposed classification according to the CLP Regulation	
Hazard Class and Category Codes	Specific Target Organ Toxicity after Single Exposure category 3 [STOT SE 3] Carcinogen category 2 [Carc. 2] Aquatic Acute 1 Aquatic Chronic 1
Labelling	
Pictograms	GHS07, GHS08, GHS09
Signal Word	Warning
Hazard Statement Codes	H335, H351, H400, H410
Supplemtary hazard warning	EUH066, EUH401

Specific Concentration limits, M-Factors	M = 1 (for acute toxicity) M = 1 (for chronic toxicity)
Justification for the proposal	
STOT SE 3: acute & 3-month inhalation toxicity studies in rats confirmed by human epidemiology data **Carc. 2:** Mouse carcinogenicity study & lack of robust mechanistic data. **Aquatic Acute 1:** Acute toxicity to aquatic invertebrates (48-hour EC_{50} for *Daphnia magna*=0.51 mg/L; 96-hour LC_{50} for *Americamysis bahia*=0.32 mg/L; 96-hour EC_{50} for *Crassostrea virginica*=0.23 mg/L). **Aquatic Chronic 1:** Chronic toxicity to aquatic invertebrates (21-day NOEC for *Daphnia magna*=0.030 mg/L*;* 28-day NOEC for *Chironomus riparius*=0.0148 mg/L) and the fact that the active substance is not readily biodegradable. **EUH066:** 21-day dermal study in New Zealand White rabbits	

b) Intended use, target species and effectiveness

Piperonyl Butoxide has been used in insecticidal formulations for over 50 years and always in combination with other insecticides mainly belonging to pyrethrins and synthetic pyrethroids. Piperonyl Butoxide is intended for professional indoor use in public and domestic premises and outdoor use in amenity areas and woodlands to control flying insects such as houseflies and mosquitoes. The product is applied by fogging for indoor as well as outdoor use.

The mode of action of Piperonyl Butoxide is complex. Piperonyl Butoxide stabilises the co-applied insecticide inside the insect body and potentiates more toxins to reach their target molecules. This, results in an increased mortality of the target organism, and likewise, the same effect may be observed by using decreased amounts of insecticide, i.e. synergism. There is strong evidence from the literature, that Piperonyl Butoxide inhibits the oxidative and esterase-based metabolism (detoxyfication) of the co-applied insecticide. Therefore, Piperonyl Butoxide delays the degradation of co-applied insecticidal substances and thereby prolongs the potential action of the compounds.

Piperonyl Butoxide is usually applied at a dose that on its own is sublethal to the target species. When Piperonyl Butoxide is applied in combination with a known toxicant, the performance of the latter is enhanced at a rate that becomes lethal when on its own would be sublethal. Nevertheless, Piperonyl Butoxide on its own can exhibit some toxic effects, and hence at sublethal doses is likely to exert some stress on the insect.

A number of submitted efficacy studies documented the synergistic effect of Piperonyl Butoxide with natural pyrethrins and some indicative synthetic pyrethroids against houseflies, mosquitoes and cockroaches.

In order to demonstrate the innate killing effect of Piperonyl Butoxide, a number of efficacy laboratory studies, in which Piperonyl Butoxide was formulated in simple formulations alone ("dummy products"), were evaluated. According to these studies, Piperonyl Butoxide exerts innate lethal effect against house dust mites, mosquitoes, houseflies and cockroaches. In two of these studies the application method with "dummy products" was similar to the intended uses of the representative product, namely indoor space spray application. The "dummy products" applied as indoor space spray treatment contained high doses of Piperonyl Butoxide, which are not indicated in the evaluated intended uses. Therefore, these doses were not considered further in the evaluation. Human and environmental risk assessments have been performed considering Piperonyl Butoxide concentrations at the efficacious dose of the representative product (4.5 mg Piperonyl Butoxide/m^3) when applied as an indoor space spray treatment.

It is noted that only a basic efficacy of Piperonyl Butoxide was demonstrated at the active substance approval stage and for product authorisation, studies representative for the intended use have to be provided.

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

Human health

Piperonyl butoxide is of low acute oral, dermal and inhalation toxicity. It is readily and almost completely absorbed after oral administration. It is not irritating to rabbit skin and is slightly irritating to rabbit eyes, but repeated dermal application mat cause dermal effects and the additional hazard statement EUH066 [Repeated exposure may cause skin dryness or cracking] should be assigned. Piperonyl Butoxide causes respiratory tract irritation and should be classified as STOT SE with H335 [May cause respiratory irritation]. It does not show potential for skin sensitisation.

