

**WHO SPECIFICATIONS AND EVALUATIONS  
FOR PUBLIC HEALTH PESTICIDES**

**PIPERONYL BUTOXIDE**

**5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-  
1,3-benzodioxole**



**World Health  
Organization**

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## **DISCLAIMER<sup>1</sup>**

WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

WHO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, WHO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

WHO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, WHO does not in any way warrant or represent that any pesticide claimed to comply with a WHO specification actually does so.

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<sup>1</sup> This disclaimer applies to all specifications published by WHO.

## INTRODUCTION

WHO establishes and publishes specifications<sup>2</sup> for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the Manual for development and use of FAO and WHO specifications for chemical pesticides. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the “FAO/WHO Joint Meeting on Pesticide Specifications” (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

**Part One:** The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the above-mentioned manual.

**Part Two:** The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

**Specifications bear the date (month and year) of publication of the current version. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.**

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<sup>2</sup> The publications are available on the Internet under the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, <https://extranet.who.int/prequal/vector-control-products>

**PART ONE: SPECIFICATIONS**

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**PIPERONYL BUTOXIDE**

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## Piperonyl Butoxide Information

### ISO common names

Piperonyl butoxide (BAN; accepted in lieu of a common name by BSI, E-ISO, ESA); piperonyl butoxyde (F-ISO)

### Synonyms

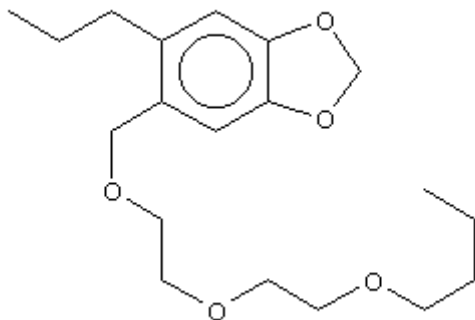
PBO

### Chemical names

*IUPAC* 5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole

*CA* 5-[[2-(2-butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxole

### Structural formula



### Empirical formula

$C_{19}H_{30}O_5$

### Relative molecular mass

338.4

### CAS Registry number

51-03-6

### CIPAC number

33

### Identity tests

GC retention time, mass spectrum (from GC-MS)

**Piperonyl Butoxide Technical Material**  
**WHO Specification 33/TC (October 2023\*)**

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (33/2010, 33/2011, 33/1018, 33/2023). It should be applicable to technical material produced by these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for technical material produced by other manufacturers. The evaluation reports (33/2010, 33/2011, 33/1018, 33/2023), as PART TWO, form an integral part of this publication.*

**1 Description**

The material shall consist of piperonyl butoxide together with related manufacturing impurities, in the form of a viscous, colourless to slightly yellow liquid, and shall be free from visible extraneous matter and added modifying agents.

**2 Active ingredient**

**2.1 Identity tests** (33/TC/M2/2, CIPAC Handbook O, p. 104, 2017)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

**2.2 Piperonyl butoxide content** (33/TC/M2/3, CIPAC Handbook O, p. 104, 2017)

The piperonyl butoxide content shall be declared (not less than 920 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

**3 Relevant impurities**

**3.1 Dihydrosafrole** (33/TC/M2/4, CIPAC Handbook O, p. 107, 2017)

Maximum: 0.1 g/kg.

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\* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website: <https://extranet.who.int/prequal/vector-control-products/specifications-new-procedure>

**PART TWO: EVALUATION REPORTS**

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**PIPERONYL BUTOXIDE**  
**FAO/WHO Evaluation Report 33/2023**

**Recommendations**

The Meeting recommended that:

- (i) The PBO TC as proposed by Catasynth Speciality Chemicals Pvt. Ltd. should be accepted as equivalent to the PBO reference profile.
- (ii) The existing FAO PBO TC specification should be extended to encompass the technical material produced by Catasynth Speciality Chemicals Pvt. Ltd.
- (iii) The existing WHO PBO TC specification should be extended to encompass the technical material produced by Catasynth Speciality Chemicals Pvt. Ltd.

**Appraisal**

The Meeting considered data and information submitted between April 2021 and June 2023 by Catasynth Speciality Chemicals Pvt. Ltd. (Catasynth) in support of extension of the existing FAO and WHO specifications for piperonyl butoxide (PBO) TC.

The data submitted met the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (2022, second edition).

The manufacturer submitted confidential data on the manufacturing process, together with the manufacturing specification and 5-batch analysis data on PBO TC purity and all detectable impurities below, at or above 1 g/kg.

Catasynth stated that their PBO TC has been registered in Australia. A notice of approval has been received (APVMA, February 2023).

The batches analyzed in the 5-batch study were produced over 6 months in 2019. The mass balance in the 5 batches ranged from 988.94 to 994.78 g/kg. The specified minimum purity of PBO in the TC is 950 g/kg, which is higher than the limit of 920 g/kg specified in the published TC specification. The specified maximum limit of 0.0058 g/kg for the relevant impurity dihydrosafrole (DHS) is lower than the current maximum FAO/WHO specification limit of 0.1 g/kg. The maximum limits for the impurities were supported by the 5-batch data and are statistically justified. No new impurities were detected in the 5-batch data. The 5-batch analysis study report indicates that no other significant impurities (each at or above 1 g/kg) were found in any of the 5 batches.

