# WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

# BIFENTHRIN

2-methylbiphenyl-3-ylmethyl (*Z*)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropanecarboxylate

World Health Organization

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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 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.

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

# INTRODUCTION

WHO establishes and publishes specifications[1] 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. Evaluation reports include 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 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.**

[1] 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

## BIFENTHRIN

## Bifenthrin Information

*ISO common name*

Bifenthrin (ISO 1750 published)

*Synonyms*

FMC 54800

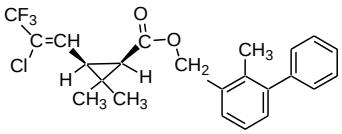
*Chemical name(s)*

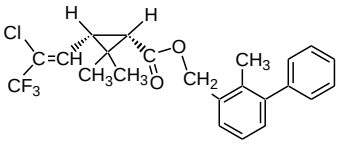
*IUPAC* 2-methylbiphenyl-3-ylmethyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

*CA* (2-methyl[1,1'-biphenyl]-3-yl)methyl 3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate

*Structural formulae*

(*Z*)-(1*R*)-*cis*-





(*Z*)-(1*S*)-*cis*-

*Molecular formula*

$C_{23}H_{22}ClF_3O_2$

*Relative molecular mass*

423.0

*CAS Registry number*

82657-04-3

*CIPAC number*

415

*Identity tests*

GC relative retention time, IR spectrum, electron ionization mass spectrum (from GC-MS), $^1$H-NMR spectrum

## Bifenthrin Technical Material

## WHO specification 415/TC (January 2022*)

*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 (415/2009, 415/2010, 415/2014, 415/2016, 415/2021). This specification should be applicable to TC 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 TC produced by other manufacturers. The evaluation reports (415/2009, 415/2010, 415/2014, 415/2016, 415/2021), as PART TWO, form an integral part of this publication.*

## 1 Description

The material shall consist of bifenthrin, together with related manufacturing impurities, in the form of a light brown to amber viscous liquid, crystalline solid, or waxy solid with a faint, slightly sweet odour free from visible extraneous matter and added modifying agents.

## 2 Active ingredient

2.1 **Identity test** (AOAC INTERNATIONAL: Bifenthrin Analysis in Technical Material and Formulations by Capillary Gas Chromatography, Note 1)

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 **Bifenthrin content** (AOAC INTERNATIONAL: Bifenthrin Analysis in Technical Material and Formulations by Capillary Gas Chromatography, Note 1)

The bifenthrin content shall be declared (not less than 930 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

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Note 1 Gas Chromatographic Determination of Bifenthrin in Technical and Selected Formulated Products: Collaborative Study. Edward J. Kikta et al, Journal of AOAC INTERNATIONAL, Volume: 94, Issue: 2 (2011), pages 453 to 458 or through the AOAC International Official Method of Analysis website (www.aoac.org).

* 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/pqweb/vector-control-products

## Bifenthrin Wettable Powder

## WHO specification 415/WP (January 2022*)

*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 (415/2009, 415/2010, 415/2021). This specification should be applicable to relevant products of this manufacturer and those of any other formulators who use only 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 TC from other sources. The evaluation reports (415/2009, 415/2010, 415/2021), as PART TWO, form an integral part of this publication.*

### 1 Description

The material shall consist of a homogeneous mixture of technical bifenthrin, complying with the requirements of WHO specification 415/TC, in the form of an off-white to tan powder, together with fillers and any other necessary formulants. It shall be in the form of a fine powder free from visible extraneous matter and hard lumps.

### 2 Active ingredient

**2.1 Identity tests** (AOAC INTERNATIONAL: Bifenthrin Analysis in Technical Material and Formulations by Capillary Gas Chromatography, Note 1)

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 Bifenthrin content** (AOAC INTERNATIONAL: Bifenthrin Analysis in Technical Material and Formulations by Capillary Gas Chromatography, Note 1)

The bifenthrin content shall be declared (100 g/kg), and, when determined, the average content measured shall not differ from that declared by more than 10% of the declared content.

### 3 Relevant impurities

**3.1 Water** (MT 30.6, CIPAC Handbook P, p. 222, 2021)

Maximum: 30.0 g/kg.

### 4 Physical properties

**4.1 Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003)

Maximum: 2 % retained on a 75 µm test sieve.

**4.2 Suspensibility** (MT 184.1, CIPAC Handbook P, p. 245, 2021) (Notes 2, 3 & 4)

Suspensibility: minimum 60% after 30 minutes in CIPAC Standard Water D at 25 ± 5°C

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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/pqweb/vector-control-products

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

Maximum: 15 ml after 1 min.4.4 **Wettability** (MT 53.3.1, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 3 min without swirling.

