WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

S-BIOALLETHRIN* + PERMETHRIN (25:75 *cis:trans*, nonracemic) + PIPERONYL BUTOXIDE

OIL-IN-WATER EMULSION

(*S*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate*

+

3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

+

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

World Health Organization

* *S*-bioallethrin is defined here, in the absence of an ISO common name, as a mixture of allethrin isomers which is predominantly comprised of the (*S*)(1*R*,3*R*) enantiomer.

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Disclaimer[1]

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.

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[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications* 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 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.

* Footnote: The publications are available on the Internet under (http://www.who.int/whopes/quality/en/).

PART ONE

SPECIFICATIONS

S-BIOALLETHRIN + PERMETHRIN (25:75 *cis:trans*, nonracemic) + PIPERONYL BUTOXIDE

S-BIOALLETHRIN

INFORMATION

ISO common name

None

Synonyms

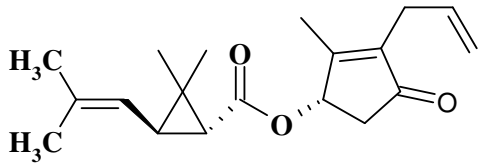
S-bioallethrin*; esdepalléthrine (France AFNOR); esbiol; bioallethrin *S*-cyclopentenyl isomer

Chemical names

IUPAC (*S*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate*

CA [1*R*-[1α(*S**),3β]-2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate*

*Structural formula**



Empirical formula

$C_{19}H_{26}O_3$

Relative molecular mass

302.4

CAS Registry number

28434-00-6

CIPAC number

750

Identity tests

Capillary GC-FID retention time; chiral HPLC retention time and peak pattern.

* *S*-bioallethrin is defined here, in the absence of an ISO common name, as a mixture of allethrin isomers which is predominantly comprised of the (*S*)(1*R*,3*R*) enantiomer.

PERMETHRIN (25:75 *cis:trans*, nonracemic)

INFORMATION

ISO common name

permethrin (ISO 1750 published), permethrine (F-ISO)

Chemical names

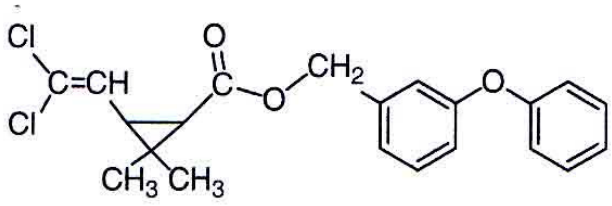
IUPAC: 3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propanecarboxylate

CA: (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate

Synonyms

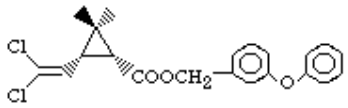
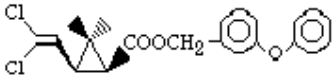
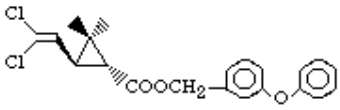
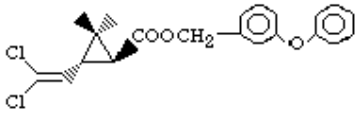
None

Structural formula



Two pairs of diastereomers (each consisting of a nonracemic pair of enantiomers; see below) are present in a ratio of approximately 25:75. In the context of the current specification, the hybrid nomenclature for pyrethroids developed at Rothamsted[1] is used, where the absolute configuration at carbon atom 1 of the cyclopropane moiety is given. The relative position of the C3 substituent (*cis* or *trans*) is then given, followed by the absolute configuration (if necessary, not necessary in the case of permethrin) of the alkyl α-carbon of the esterifying group.

[1] M. Elliott and N.F. Janes, Chem. Soc. Rev. 7, 473 - 505, 1978.

Sl No	Name of isomer	Structure	Proportions
1	1*R*, *cis*	 (2) (1R,cis)	sum ≈ 25%
2	1*S*, *cis*	 (4) (1S,cis)	
3	1*R*, *trans*	 (1) (1R,trans)	sum ≈ 75%
4	1*S*, *trans*	 (3) (1S,trans)	

The ratio of 1*S-cis* to 1*R-cis* and of 1*R-trans* to 1*S-trans* is ≈ 70 to 30.

Molecular formula

$C_{21}H_{20}Cl_2O_3$

Relative molecular mass

391.3

CAS Registry number

52645-53-1

CIPAC number

331

Identity tests

GC retention times, GC mass spectrum, IR spectrum, enantioselective HPLC retention times and enantiomer ratios.