The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 33/TC/M2/3 (GC with flame ionization detection and internal standard) was used for the determination of PBO in the technical material. The CIPAC method 33/TC/M2/4 (GC with flame ionization detection and internal standard) was used for the determination of relative impurity dihydrosafrole (DHS) in the PBO TC, whereas in-house methods (HPLC with diode-array detection, or GC with flame ionization detection) were used for the determination of other organic manufacturing impurities. Water was determined using the CIPAC method MT 30.6 (Karl Fischer). All the analytical methods used in the 5-batch analysis study were adequately validated with their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities). PBO TC solubility in organic solvents test reports (CIPAC MT 181) were submitted.

A bacterial reverse mutation test (OECD 471) with tester strains *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2uvrA (pKM101) was submitted. The results of the study show that the PBO TC produced by Catasynth does not induce bacterial reverse mutations under the conditions of this study.

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On basis of Tier-1 data provided by Catasynth (manufacturing process, purity/impurity profile, 5-batch analysis data, mutagenicity profile), the Meeting concluded that the PBO TC from Catasynth should be considered as equivalent to the reference profile supporting the existing FAO and WHO specifications 33/TC.

**Supporting Information  
for  
Evaluation Report 33/2023**

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

**Table 1. Chemical composition and properties of piperonyl butoxide technical material (TC)**

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data		Confidential information supplied and held on file by FAO or WHO. Mass balances were 98.89–99.48% and percentages of unknowns were 0.52–1.11%.		
Declared minimum piperonyl butoxide content		950 g/kg		
Relevant impurities $\geq 1$ g/kg and maximum limits for them		None		
Relevant impurities $< 1$ g/kg and maximum limits for them:		Dihydrosafrole Maximum limit: 0.0058 g/kg		
Stabilisers or other additives and maximum limits for them:		None		
Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	Piperonyl butoxide is a liquid both at ambient temperature and also at $-10$ °C	-	-	-
Solubility in organic solvents	$>250$ g/L in acetone, methanol, propan-2-ol, ethyl acetate, 1,2-dichloroethane, <i>p</i> -xylene, <i>n</i> -heptane at $20 \pm 0.5$ °C	95.77	CIPAC method MT 181	AG-G1527

# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## **Annex 1: Hazard Summary Provided by the Proposer**

Notes.

- (i) The proposer confirmed that the toxicological data included in the summary below were derived from piperonyl butoxide having impurity profiles similar to those referred to in the table above.
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

**Table 1. Mutagenicity profile of technical PBO based on *in vitro* test**

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
<i>Salmonella typhimurium</i> test strains: TA98, TA100, TA1535, TA1537 and <i>Escherichia coli</i> test strain: WP2uvrA (pKM101)	Bacterial reverse mutation	95.56	OECD No. 471 (2020) in triplicate at 50, 158, 500, 1581 and 5000 µg/plate (in both the presence and absence of S9 mix) 37±1 °C for 67 hours	Not mutagenic	G22060

# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## Annex 2: References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [If GLP]. Company conducting the study.
G18303	Ravikanth Gogineni	2020	Five Batch Analysis of Piperonyl Butoxide Technical, GLP compliant, conducted by Analytical R&D Department Eurofins Advinus Limited, India
G22060	S.D. Rani	2022	Piperonyl Butoxide Technical: Bacterial Reverse Mutation Test, GLP compliant, conducted by Adgyl Lifesciences Private Limited, India
AG-G1527	Nagarathna	2023	Determination of Solubility of Piperonyl Butoxide Technical in Organic Solvents, GLP compliant, conducted by Eurofins Advinus Agroservices India Private Limited, India
	APVMA	2023	Notice of approval for PBO TC produced by Catasynth

**PIPERONYL BUTOXIDE**  
**FAO/WHO Evaluation Report 33/2018**

**Recommendations**

The Meeting recommended the following.

- (i) The PBO TC as proposed by Tagros Chemicals India Private Ltd. should be accepted as equivalent to the PBO reference profile.
- (ii) The FAO PBO TC specification should be extended to encompass the material produced by Tagros Chemicals India Private Ltd.
- (iii) The WHO PBO TC specification should be extended to encompass the material produced by Tagros Chemicals India Private Ltd.

**Appraisal**

The Meeting considered data and information submitted by Tagros Chemicals India Ltd. (Tagros) in 2017 in support of extension of the existing FAO and WHO specifications for piperonyl butoxide (PBO) TC. The data submitted by Tagros were broadly in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010 - second revision of the First Edition) (Section 3.2).

The Meeting was provided by Tagros with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for PBO and all detectable impurities below, at or above 1 g/kg. The manufacturing process used by Tagros is similar to the reference process used by Endura.

Tagros stated that their PBO TC has been registered in Australia. A certificate of registration, a letter of access for the Australian APVMA, a confirmation of registration and a comparison of the confidential data submitted to the authority has been received (APVMA, 2018).