Piperonyl butoxide is not considered to be neurotoxic, immunotoxic, mutagenic or toxic to reproduction. Based on the information available, not having part of mechanistic data, Piperonyl Butoxide is considered as a potential carcinogen of category 2 with a threshold mode of action.

The table below summarises the exposure scenarios assessed:

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusion**
Outdoor Fogging	Primary exposure during outdoor ground cold (ULV) space fogging using either hand- held of vehicle-mounted equipment	Professionals	Acceptable without use of PPE
Indoor Fogging	Primary exposure during indoor application *via* cold (ULV) or *via* thermal fogging equipment	Professionals	Acceptable without use of PPE
Fogging	Secondary exposure when re-entering an area before the fog has disappeared	Bystanders (adult and child)	Acceptable
Fogging	Secondary exposure following indoor fogging	Bystanders (infant-worst case)	Acceptable

Professional indoor/outdoor use of Piperonyl Butoxide products *via* fogging is considered to be safe even when no PPE is used. The risks are considered acceptable for bystanders (adults and children) following indoor or outdoor application. However, following good hygiene practice, the general public should not enter the area treated during application by fogging.

Environment

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
Fogging (cold and thermal) for indoor and outdoor uses by professionals.	Indoor use considering air space treatment with thermal or cold fogging equipment. Sewage Treatment Plant (STP) is expected to be directly exposed while soil, groundwater, surface and sediment are considered to be secondarily exposed.	Unacceptable risks for surface water and sediment have been identified for indoor use via STP emissions. Acceptable risks for STP, soil and groundwater have been demonstrated.
	Outdoor use on woodlands and amenity areas with thermal or cold fogging equipment. Environmental compartments of soil, groundwater, surface water and sediment have been considered to be exposed due to drift.	Regarding **outdoor** use in woodlands and/or amenity areas considering **single** applications, unacceptable risk for sediment has been identified. Acceptable risks for soil, surface water and groundwater have been demonstrated. **Regarding outdoor** uses in woodlands and/or amenity areas considering **multiple** applications, unacceptable risks for surface water, sediment and soil have been identified. Acceptable risk for groundwater has been demonstrated. Acceptable risk for sediment considering **single** application has been demonstrated when a 30 m non-sprayed buffer zone is applied. Acceptable risks for surface water and sediment, considering a **threefold** application, have been demonstrated when a 30 m non-sprayed buffer zone is applied.

Piperonyl Butoxide:

Aquatic compartment (including STP, surface water and sediment)

The risk to STP microorganisms has been calculated to be acceptable following the intended indoor use (no exposure of STP microorganisms is anticipated following the outdoor use of the representative biocidal product). The risk to surface water has been calculated to be acceptable following the proposed outdoor uses, but unacceptable for the intended indoor

use. Regarding outdoor use/single application scenario, the risk for surface water has been found to be acceptable without considering any mitigation measures while the risk for the outdoor use/multiple applications scenario has been found to be acceptable only when a 30 m unsprayed buffer zone between the treated area and surface water was considered. The risk to sediment-dwelling organisms has been calculated to be unacceptable for all intended uses when no mitigation measures were considered. However, an acceptable risk for the sediment compartment following the intended outdoor uses (single and multiple applications) has been indentified when a 30 m unsprayed buffer zone between the treated area and surface water was considered.

Terrestrial compartment (including soil, groundwater, fish- and earthworm eating predators, bees and other non-target arthropods)

The risk to soil organisms has been calculated to be acceptable for the indoor and outdoor use/single application scenarios. Regarding the outdoor use/multiple applications scenario, minor risks are identified with a PEC/PNEC ratio slightly above the trigger value, provided the number of applications is limited to three. Due to the conservative approach used for deriving the PNEC for soil, this minor risk is considered acceptable. Regarding groundwater, the calculated PEC values have been found to be below the threshold value of 0.1 µg/L indicating no unacceptable risk to drinking water.

The risk to fish- and earthworm- eating predators has been calculated to be acceptable following all intended uses (indoor, outdoor/single application, outdoor/multiple applications).

The risk to bees has been assessed to be acceptable following the intended indoor use. Regarding outdoor uses, the risk to bees could not be assessed since no guidance on how to perform such an assessment is available.. The risk to other non-target (beneficial) arthropods has been assessed to be acceptable following the intended indoor and outdoor uses.