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

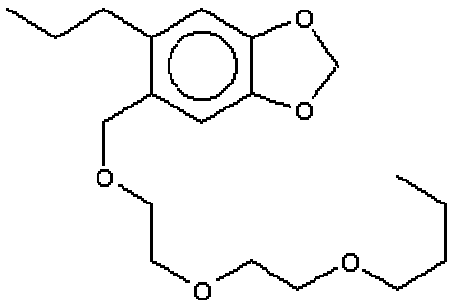
PBO

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)

S-BIOALLETHRIN + PERMETHRIN (25:75 *cis:trans*, nonracemic) + PIPERONYL BUTOXIDE EMULSION, OIL-IN-WATER

WHO specification 750+331+33/EW (July 2015*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation reports (750+331+33/2005, 750+331+33/2014). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only S-bioallethrin TC, permethrin (25:75 cis:trans, nonracemic) TC and piperonyl butoxide TC from the evaluated sources. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use S-bioallethrin TC, permethrin (25:75 cis:trans, nonracemic) TC and piperonyl butoxide TC from other sources. The evaluation reports (750+331+33/2005, 750+331+33/2014), as PART TWO, form an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical *S*-bioallethrin, complying with the requirements of WHO specification 750/TC (April 2006); technical permethrin (25:75 *cis:trans*, nonracemic) compying with the requirements of WHO specification 331/TC (July 2015); and piperonyl butoxide TC complying with the requirements of specification 33/TC (September 2011), in an aqueous phase together with suitable formulants. After gentle agitation, the formulation shall be homogeneous (Note 1) and suitable for dilution in water.

2 Active ingredients

2.1 **Identity tests** (750/EW/M/2 for *S*-bioallethrin, CIPAC Handbook M, p.18, 2009; 331/EW/M/2 for permethrin, CIPAC Handbook M, p.158, 2009; 33/EW/M/2 for piperonyl butoxide, CIPAC Handbook M, p.163, 2009).

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

2.2 ***S*-bioallethrin content** (750/EW/M/3, CIPAC Handbook M, p.18, 2009) (Note 2)

The *S*-bioallethin content shall be declared (1.4 g/kg or g/l at 20 ± 2ºC, Note 4) and, when determined, the average measured content shall not differ from that declared by more than ± 15%.

2.3 ***S*-bioallethrin isomer composition** (750/TC/M/2.2, CIPAC Handbook M, p.18, 2009)

The proportion of *trans*-isomer in the active ingredient shall be declared (not less than 98.0%) and, when determined, the average measured *trans*-isomer proportion shall not be lower than the declared minimum.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/whopes/quality/en/

The proportion of 1*R*-isomer content in the acid moiety of the active ingredient shall be declared (not less than 98.0%) and, when determined, the average measured 1*R*-isomer proportion shall not be lower than the declared minimum.

The proportion of *S*-isomer content in the alcohol moiety of the active ingredient shall be declared (not less than 96.0%) and, when determined, the average measured *S*-isomer proportion shall not be lower than the declared minimum.

2.4 **Permethrin content** (331/EW/M/3, CIPAC Handbook M, p.158, 2009)

The permethrin content shall be declared (103 g/kg or g/l at 20 ± 2ºC, Note 4) and, when determined, the average measured content shall not differ from that declared by more than ± 6%.

2.5 **Permethrin diastereomeric ranges** (331/EW/M/3, CIPAC Handbook M, p.158, 2009)

The [1*RS*,3*RS*] : [1*RS*,3*SR*] (*cis:trans*) permethrin isomer ratio shall be declared and, when determined, the average measured ratio shall be in the range of:

Diastereomer	Range
1*RS-cis*	22.0 to 28.0 %
1*RS-trans*	72.0 to 78.0 %

2.6 **Permethrin enantiomeric ranges** (Note 3)

The enantiomer content in the *cis* and *trans* diastereomers, respectively, shall be declared and, when determined, the average measured shall be in the range of:

Enantiomer	Range g/kg
1*R-cis*	50 to 100
1*S-cis*	150 to 200
1*R-trans*	450 to 550
1*S-trans*	170 to 270

2.7 **Piperonyl butoxide content** (33/EW/M/3, CIPAC Handbook M, p.163, 2009)

The piperonyl butoxide content shall be declared (98 g/kg or g/l at 20 ± 2ºC, Note 4) and, when determined, the average measured content shall not differ from that declared by more than ± 10%.

3 Physical properties

3.1 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000) (Note 5)

pH range of a 1% aqueous solution: 4.0 to 7.0.

3.2 **Pourability** (MT 148.1, CIPAC Handbook J, p.133, 2000)

Maximum "residue": 5%.

3.3 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K p.137, 2003) (Note 6)

The formulation, when diluted (Note 7) at 30 ± 2ºC with CIPAC standard waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream": maximum 2 ml
2.0 h	"Cream", maximum 2 ml "Free oil", maximum 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum 2 ml "Free oil", maximum 0 ml
Note: tests after 24 h are required only where results at 2 h are in doubt	

3.4 **Persistent foam** (MT 47.3) (Notes 8 & 9)

Maximum: 60 ml after 1 min.

4 Storage stability

4.1 **Stability at 0°C** (MT 39.3, CIPAC Handbook J p. 126, 2000)

After storage at 0 ± 2°C for 7 days, no separation of particulate or oily matter shall be visible after gentle agitation.

4.2 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J p.149, 2000)

After storage 54 ± 2°C for 14 days, the determined average active ingredients content must not be lower than 95%, relative to the determined average content found before storage (Note 10), and the formulation shall continue to comply with the clauses for:

- *S*-bioallethrin isomer composition (2.3),
- Permethrin diastereomeric ranges (2.5),
- Permethrin enantiomeric ranges (2.6),
- emulsion stability and re-emulsification (3.3).