Tagros utilizes a similar manufacturing pathway as the producer of the reference TC. The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 33/TC/M2/3 (capillary GC with flame ionization detection and internal standard) was used for determination of the PBO content in the technical material. The PBO organic manufacturing impurities were determined by HPLC with UV detection, except for water that was determined using the CIPAC Karl Fischer method. All the analytical methods used in the 5-batch analysis study were adequately validated with their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

The Meeting concluded that the PBO TC produced by Tagros is manufactured according to a similar pathway as the process used to produce the reference TC. The TC produced by Tagros is equivalent to the material produced by Endura by the following aspects:

- minimal content of active ingredient: 950 g/kg vs. 920 g/kg



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- a number of impurities that occur both in the Endura material and Tagros material
- the analytical methods are sufficiently described and validated.

The study on reverse mutation of the technical material following OECD technical guideline 471 allows the conclusion that the material does not induce reverse mutations in the strains tested.

However, there are two impurities in the Endura material (butylcarbitol and dipiperonylmethane) that have manufacturing specifications allocated (40 and 20 g/kg) that were not analyzed in the Tagros material. These impurities are expected to be formed in the Tagros material as well. Though these impurities are not relevant, they are disclosed in the published specification of the Endura material<sup>1</sup> and are hence in the public domain.

The data package submitted before the 2017 JMPS contained a study on content of PBO and impurities in 5 batches of the technical material. The laboratory, however did not utilize the peer validated method for determination of dihydrosafrole (DHS) in PBO TC. This compound was identified as a relevant impurity in the material produced by Endura with a maximum level of 100 mg/kg. These points are data requirements and no decision on equivalence or non-equivalence of the PBO TC produced seemed possible until the data package had been completed and evaluated. Later on (beginning of May 2017) a study was received on determination of DHS and a residual hydrocarbon solvent in 5 batches of PBO. The study (Study Nr. G 12762) was done under GLP and reports on the levels of DHS and cyclohexane in the same batches as used in the 5-batch-study. However, though a detailed description of the GC-FID method is missing, the information provided leads to the conclusion that the contract lab did not closely follow the peer validated method and significant deviations from the peer validated method were noted. DHS was, according to the study, not detected above the limit of quantitation of 30 mg/kg.

Later on and on request by JMPS, a new study on residues of DHS in PBO TC has been received. DHS has been analyzed in the 5 batches now closely following the peer validated method, the residues of butylcarbitol and the correct assignment of dipiperonylmethane have been determined. The Meeting reconsidered all data in the JMPS 2018 Meeting and concluded, that based on the additional studies, the PBO TC produced by Tagros is equivalent to the reference profile by Tier-1. The confirmation of the registration of PBO TC produced by Tagros for use in pesticide formulations was obtained in August 2018, thus fulfilling all data requirements.

In addition, the Meeting recommended an editorial update of the 2011 PBO TC specification with regard to the CIPAC methods for determination of PBO and of dihydrosafrole both in PBO TC now published in Handbook O. For this reason, the Annex I in the 2011 evaluation report with the method for DHS was no longer necessary and could be removed.

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<sup>1</sup> <http://www.endura.it/en/products/insect-control/piperonyl-butoxide> (April 2017)

**Supporting Information  
for  
Evaluation Report 33/2018**

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## WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

**Table 1. Chemical composition and properties of piperonyl butoxide technical material (TC)**

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.32-99.67% and percentages of unknowns were 0.33-0.68 %.
Declared minimum piperonyl butoxide content	950 g/kg
Relevant impurities $\geq 1$ g/kg and maximum limits for them	None
Relevant impurities $< 1$ g/kg and maximum limits for them	Dihydrosafrole, 100 mg/kg
Stabilisers or other additives and maximum limits for them	None

**Annex 1: Hazard Summary Provided by the Proposer**

Notes.

- (i) The proposer confirmed that the toxicological data included in the summary below were derived from piperonyl butoxide having impurity profiles similar to those referred to in the table above.
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

**Table 1. Mutagenicity profile of technical PBO based on *in vitro* test**

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
<i>Salmonella typhimurium</i> test strains: TA98, TA100, TA102, TA1535, TA15375	Ames test	94.0	OECD 471 0.31, 0.62, 1.25, 2.5 and 5.0 mg/plate (in both the presence and absence of S9 mix) 37°C for 48 hours	Not mutagenic	16_14_169

# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
G13332	Jagadish B.	2017	5-Batch Analysis of Piperonyl Butoxide Technical. GLP, Unpublished.
16_14_169	J. Daniel Z Paul	2017	Bacterial Reverse Mutation Test of Piperonyl Butoxide Technical in Salmonella typhimurium, Tester Strains. sa-FORD, Taloja, Dist: Ralgad Navi Mumbai. India. GLP, non-published.
7211	U. Ganesh	2017	Validation of Analytical Method And Determination Of Impurity Dihydrosafrole In Five Batches of Piperonyl Butoxide Technical. RCC Laboratories India Private Limited, Hyderabad - 500 India. GLP, non-published.
G15684	Ra Vikanth Gogineni.	2017	Method Validation and Quantification of Butylcarbitol In Piperonyl Butoxide Technical, Advinus, Bengaluru, India, GLP, non-published.
G13762	Ra Vikanth Gogineni	2017	Method Validation And Quantification Of Impurities In Piperonyl Butoxide Technical. Advinus, Bengaluru, India, GLP, non-published.
G13332	Jagadish B.	2017	Amendment No. 1. to Final Report, Advinus, Bengaluru, India, GLP.
	APVMA	2018	Note of approval for PBO produced by Tagros India.