Major metabolites of Piperonyl Butoxide:

The risk to aquatic and sediment-dwelling organisms from metabolites M-1, M-2 and M-12 (or EN 1-93/3), the risk to soil organisms from metabolites M-1, M-2, M-8, M-12 (or EN 1-93/3) and EN 1-101/4 (or Metabolite F) and risk to fish- and earthworm- eating predators from metabolite M-12 (or EN 1-93/3) has been calculated to be acceptable following the intended indoor and outdoor (single and multiple) applications.

Overall, an acceptable risk for all environmental compartments under concern has been identified only for the outdoor use scenario provided that:

- a 30 m unsprayed buffer zone between the treated area and the water body is established in order to protect aquatic and sediment-dwelling organisms, and;

- the number of applications is limited to three.

Overall conclusion

In human health risk assessment all relevant scenarios i.e. indoor/outdoor fogging, have been assessed separately and have been considered acceptable for professional users without the use of appropriate personal protective equipment.

Regarding environmental risk assessment unacceptable risks are identified for indoor use applying thermal or cold fogging equipment. For the outdoor use, acceptable risks could be demonstrated only if a 30 m unsprayed buffer zone between the treated area and the water body is considered and the number of applications is limited to three.

Overall it can be concluded that only for outdoor use applying fogging a safe use is demonstrated, provided adequate risk mitigation measures are taken to prevent environmental risks.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

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

Property		Conclusions	
CMR properties	Carcinogenicity (C)	Carc. 2	Piperonyl Butoxide does not fulfil criterion (a), (b) or (c) of Article 5(1)
	Mutagenicity (M)	no classification required	
	Toxic for reproduction (R)	no classification required	
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	vP	Piperonyl Butoxide does not fulful criterion (e) of Article 5(1) and does not fulfil criterion (d) of Article 10(1)
	Bioaccumulative (B) or very Bioaccumulative (vB)	Not B	
	Toxic (T)	Not T	
Endocrine disrupting properties	Piperonyl Butoxide is not considered to have endocrine disrupting properties. Piperonyl butoxide does not fulfil criterion (d) of Article 5(1).		
Respiratory sensitisation properties	No classification required. Piperonyl Butoxide does not fulfil criterion (b) of Article 10(1).		
Concerns linked to critical effects	Piperonyl Butoxide does not fulful criterion (e) of Article 10(1).		
Proportion of non-active isomers or impurities	With regard to the proportion of non-active isomers or impurities, Piperonyl Butoxide is put on the market with 94% w/w minimum purity. Given this, Piperonyl Butoxide does not fulfil criterion (f) of Art 10.		

Based on the available QSAR data, the relevant impurities dipiperonyl methane (DPM) and dipiperonyl ether (DPE) seem to fulfil the PBT and vPvB criteria. The individual concentrations of these impurities in the specification are above the limit of 0.1 % w/w. Further data are required for these impurities to clarify their PBT status.

The metabolites M-1 fulfils the P criterion while the metabolites M-2, M-12 (or EN 1-93/3) and EN 1-101/4 (or Metabolite F) fulfil the vP criterion.

Consequently, the following is concluded:

Piperonyl Butoxide does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

Piperonyl Butoxide does not meet the conditions laid down in Article 10 of Regulation (EU) No 528/2012, and is therefore not considered as a candidate for substitution. The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking

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

2.2.2. POP criteria

Piperonyl Butoxide is considered persistent and does not demonstrate the potential of long-range transport based on overall OH rate constant of 0.5E6 OH radicals/cm3 a half-life of 3.597 hrs using a 24-hour days. However, the available (eco)toxicological data do not indicate a concern to human health, animals and the environment. Therefore, Piperonyl Butoxide does not meet the POP criteria.