## 5 Storage stability

**5.1 Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p. 232, 2021)

After storage at 54 ± 2ºC 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:

- wet sieve test (4.1)
- suspensibility (4.2)
- wettability (4.4).

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Note 1 Gas Chromatographic Determination of Bifenthrin in Technical and Selected Formulated Products: Collaborative Study. Edward J. Kikta et al., Journal of AOAC INTERNATIONAL, Volume: 94, Issue: 2 (2011), pages 453 to 458 or through the AOAC International Official Method of Analysis website (www.aoac.org).

Note 2 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.1.

Note 3 This test will normally only be carried out after the heat stability test 5.1.

Note 4 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

The AOAC method does not provide a method for chemical assay. The following procedure can be used to determine the remaining 10 % in the cylinder. For calculation, use the formula provided in MT 184.1. After removing the 9/10 top layer of the water/WP suspension, carefully remove the remaining bottom 1/10 residue and concentrate the solids either by filtration or centrifugation. Make sure to rinse the tube, lower 1/10 section only, at least twice with a small amount of water, to remove any of the remaining bottom material. Add the rinse to the filter or centrifuge tube for isolation. Dry the isolated WP to a constant weight under 50°C in a vacuum oven. After drying, analyze the WP according to the method referenced in Note 1 for the WP. If the WP quantity is less than that specified in the procedure, the actual extraction volume should be proportionally adjusted.

Note 5 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5°C.

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

# PART TWO: EVALUATION REPORTS

## BIFENTHRIN

**BIFENTHRIN**

**FAO/WHO Evaluation Report 415/2021**

## Recommendations

The meeting recommended that:

(i) The bifenthrin TC as proposed by UPL Limited should be accepted as equivalent to the bifenthrin reference profile.

(ii) The existing FAO specification for bifenthrin TC should be extended to encompass the technical material produced by UPL Limited.

(iii) The existing WHO specification for bifenthrin TC should be extended to encompass the technical material produced by UPL Limited

## Appraisal

The Meeting considered data and supporting information submitted between October 2019 and April 2021 by UPL Limited (UPL) for the determination of the equivalence of their technical material with the existing FAO and WHO specifications for bifenthrin TC. The data submitted were broadly in accordance with the requirements of the 2016 revision of the FAO/WHO Manual on specifications for pesticides.

The reference specifications and supporting data for bifenthrin TC and WP were provided by FMC in 2008, and the FAO/WHO specifications were published in 2009. The Meeting noted that the data still belongs to FMC, and the company still supports the reference specifications.

Bifenthrin is not under patent.

Bifenthrin was evaluated by the FAO/WHO JMPR in 1992 and 2009 for toxicology and several times between 1992 and 2015 for residues.

The manufacturer submitted confidential data on the manufacturing process, together with the manufacturing specification and 5-batch analysis data on purity and impurities ≥ 1 g/kg.

UPL stated that the confidential data (manufacturing process, purity and impurity profile) submitted to FAO/WHO are identical to those submitted for registration in Brazil. At the request of the Meeting, the manufacturer provided a certificate of registration from the Brazilian authorities.

The 5 batches were produced within two months. The mass balances in the 5 batches ranged from 993.9 g/kg to 994.3 g/kg. The specified minimum purity of bifenthrin in the TC is 970 g/kg, which is higher than the limit of 930 g/kg specified in the published FAO/WHO TC specification.

There are no relevant impurities in the existing specification for bifenthrin TC. Toluene and another residual solvent were considered for their potential relevance, and the Meeting concluded that, based on the criteria of the Manual, these impurities are not relevant at the specified limits. No new impurity was detected in the 5-batch data.

While the method recommended for bifenthrin content in the published TC specification is the AOAC method using GC-FID, the company used in the 5-batch data an in-house reversed phase HPLC method with UV detection at 200 nm. Additionally, an analytical bridging study was submitted by UPL comparing, for 5 batches of 2019, the results of

the in-house method with those of the AOAC method. Results of bifenthrin content obtained by the two methods are in acceptable agreement.

The company was asked to submit the full 5-batch analysis study report, as requested by the Manual. A screening study was also submitted in which the company analysed the 5 batches by HPLC-DAD and LC-MS/MS that confirmed that no other compound > 0.1% w/w was detected except for bifenthrin and the impurities already stated in the 5-batch data.