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**FAO/WHO Evaluation Report 33/2011**

**Recommendations**

The Meeting recommended the following.

- (i) The revision of the specification for piperonyl butoxide TC by including dihydrosafrole as relevant impurity with a limit of 0.1 g/kg should be adopted by FAO and WHO.
- (ii) The existing FAO draft specification 33/1/S/4 for piperonyl butoxide TC developed under the old procedure should be withdrawn.

**Appraisal**

The PBO specification for WHO and FAO based on data submitted by Endura was adopted at the 2010 JMPS. The main issues in the specification were, among other points, the reference profile and the evaluation of dihydrosafrole (DHS), an impurity in PBO TC, as relevant impurity (see appraisal of the evaluation report 33/2010).

As the level of DHS was lower than 10 % of the GHS classification limit for carcinogenic mixtures substances (1 g/kg), the Meeting concluded that DHS was not a relevant impurity. In the meantime, Endura has conducted a collaborative trial on determination of PBO in TC and a peer validation for determination of DHS in TC. Based on the carcinogenic properties of DHS, and on the concentrations of this impurity found in the batches used for toxicological studies and in the production batches, the company has proposed (letter dating of 17 March 2011 addressed to WHO) to revise the published WHO specification by including DHS as relevant impurity with a maximum limit of 0.085 g/kg.

The Manual (November 2010 - second revision of the First Edition) states that if a limit below the maximum acceptable for the relevant impurity has been shown to be practical for routine manufacturing (Section 3.1, paragraphs A.5 or A.6), the JMPS will normally adopt it in preference. The current case falls in this category.

Taking into account the recent availability of a peer-validated method to determine DHS in PBO TC (see Appendix 1) and in accordance with the FAO/WHO Manual, the Meeting recommended to adopt the revision by inclusion of DHS as relevant impurity with a limit of 0.1 g/kg. In the same instance, the newly adopted CIPAC method for PBO TC based on capillary GC instead of the packed column method in Handbook H can be referenced to.

**Supporting Information  
for  
Evaluation Report 33/2011**

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**Physico-chemical properties of piperonyl butoxide****Table 1. Chemical composition and properties of piperonyl butoxide technical materials (TC)**

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 98.59 – 99.35% and percentages of unknowns / unaccountables were 0.65 – 1.41% (water accounts for about 0.1% of this fraction but was not analyzed as part of the GLP 5 batch analysis report).
Declared minimum piperonyl butoxide content	920 g/kg
Relevant impurities $\geq 1$ g/kg and maximum limits for them	None
Relevant impurities $< 1$ g/kg and maximum limits for them	Dihydrosafrole Maximum limit: 0.1 g/kg
Stabilisers or other additives and maximum limits for them	None
Melting or boiling temperature range of the TC	Piperonyl butoxide is a liquid both at ambient temperature and also at $-10$ °C

**PIPERONYL BUTOXIDE**  
**FAO/WHO Evaluation Report 33/2010**

**Recommendations**

The Meeting recommended the following.

The specification for piperonyl butoxide TC proposed by Endura, as amended, should be adopted by FAO and WHO, subject to clarification of the representativeness of the hazard data elaborated with a composite tox batch for the material produced by Endura and relevance of some impurities detected in the latter material.

**Appraisal**

The data submitted were broadly in accordance with the requirements of the FAO/WHO Manual March 2006 revision of the first edition and supported the draft specifications for new FAO and WHO specifications.

The toxicology of piperonyl butoxide was evaluated by JMPR in 1995 and an ADI of 0-0.2 mg/kg bw was set. The WHO hazard classification of piperonyl butoxide is: "unlikely to present acute hazard in normal use". The 2001 JMPR concluded that setting an ARfD for piperonyl butoxide was not justified. The GHS acute toxicity category of piperonyl butoxide is 5.

Piperonyl butoxide is classified by US EPA as category III by oral and dermal and as category IV by inhalation exposure routes, as minimally irritating to eyes and skin.

Piperonyl butoxide is an oily liquid at room temperature. It has a low volatility (vapor pressure:  $1.33 \times 10^{-5}$  Pa at 25 °C). The octanol-water partition coefficient indicates that piperonyl butoxide could have a potential to bioaccumulate (log Pow = 4.8 at 20°C, independent of pH), but studies show rapid degradation in the mammalian metabolism and in the environment.

Confidential information regarding the manufacturing process and the identity of the impurities at a level > 1 g/kg was presented. Mass balances were in the range of 985.9 to 993.5 g per kg. The data supported a minimum content of 920 g/kg for piperonyl butoxide in the TC.

