WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

FLUPYRADIFURONE + TRANSFLUTHRIN

EMULSION, OIL IN WATER

4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl) amino]furan-2(*5H*)-one

+

2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

World Health Organization

TABLE OF CONTENTS

Page

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 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.

---

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

INTRODUCTION

WHO establishes and publishes specifications[2] 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.

[2] Publications available on the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website: https://extranet.who.int/pqweb/vector-control-products

PART ONE: SPECIFICATIONS

FLUPYRADIFURONE + TRANSFLUTHRIN

Page

FLUPYRADIFURONE INFORMATION

ISO common name

Flupyradifurone (ISO 1750 provisionally approved)

Synonym

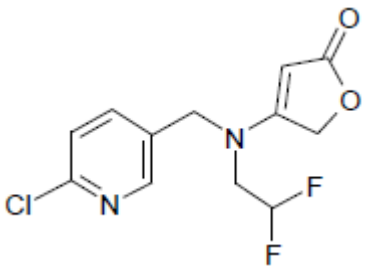
BYI 02960

Chemical names

IUPAC 4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(*5H*)-one

CA 4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]-2(5H)-furanone

Structural formula



Molecular formula

$C_{12}H_{11}ClF_2N_2O_2$

Relative molecular mass

288.68

CAS Registry number

951659-40-8

CIPAC number

987

Identity tests

Retention time in HPLC with UV-detection

TRANSFLUTHRIN INFORMATION

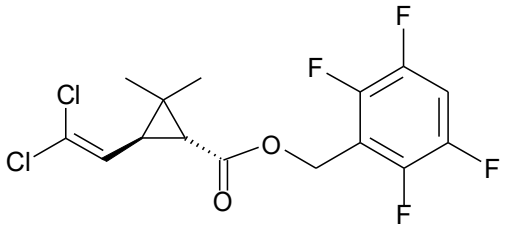
ISO common name
Transfluthrin

Synonym
Benfluthrin

Chemical names
IUPAC 2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA (1*R*,3*S*)-(2,3,5,6-tetrafluorophenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Structural formula



Empirical formula

$C_{15}H_{12}Cl_2F_4O_2$

Relative molecular mass
371.16

CAS Registry number
118712-89-3

CIPAC number
741

Identity tests
GC retention time and IR spectrum (CIPAC Handbook K, p.122, 2003); Enantioselective HPLC (CIPAC Handbook O, p.158, 2017).

FLUPYRADIFURONE + TRANSFLUTHRIN EMULSION, OIL IN WATER

WHO specification 987+741/EW (September 2023[3])

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 report (987+741/2018). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only flupyradifurone TC and transfluthrin 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 flupyradifurone TC and transfluthrin TC from other sources. The evaluation report (987+741/2018), as PART TWO, forms an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical flupyradifurone, complying with the requirements of WHO specification 987/TC and transfluthrin, complying with the requirements of WHO specification 741/TC in the form of a turbid milky white emulsion 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** (987/EW/M/2, CIPAC Handbook P, p. 115, 2021 for flupyradifurone; and 741/VL/M/2, CIPAC Handbook L, p.130, 2006 for transfluthrin (Note 2)). 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 **Flupyradifurone content** (987/EW/M/3, CIPAC Handbook P, p. 115, 2021) (Note 3)
The flupyradifurone content shall be declared (26.3 g/L) and, when determined, the average content measured shall not differ from that declared by more than ± 10% of the declared content.

2.3 **Transfluthrin content** (741/VL/M/3, CIPAC Handbook L, p.130, 2006) (Notes 2 & 3)
The transfluthrin content shall be declared (52.5 g/L) and, when determined, the average content measured shall not differ from that declared by more than ± 10% of the declared content.

[3] Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

3 Physical properties

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

Maximum "residue": 5%

3.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p. 137, 2003)
The formulation, when diluted at 30 ± 2°C (Note 4) 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": none
2.0 h	"Cream": none "Free oil": none
24 h	Re-emulsification complete
24.5 h	"Cream": none "Free oil": none
Note: tests after 24 h are required only where the results at 2 h are in doubt.	

3.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 5)

Maximum: 30 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, a turbid milky white emulsion shall be visible after gentle agitation.

4.2 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p.232, 2021)
After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95%, relative to the determined average content found before storage (Note 6), and the formulation shall continue to comply with the clauses for:

- emulsion stability and re-emulsification (3.2).

Note 1 All physical and chemical tests listed in this specification are to be performed with a laboratory sample taken after the recommended homogenization 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 homogenized 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 The published method for determination of transfluthrin in TC and VL published in Handbook L is considered to be applicable to the EW containing transfluthrin and flupyradifurone as well. A sample of the formulation is dissolved in *iso*-propanol and determined by capillary gas chromatography.

Note 3 If the buyer requires both g/kg and g/l at 20°C, then in case of dispute, the analytical results shall be calculated as g/kg.

Note 4 As outlined in CIPAC MT 36.3, the test concentrations should be based on those in the recommended directions for use supplied with the product. Where several concentrations are recommended, the highest and lowest concentrations within the scope of the method should be used.

Note 5 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 6 Samples of the formulation taken before and after the storage stability test may be analysed concurrently after the test in order to reduce the analytical error.

Part Two: Evaluation Reports

FLUPYRADIFURONE + TRANSFLUTHRIN

FLUPYRADIFURONE + TRANSFLUTHRIN

FAO/WHO Evaluation Report 987+741/2023

Summary of Action

The clauses for identity, content and storage stability in the specification 987+741/EW were amended to reflect the current published CIPAC methods and remove the relevant footnotes.