2.3. BPC opinion on the application for approval of the active substance Piperonyl Butoxide in product type PT18

In view of the conclusions of the evaluation, it is proposed that Piperonyl Butoxide shall be approved and be included in the Union list of approved active substances, subject to the following specific conditions:

1. Specification: minimum purity of the active substance evaluated: 94 % w/w.

2. Relevant impurities:

   Safrole: max. content <0.004% w/w

   Dihydrosafrole: max. content ≤0.0085% w/w

   Dipiperonyl methane: max. content 1.95% w/w

   Dipiperonyl ether: max. content 0.9%w/w

   Isosafrole: max. content <0.004% w/w

   Methyl dihydrosafrole: max. content 0.5%w/w

   Piperonyl Butoxide-x (Piperonyl Butoxide homologue): max. content 0.47 % w/w

   ortho-Piperonyl Butoxide (Piperonyl Butoxide homologue): max. content 0.51 % w/w

   N.N-dimethylformamide: max. content <0.04% w/w

   Dichloromethane: max. content <0.05% w/w

3. The authorisations of biocidal products are subject to the following condition(s):

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

   b. In view of the risks identified for the uses assessed, the product assessment shall pay particular attention to:

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

i. surface water and sediment compartments for products used indoor for fogging;

ii. surface water, sediment and soil for products used outdoor for fogging.

c. For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009[3] or Regulation (EC) No 396/2005[4] shall be verified, and any appropriate risk mitigation measures shall be taken to ensure that the applicable MRLs are not exceeded.

The placing on the market of treated articles is subject to the following condition(s):

1. The person responsible for placing on the market of a treated article treated with or incorporating the active substance Piperonyl Butoxide shall ensure that the label of that treated article provides the information listed in the second subparagraph of Article 58(3) of the Regulation (EU) 528/2012.

As Piperonyl Butoxide is proposed to be classified as STOT SE 3, Carc. 2, Aquatic Chronic I and Aquatic Acute 1 and is very persistent (vP) and therefore gives rise to concern according to Article 28(2) being of an equivalent level of concern it can not be included in Annex I of Regulation (EU) 528/2012.

2.4. Elements to be taken into account when authorising products

The following recommendations and risk mitigation measures have been identified for the uses assessed. Authorities should consider these risk mitigation measures when authorising products, together with possible other risk mitigation measures, and decide whether these measures are applicable for the concerned product:

a. If an unacceptable risk for industrial and professional users is identified for the product, safe operational procedures and appropriate organisational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products should be used with appropriate personal protective equipment.

b. In case of indoor or outdoor application by fogging, the general public should not enter the treated area following good hygiene practice.

c. Unacceptable risks are identified in case of indoor application by fogging for surface water and sediment organisms. If the risk cannot be reduced to an acceptable level by appropriate risk mitigation measures or by other means, these uses should not be authorised.

d. Unacceptable risks are identified in case of outdoor application by fogging to surface water and sediment. If the risk cannot be reduced to an acceptable level by appropriate risk mitigation measures like introducing a non-sprayed buffer zone, or by other means, these uses should not be authorised.

e. In case of outdoor application, the risk to bees should be particularly considered.

f. An assessment of the risk in food and feed areas may be required at product authorisation where use of the product may lead to contamination of food and feeding stuffs.

g. At product authorization level, synergism should be addressed when the concerning

[3] Regulation (EC) No 470/2009 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 11
[4] Regulation (EC) No 396/2005 of the European Parliament and of the Council (OJ L 70, 16.3.2005, p. 1

biocidal product contains other insecticides besides Piperonyl Btuxoide.

2.5. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of Piperonyl Butoxide. However, the following further data must be submitted to the evaluating Competent Authority (Greece) as soon as possible but no later than 6 months before the date of approval of the active substance:

Identity:

- The presence of isosafrole should be analysed by an appropriate analytical method. Hence, a validated method should be provided including the limit of quantification and limit of detection of isosafrole.

Methods of analysis:

- N,N-dimethylformamide and Dichloromethane were analysed in the 5-batch analysis. However full validation data must be submitted for the analytical method.

- in case of setting a MRL for Piperonyl Butoxide, analytical methods for the determination in potentially (directly or indirectly) exposed food and feedstuffs should be provided.

Human health:

- The Phase III of the ongoing study on cultured mouse and human hepatocytes should be provided as soon as possible. When available, these data will be considered in the weight-of-evidence approach towards the determination of the MoA for carcinogenicity of Piperonyl Butoxide.

Environment:

- Based on the available QSAR data, the impurities Dipiperonyl methane (DPM) and Dipiperonyl ether (DPE) seem to fulfil the PBT and vBvP criteria. As the individual concentrations of these impurities in the technical specification are above the limit of 0.1 % w/w, i.e. 1.95 % w/w for Dipiperonyl methane (DPM) and 0.90 % w/w for Dipiperonyl ether (DPE), further data are required in order to enable a definite conclusion on the specific exclusion or substitution criteria of the active substance.

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