The necessity to control residual water or acidity/alkalinity in piperonyl butoxide TC was discussed by the Meeting. Noting the stability of piperonyl butoxide against hydrolytic attack in the pH range of 5 to 9 and taking into consideration that the manufacturing process for piperonyl butoxide includes a purification step for the technical material, the Meeting agreed that limits for water, alkalinity or acidity in the TC were not necessary for the material under consideration and could be removed.

The question of relevant impurities was discussed by the Meeting. During the manufacturing process traces of an intermediate, dihydrosafrole (DHS) could be carried forward to the finished technical material. DHS has been evaluated for carcinogenicity by IARC and classified as possibly carcinogenic to humans (2B)

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(Ref. 3). DHS has not been detected in 5 batch analysis data submitted by the proposer. The detection limit was lower than 10 % of the GHS limit and DHS was therefore considered non relevant in the TC produced by Endura.

However, this compound could become a relevant impurity if present in other products at higher levels.

The hazard data on piperonyl butoxide was elaborated by a task force using tox batches representing composite products from batches produced by companies participating in the piperonyl butoxide consortium indicated in a footnote in the hazard tables. Information on purity and composition of the tox batches as well as that actually produced by Endura has been provided.

Therefore, a combination of equivalence assessment and bridging was necessary, where the tox batches supported by hazard data was compared with the impurity profile and manufacturing specification of the actual TC produced by Endura.

The Meeting noted that the TC produced by Endura is manufactured using a different route, not starting with sassafras oil but that the toxicity studies were mainly performed using different batches of a sassafras-based product. However, all impurities in the Endura product – including DHS - were present also in the Sassafras-based products actually tested, and their concentrations in these products were similar or higher than in the Endura product; they were thus covered by the toxicity studies. Not surprising, safrole has not been detected in the Endura product, and based on the information on the manufacturing process, it is not expected to be present. In addition, a recent study on the bacterial mutagenicity test with *S. typhimurium* and *E. Coli* strains and carried out with the Endura material was submitted to JMPS and no mutagenicity was observed.

As far as impurities are concerned, the reported limits have been supported by the 5-batch data. The dates of production of the batches tested have been provided. The analytical methods used for quantification and identification of impurities were sufficiently validated for the concentration ranges the impurities occurred in the TC.

The Meeting concluded, that the active ingredient content of the Endura product is higher than that of the sassafras-based product, and all impurities found in the Endura product are present at higher or similar concentrations in the sassafras-based product used in the toxicity studies. The mass-balance is  $\geq 980\text{g/kg}$ . Thus the toxicity and ecotoxicity studies performed with the sassafras-based product reflect the hazards of the Endura product too, and represent a worst-case scenario.

A draft specification for TC has been submitted by the proposer, which was broadly in agreement with the requirements of the FAO and WHO Manual (2006). As the proposer produces the TC and sells its piperonyl butoxide to various formulators, a specification for TC only was submitted.

### References for the appraisal

- 1 1995 JMPR Evaluation of piperonyl butoxide, p. 156 Toxicology.
- 2 Pesticide Synthesis Handbook, Th. A. Unger, Noyes Publication 1996, p. 1004, Piperonyl butoxide.
- 3 IARC (1987) Supplement No. 7. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, page 62.

**Supporting Information  
for  
Evaluation Report 33/2010**

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**Physico-chemical properties of piperonyl butoxide**

**Table 1. Physico-chemical properties of pure piperonyl butoxide**

Parameter	Value(s) and conditions	Purity %	Method reference and company report number/date
Vapour pressure	2.11 x 10 <sup>-5</sup> Pa at 60°C (The calculated vapour pressure at 25 °C will be less than 1.33 x 10 <sup>-5</sup> Pa)	93.0	EPA 796.1950 ABC Laboratories Report No. 38007 (1989)
Melting point, boiling point and/or temperature of decomposition	Melting point: liquid at room temperature Boiling point: 203°C at 0.278 kPa  Decomposition temperature: >300°C	94.0  94.47  94.0/97.2	ASTM E537-76  Endura Report No. 735 (2011) Endura Report No. 652 (2009)
Solubility in water	0.034 g/l at 8.4°C at pH 7.02 0.027 g/l at 20.4°C at pH 7.02 0.022 g/l at 33.4°C at pH 7.02	99.35	EEC A6 GAB Report No. 20051476/01/01-PCSB (2006)
Octanol/water partition coefficient	log P <sub>ow</sub> = 4.8 at 20°C at pH 6.5	99.35	EEC A8 GAB Report No. 20051476/01-PCPC (2006)
Hydrolysis characteristics	Half-life = > 500 days at 25°C at pH 5, 7 and 9, in the dark	92.43	EPA 161-1 HRC Report No. PBT 4/943285 (1995)
Photolysis characteristics	Half-life = 8.4 hours at 25°C at pH 7 when exposed to natural sunlight.	98.3	EPA 161-2 BTC Report No. P0594010A (1995)
Dissociation characteristic	Does not dissociate.	-	-

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**Table 2. Chemical composition and properties of piperonyl butoxide technical materials (TC)**

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 98.59 – 99.35% and percentages of unknowns / unaccountables were 0.65 – 1.41% (water accounts for about 0.1% of this fraction but was not analyzed as part of the GLP 5 batch analysis report).
Declared minimum piperonyl butoxide content	920 g/kg
Relevant impurities $\geq 1$ g/kg and maximum limits for them	None
Relevant impurities $< 1$ g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them	None
Melting or boiling temperature range of the TC	Piperonyl butoxide is a liquid both at ambient temperature and also at $-10$ °C

### Hazard summary

The data for piperonyl butoxide were evaluated in support of a new FAO/WHO specification for the TC only.