Note 1 All physical and chemical tests listed in this specification are to be performed with a laboratory sample taken after the recommended homogenisation procedure. Before sampling to verify the formulation quality, the commercial container must be inspected carefully. On standing, emulsions may develop a concentration gradient which could even result in the appearance of a clear liquid on the top (sedimentation of the emulsion) or on the bottom (creaming up of the emulsion). Therefore, before sampling, the formulation must be homogenised according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example, by inverting the closed container several times). Large containers must be opened and stirred adequately.

Note 2 *S*-bioallethrin is quantified as a mixture of allethrin isomers, though predominantly comprised of the (*S*)(1*R*,3*R*) enantiomer. Identification of the active ingredient as *S*-bioallethrin requires compliance with clause 2.3.

Note 3 The peer validated chiral HPLC method (CIPAC/4946) for determination of the permethrin enantiomeric ranges in EW formulations containing also *S*-bioallethrin and piperonyl butoxide was presented at the CIPAC Meeting in 2014 in Belgium and accepted as a quantitative stereoselective identity test for permethrin stereoisomers content in permethrin EW. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm

Note 4 If the buyer requires both g/kg and g/l at 20ºC, then in case of dispute the analytical results shall be calculated as g/kg.

Note 5 In case of drifting pH values, the reading on the pH-meter is taken as constant and valid if the deviation in value is less than 0.1 pH unit over a period of 10 min (without stirring).

Note 6 This test will normally be carried out only after the test of stability at elevated temperature (4.2).

Note 7 The formulation should be tested at the highest (10%) and lowest (1%) rates of use recommended by the supplier.

Note 8 The CIPAC method MT 47.2 published in Handbook F for determination of persistent foam created when formulations are added to water before use was updated to MT 47.3. This new method was accepted as a full CIPAC method in 2013. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/cipacpub.htm

Note 9 The test should be carried out at the highest application concentration (10%), in CIPAC standard water D.

Note 10 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

S-BIOALLETHRIN + PERMETHRIN (25:75 *cis:trans*, nonracemic) + PIPERONYL BUTOXIDE

S-BIOALLETHRIN + PERMETHRIN (25:75 *cis:trans*, nonracemic) + PIPERONYL BUTOXIDE OIL-IN-WATER EMULSION

EVALUATION REPORT 750+331+33/2014

Recommendation

The Meeting recommended that the revised specification for *S*-bioallethrin + permethrin (25:75 *cis:trans*, nonracemic) + piperonyl butoxide EW, proposed by Bayer CropScience, as amended, should be adopted by WHO.

Appraisal

The Meeting considered information in support of the revision of the WHO specification for an EW formulation containing a mixture of *S*-bioallethrin, permethrin (25:75 *cis:trans*, nonracemic) and piperonyl butoxide. Piperonyl butoxide is widely used as a synergist in formulations of pyrethrins and pyrethroids, as it inhibits the natural detoxification systems of insects and thus increases the efficacy of these pesticides.

The first specification was published in 2006. At that time, the existing specification for permethrin 25:75 TC was referenced and no specification for piperonyl butoxide under the new procedure was published.

A WHO specification for permethrin (25:75 *cis:trans*, nonracemic) TC (331/TC) was developed under the new procedure in 2013 and published in July 2015. The company informed the Meeting that the permethrin incorporated into the EW formulation was actually a nonracemic TC, where the *cis* and *trans*-diastereomers do not show a 1:1 ratio in their respective enantiomeric pairs. BCS explained that previously the analytical methods to determine the stereoisomer ratios in permethrin TC and EW were not available. This is no longer the case, as CIPAC has adopted peer validated methods to determine the stereoisomer ratios in TC and in EW formulations also containing piperonyl butoxide and *S*-bioallethrin.

As for piperonyl butoxide TC a WHO and FAO specification has been published in 2011. Beside some minor editorials, the following changes were introduced in the revised specification:

- The "Information" sections for permethrin (25:75 *cis:trans*, nonracemic) and piperonyl butoxide were updated.
- All references to published CIPAC methods for *S*-bioallethrin identity tests, content and isomer composition, permethrin content and *cis:trans* ratio and for the piperonyl butoxide content respectively were updated.
- A clause for permethrin enantiomer ranges was inserted.

- The tolerance range for piperonyl butoxide content was updated to bring it in line with the Table of tolerances, Section 4.3.2 Content of active ingredient, of the 2010 Edition of the Manual.
- The clause for pourability refers to latest CIPAC method, MT 148.1.
- The clause for persistent foam refers to the latest CIPAC method, MT 47.3.
- The clauses in the accelerated storage to comply with after storage were amended by *S*-bioallethrin isomer composition, permethrin *cis:trans* isomer ratio and permethrin enantiomeric ranges, as these parameters may significantly change under accelerated storage conditions. Pyrethroids tend to be stable under slightly acidic conditions but may undergo racemization under basic conditions. This could affect the *S*-bioallethrin isomer composition and the permethrin enantiomeric ranges.