FLUPYRADIFURONE + TRANSFLUTHRIN

FAO/WHO Evaluation Report 987+741/2018 (*)

Recommendations

The Meeting recommended that the specifications for flupyradifurone TC and EW, in combination with transfluthrin, proposed by Bayer CropScience and as amended, should be adopted by WHO.

Appraisal

The meeting considered data on flupyradifurone submitted by Bayer CropScience (BCS), in support of new FAO specifications for TC, EC, FS and SL and new WHO specifications for TC and a combination product of flupyradifurone with transfluthrin in an oil in water formulation (EW).

The ISO common name flupyradifurone designates a molecule consisting of a five-membered lactone attached to a chloronicotinyl moiety through a difluoroamin-bridge. The lactone moiety is called a butenolide. Flupyradifurone is an insecticide and has a similar mode of action as the neonicotinoids - it acts as a competitive modulator on the nicotinic acetylcholine receptor of pests and vectors. Flupyradifurone was developed after the lead compound, stemofoline, a plant alkaloid sharing the butenolide moiety as toxophore.

Flupyradifurone has a fairly low volatility and a melting point of 69 and 67°C (pure compound and TC, respectively). As a medium polarity compound, it is soluble in water with 3.2 g/L and has an octanol/water partition coefficient (log Pow) of 1.2. It does not dissociate at pH of 1 to 12 and is stable to hydrolysis. It is interesting to note that flupyradifurone, due to its physical-chemical properties, is amenable to many different types of formulations like EC, EW, FS and SL.

The Meeting was provided with confidential information on the manufacturing process and specification limits for the technical material as manufactured. The minimum purity of the active and maximum impurity limits as proposed by BCS were supported by 5 batch analysis data. Flupyradifurone is produced in a one-step synthesis. The minimum purity of 980 g/kg was justified by the 5-batch data. Mass balances were high (99.76 - 100.52 %). The analytical methods for the majority of organic impurities are based on HPLC and are fully validated and support the results in the 5-batch study. The limits of quantitation were determined as part of the validation.

The Meeting concluded that none of the impurities included in the manufacturing specification should be considered as relevant. A CIPAC method based on reversed phase HPLC has been developed for determination of flupyradifurone in TC, EC, EW, FS and SL formulations and was accepted as full CIPAC method in 2018.

---

* Flupyradifurone TC and EW in mixture with transfluthrin for public health uses was evaluated together with flupyradifurone TC, EC, FS and SL formulations for agricultural uses. This FAO/WHO evaluation report 987+741/2018 refers to the evaluation of the TC and all formulations.

The proposed specifications for TC, EC, EW, FS and SL were essentially in accordance with the requirements of the Manual (FAO/WHO 2016).

As flupyradifurone is hydrolytically stable, no clause for pH or acidity was proposed in any of the formulation specification. This was accepted by the Meeting.

The WHO product flupyradifurone coformulated with transfluthrin in an EW is intended for space spraying vector control and is currently under clearance by the WHO PQT Scheme.

The following issues were identified in the following specifications:

Emulsion, oil in water (EW)

The low temperature stability test (CIPAC MT 39.3) apparently leads to some crystallization of the active ingredient resulting in a turbid liquid with faint sedimentation. The company explained that the turbidity of the formulation does not have an adverse effect on the use of the formulation in reality. Later on, Bayer withdrew the EW formulation, revised the composition to render it more tolerant to lower temperature and submitted a full data package on physical-chemical properties of the changed EW formulation (Ref. M-617956-01-1). The data show that the new EW has indeed a clearly better low temperature stability and complies with all generic limits and requirements of the Manual. The Meeting therefore recommended that the changed EW formulation being adopted by WHO.

The Meeting discussed whether the relevant impurity permethric acid anhydride (PAA), specified at a maximum limit of 0.1 g/kg in transfluthrin TC, should be included in the EW specification. Considering that PAA is reactive to water, that an EW contains water as the continuous phase, and given the low concentration of transfluthrin in the EW, the Meeting concluded that it is very unlikely that PAA would occur in the EW formation.

Suspension concentrate for seed treatment (FS)

The formulation is intended to be used without or with minimal dilution only. The minimal dilution (e.g. 50 % concentration) is out of the scope of the test to determine suspensibility (MT 184) which is approximately 10 %. For that reason the suspensibility clause was removed from the specification.

Adhesion to seed (FS): the proposed limit for adhesion to rapeseed was 90 %, a value that was considered as very low by the Meeting. Even though for the moment no general limits are given in the Manual, experience of last years with a number of FS formulations has shown that typical adhesion/seed retention values are around 95 % or higher. The Meeting challenged the 90 % on rape seed - in morphological terms these seeds are not more difficult to coat than cereal seed like maize. The company then proposed a higher value (95 %) that was accepted by the Meeting.

The Meeting noted the exceptionally low temperature proposed by the company to carry out the stability test at elevated temperature (MT 46.3). The company explained that the formulation tends to solidify under higher temperature (54°C for 2 weeks) or to show a reduced pourability (storage at 40° for 8 weeks) so a temperature / time combination was chosen (35°C for 12 weeks) where no clear adverse effect could be observed. As the product shows appropriate stability when stored in original packaging at 25°C for two years, the Meeting considered the explanations as adequate and accepted the unusually low temperature in the accelerated storage test.

Annex 1: References

Study reference	Author(s)	Year	Study title. Company conducting the study. Report identification number. Date. GLP yes/no
M-617956-01-1	Manka, S.	2018	Determination of Physico-chemical Properties and Accelerated Storage StabilityTests for Flupyradifurone + Transfluthrin EW 78.8 (26.3+52.5 g/L in HDPE. BioGenius, Bergisch Gladbach, Germany. Study number : Mo6043 Date : March 19, 2018. GLP: yes, unpublished.