Piperonyl butoxide, when manufactured by the Endura process, is under patent in several countries worldwide like Australia, Brazil, Germany, India and many others.

The patent has been granted in all the listed countries except BR and JP where the patent application has been published and is being examined.

The draft specification and the supporting data were provided by Endura S.p.A. in 2008.

Piperonyl butoxide has not been evaluated by the WHO IPCS but has been evaluated by the FAO/WHO JMPR last in 1995 for toxicology and last in 2001/2002 for residues. In 1995, the ADI was set at 0 to 0.2 mg/kg bw/day, on the basis of the lowest NOAEL of 16 mg/kg bw/day, determined in the 1 year dog study. In 2002, IEDIs for the five GEMS/Food regional diets were estimated to be between 20% and 40% of the ADI. The Meeting concluded that the intake of residues of piperonyl butoxide resulting from its uses that have been considered by the JMPR was unlikely to present a public health concern. An ARfD for piperonyl butoxide was considered unnecessary. The Meeting therefore concluded that short-term dietary intake of piperonyl butoxide residues is unlikely to present a risk to consumers.

It was evaluated/reviewed by the US EPA last in 2006 (Date of the Reregistration Eligibility Document) and is currently under evaluation/review by the European Commission (dossier submitted under Directive 98/8/EC).

The WHO hazard classification of piperonyl butoxide is: unlikely to present acute hazard in normal use. The GHS acute toxicity category is 5.

Piperonyl butoxide is classified by US EPA as category III by oral and dermal and as category IV by inhalation exposure routes, as minimally irritating to eyes and skin.

### Uses

Piperonyl butoxide (PBO) is an insecticide synergist. It acts by protecting the co-applied insecticide (e.g. pyrethrins, pyrethroids and other pesticides) from metabolic attack thus allowing them to reach their biochemical targets.

Since piperonyl butoxide inhibits an enzyme system which is catalysing oxidative processes in living systems, it also has an intrinsic toxic potential to arthropods. It is widely used in combination with pyrethrins, pyrethroids and other pesticides, in public health, household and human and veterinary medicinal products, agriculture, stored product protection, home and garden, etc. against a variety of flying and crawling arthropod species, e.g. mosquitoes, houseflies, cockroaches, storage pests, mites, moths, ticks, lice, etc. (*Glynn-Jones, 1998*).

### **Formulations and co-formulated active ingredients**

Piperonyl butoxide is typically co-formulated with pyrethrins or pyrethroids, as well as with other active ingredients. The compound is used in classical formulations like EC, EW as well as in insecticidal treated long-lasting nets (LN).

These formulations are widely registered and sold globally.

### **Methods of analysis and testing**

The analytical method for determination of piperonyl butoxide in the technical material is currently a CIPAC Method published in Handbook 1C. It is a packed column GC method using dicyclohexylphthalate as internal standard and allows the determination of piperonyl butoxide in technical material with a concentration of 800 g/kg. With reference to the CIPAC Guideline "Extension of the scope of methods", the acceptability range where no additional validation has to be performed is 200 to 50 % from that studied in a collaborative trial. The extension of 800 to 920 g/kg with the new proposed minimum content is therefore well within that range.

As the method in Handbook 1C has been declared as "no longer supported" by CIPAC but still can be used, no method extension to long-lasting insecticidal nets containing piperonyl butoxide is possible. CIPAC has adopted in 2009 a method on determination of piperonyl butoxide in LN by capillary gas chromatography. For consistency reasons, the renewal of the packed column GC method with a capillary column GC method is currently under way and the presentation and possible adoption is scheduled for the 2011 CIPAC Meeting.

Test methods for determination of physico-chemical properties of the technical active ingredient, as presented in *Table 1*, were EPA 796.1950 (Vapour Pressure), EEC A6 (Solubility in water), EEC A8 (Octanol/water partition coefficient), EPA 161-1 (Hydrolysis) and EPA 161-2 (Photolysis).

### **Physical properties**

The specification for piperonyl butoxide TC does not require testing of physical properties, and specifications were not proposed for formulations, so that physical test methods for support of the specifications were not considered in this evaluation.

### **Containers and packaging**

It is recommended to use containers made of high-density polyethylene; epoxyphenolic-lined steel, dark glass or aluminium.

It should be avoided to use non-lined steel containers.

### **Expression of the active ingredient**

The active ingredient content is expressed as piperonyl butoxide.



**Annex 1: Hazard Summary Provided by the Proposer**

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Notes:

- (i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from piperonyl butoxide having impurity profiles similar to those referred in Table 2. The toxicological tests and most of the ecotoxicological tests were generated with a sample of piperonyl butoxide that was manufactured from natural sassafras oil.
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

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**Table 3. Toxicology profile of the piperonyl butoxide technical material, based on acute toxicity, irritation and sensitization**

Species	Test	Duration and conditions or guideline adopted	Batch Number	Result
Rats, male & female	oral	US EPA 81-1	Task Force FEP-100	LD <sub>50</sub> = 4570 mg/kg bw (males) LD <sub>50</sub> = 7220 mg/kg bw (females) LD <sub>50</sub> = 5630 mg/kg bw (combined)
Rabbits, male & female	dermal	US EPA 81-2	Task Force FEP-100	LD <sub>50</sub> = > 2000 mg/kg bw
Rats, male & female	inhalation	US EPA 81-3	Task Force FEP-100	LC <sub>50</sub> = > 5900 mg/m <sup>3</sup>
Rabbits, male & female	skin irritation	US EPA 81-5	Task Force FEP-100	Not irritant
Rabbits, male & female	eye irritation	US EPA 81-4	Task Force FEP-100	Not irritant
Guinea pig, male & female	skin sensitization	US EPA 81-6	Task Force FEP-100	Not sensitizing

The above toxicological data have been submitted to the FAO/WHO JMPR and were assessed in 1995. The data are property of the Piperonyl Butoxide Task Force II, members of which are Endura S.p.A., McLaughlin Gormley King Co., Prentiss Incorporated, S.C. Johnson & Son, Inc. and Valent BioSciences Corporation.

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**Table 4. Toxicology profile of technical piperonyl butoxide based on repeated administration (sub-acute to chronic)**

Species	Test, duration and conditions	Guideline adopted	Batch Number	Result
Dogs, male & female	8 week oral toxicity 0, 500, 1000, 2000 and 3000 mg/kg diet 0, 14.7, 32, 63, and 90 mg/kg bw/d for males and 0, 14.8, 37, 61, and 85 mg/kg bw/d for females	OECD 409	Task Force FEP-100	NOAEL = 14.8 mg/kg bw/d LOEL = 63 mg/kg bw/d (males) LOEL = 61 mg/kg bw/d (females)
Rabbits, male & female	3 week dermal toxicity 0, 100, 300 and 1000 mg/kg bw/d	US EPA Pesticide Assessment Guidelines, Subdivision F, 82-2	Task Force FEP-100	NOAEL = 1000 mg/kg bw/d LOEL = > 1000 mg/kg bw/d
Rats, male & female	3 months inhalation toxicity Analytical concentration: 0, 15, 74, 155, 512 mg/m <sup>3</sup>	US EPA Pesticide Assessment Guidelines, Subdivision F, 82-4	Task Force FEP-100	NOAEL = 155 mg/m <sup>3</sup> LOEL = 512 mg/m <sup>3</sup>
Mice, male & female	3 months oral toxicity 0, 10, 30, 100, 300 and 1000 mg/kg bw/d	OECD Guideline 408	Task Force FEP-100	NOAEL = 100 mg/kg bw/d LOEL = 300 mg/kg bw/d
Dogs, male & female	1 year oral toxicity 0, 100, 600 and 2000 mg/kg diet 0, 2.9, 15.5 and 53 mg/kg bw/d for males and 0, 2.7, 16.3 and 71 mg/kg bw/d for females.	OECD Guideline 452	Task Force FEP-100	NOAEL = 16 mg/kg bw/d LOEL = 53 mg/kg bw/d (males) LOEL = 71 mg/kg bw/d (females)
Rats, male & female	2 year oral toxicity and carcinogenicity 0, 30, 100 and 500 mg/kg bw/d	US EPA 83-5	Task Force FEG-32	NOAEL = 30 mg/kg bw/d LOEL = 100 mg/kg bw/d Not carcinogenic (WHO, 1995)

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Species	Test, duration and conditions	Guideline adopted	Batch Number	Result
Mice, male & female	18 months dietary oncogenicity 0, 30, 100 and 300 mg/kg bw/d	OECD 451	Task Force FEP-100	NOAEL = 30 mg/kg bw/d LOEL = 100 mg/kg bw/d Not carcinogenic (WHO, 1995)
Rats, male & female	2 generation reproduction 0, 300, 1000 and 5000 mg/kg diet 0, 27, 89 and 469 mg/kg bw/d for males 0, 30, 102, 528 mg/kg bw/d for females	US EPA Pesticide Assessment Guidelines, Subdivision F, 83-4	Task Force FEG-32	NOAEL = 1000 ppm (parents, F1, F2) (89 mg/kg bw/d for males; 102 mg/kg bw/d for females) LOAEL = 5000 ppm (parents, F1, F2) (469 mg/kg bw/d for males; 512 mg/kg bw/d for females)
Rats, male & female	Developmental toxicity 0, 200, 500 and 1000 mg/kg bw/d	US EPA Pesticide Assessment Guidelines, Subdivision EPA F, 83-3	Task Force FEP-100	NOEL (dams) = 200 mg/kg bw/d LOEL (dams) = 500 mg/kg bw/d NOEL (pups) = 1000 mg/kg bw/d LOEL (pups) = no effects No developmental toxicity
Rabbits, female	Developmental toxicity 0, 50, 100 and 200 mg/kg bw/d	US EPA Pesticide Assessment Guidelines, Subdivision EPA F, 83-3	Task Force FEG-32	NOAEL (dams) = 50 mg/kg bw/d LOAEL (dams) = 100 mg/kg bw/d NOAEL (pups) = 200 mg/kg bw/d LOAEL (pups) = no effects No developmental toxicity

The above toxicological data have been submitted to the FAO/WHO JMPR and were assessed in 1995. The data are property of the Piperonyl butoxide Task Force II, members of which are Endura S.p.A., McLaughlin Gormley King Co., Prentiss Incorporated, S.C. Johnson & Son, Inc. and Valent BioSciences Corporation.

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**Table 5. Mutagenicity profile of technical piperonyl butoxide based on *in vitro* and *in vivo* tests**

Species	Test	Duration and conditions or guideline adopted	Batch Number	Result
<i>Salmonella typhimurium</i>	Bacterial assay gene mutation (Ames test) In vitro	EPA F, 84-2	Task Force FEP-100	Negative Not mutagenic (WHO, 1995)
<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> WP2 <i>uvrA</i>	Bacterial assay gene mutation (Ames test) In vitro	OECD 471	Endura R 1006028	Negative with and without metabolic activation <sup>1</sup>
Chinese hamster ovary cells (CHO)	Mammalian cells clastogenicity chromosomal aberrations In vitro	EPA F, 84-2	Task Force FEP-100	Negative Not mutagenic (WHO, 1995)
Chinese hamster ovary cells (CHO)	Mammalian cells gene mutation in vitro	10-100 µg/mL +S9 25-500 µg/mL –S9	Task Force FEG-32	Negative Equivocal
Mice, male & female	Micronucleus test In vivo	Doses 0 (vehicle), 300, 1000, 3000 mg/kg b.w.; two applications with 24 h interval, sampling 6 h after last dose	Endura 7/88	Negative Not mutagenic (WHO, 1995)

<sup>1</sup> Study provided to JMPS by Endura in 2010. All other studies: the toxicological data have been submitted to the FAO/WHO JMPR and were assessed in 1995. The data are property of the Piperonyl butoxide Task Force II, members of which are Endura S.p.A., McLaughlin Gormley King Co., Prentiss Incorporated, S.C. Johnson & Son, Inc. and Valent BioSciences Corporation.

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**Table 6. Ecotoxicology profile of technical piperonyl butoxide**

Species	Test	Duration and conditions or guideline adopted	Batch Number	Result
<i>Daphnia magna</i> (water flea)	acute toxicity	EPA, Subdivision E, Series 72-2	Task Force FEP-100	EC <sub>50</sub> = 0.00051 g/l
<i>Cyprinodon variegatus</i> (sheepshead minnow)	acute toxicity	EPA, Subdivision E, Series 72-3	Task Force FEP-100	LC <sub>50</sub> = 0.00394 g/l
<i>Selenastrum capricornutum</i> (green alga)	growth inhibition	OECD 201	Endura EN 01-4/38	ErC <sub>50</sub> = 0.00389 g/l NOErC = 0.000824 g/l
Earthworm	acute toxicity	OECD 207 (1984)	Endura S0477062501	LC <sub>50</sub> = 423 mg/kg dry soil
<i>Apis mellifera</i> (honey bee)	acute oral toxicity	US EPA 141-1	Task Force FEP-100	LD <sub>50</sub> = > 25 µg/bee
<i>Pimephales promelas</i> (fathead minnow)	early life-stage toxicity	US EPA 72-4	Task Force PB-200	NOEC = 0.00018 g/l LOEC = 0.00042 g/l
<i>Daphnia magna</i> (water flea)	reproduction and chronic toxicity	US EPA 72-4	Task Force PB-200	NOEC = 30 or 33 µg/l LOEC = 47 µg/l
<i>Colinus virginianus</i> (bobwhite quail)	acute oral toxicity	US EPA 71-1	Task Force FEP-100	LD <sub>50</sub> = > 2250 mg/kg bw NOEL = 486 mg/kg bw
<i>Colinus virginianus</i> (bobwhite quail)	short-term toxicity	FIFRA 71-2	Task Force FEP-100	LD <sub>50</sub> = > 5620 mg/kg bw. NOEL = 1000 mg/kg bw

The above ecotoxicological data have not been submitted to the FAO/WHO JMPR before. The data are partly property of Endura S.p.A., and partly property of the Piperonyl butoxide Task Force II, members of which are Endura S.p.A., McLaughlin Gormley King Co., Prentiss Incorporated, S.C. Johnson & Son, Inc. and Valent BioSciences Corporation.

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## Annex 2: References

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