The Meeting requested clarification from the company on the Z/E ratio. The company claimed that it is 100/0. The Meeting concluded that a 100/0 ratio is acceptable considering that the purity of bifenthrin and the sum of all chemical compounds in TC are quite high. This Z/E ratio is not part of the specification, but it is reported in the evaluation reports of the reference profile and other subsequent manufacturers.

A bacterial reverse mutation test with Salmonella typhimurium tester strains (OECD 471) was submitted. The results of the study led to the conclusion that bifenthrin TC produced by UPL does not induce reverse mutations under the conditions of this study.

On basis of Tier-1 data provided by UPL (manufacturing process, purity/impurity profile, 5-batch analysis data, mutagenicity profile), the Meeting concluded that the bifenthrin TC from UPL should be considered as equivalent to the reference profile supporting the existing FAO and WHO specifications 415/TC (FAO/WHO evaluation report 415/2009).

The company submitted summary data on the toxicology profile of bifenthrin TC, based on acute toxicity, skin and eye irritation and skin sensitization. These data were not considered by the Meeting as it is not requested by the FAO/WHO Manual for equivalence assessment in Tier-1.

**Additional actions recommended by the Meeting**

The Meeting also recommended updating the FAO and WHO WP specifications to align with the most recent versions of the specification template in the Manual, in particular with the latest versions of CIPAC methods. They include:

- replacement of method for water content MT 30.5 by MT 30.6 as published in CIPAC Handbook P;
- replacement of method for suspensibility MT 184 by MT 184.1 as published in CIPAC Handbook P;
- persistent foam is now determined by the harmonised CIPAC MT 47.3 as published in CIPAC Handbook O;
- replacement of method for accelerated storage stability MT 46.3 by MT 46.4 as published in CIPAC Handbook P; and
- update of some footnotes.

These revised MT methods are considered to provide equivalent results as the previous versions, so all limits in the concerned clauses remained the same as for the previous versions.

**Supporting Information**
**for**
**Evaluation Report 415/2021**

## Physico-chemical properties of bifenthrin

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

| | | | | |
|---|---|---|---|---|
| Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data | Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.39 to 99.43 % and percentages of unknowns were 0.08 to 0.15 %. | | | |
| Declared minimum bifenthrin content | 970 g/kg | | | |
| Relevant impurities ≥ 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 | | | |
| Parameter | Value and conditions | Purity % | Method reference | Study number |
| Melting temperature range of the TC | 68.9-70.1°C | 98.39 | OECD 102, capillary method | 202-2-11-6557 |

## Formulations and co-formulated active ingredients

No formulations are proposed.

## Methods of analysis and testing

The active ingredient content of bifenthrin technical material is based on reverse phase (Gemini NX-C18) HPLC using external standard quantitation. The mobile phase used is acetonitrile/methanol/ammonium acetate (80/10/10) and detection by UV at 200 nm. This method provides baseline separation of bifenthrin cis isomer from bifenthrin trans isomer and therefore also allows determination of cis:trans isomer ratio. This analytical method was developed and adequately validated by the test facility under the US EPA Guidelines (OPPTS 830.1800).

Data has been provided to demonstrate that this HPLC method gives equivalent bifenthrin purity results to the existing AOAC GC-FID method referred to in the current FAO/WHO Specification.

Impurities are determined by reversed phase HPLC, GC and Karl-Fischer-Titration.

## Physical properties

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD.

## Containers and packaging

No special requirements for containers and packaging have been identified.

## Expression of the active ingredient

The active ingredient content is expressed as bifenthrin.

## 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 bifenthrin 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.

**Table A. Mutagenicity profile of bifenthrin technical material based on bacterial *in vitro* test**

| Species | Test | Purity % | Duration and conditions or Guideline adopted | Result | Study number |
|---|---|---|---|---|---|
| *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537 | Bacterial reverse mutation | 98.39 | OECD 471<br>156, 312, 625, 1250, 2500, 5000 µg/plate (with and without S-9 mix)<br>37°C for 48 hours | Not Mutagenic | 481-1-06-6554 |

## Annex 2: References


| Study number | Author(s) | Year | Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study. |
|---|---|---|---|
| - | E.J. Kitka | 2011 | Gas Chromatographic Determination of Bifenthrin in Technical and Selected Formulated Products: Collaborative Study, Journal of AOAC INTERNATIONAL, Volume: 94, Issue: 2 (2011), pages 453 to 458. |
| 202-2-11-6557 | D.B. Ghate | 2013 | Melting point/melting range of Bifenthrin Technical. Study No. 202-2-11-6557. GLP. Jai Research Foundation. Unpublished. |
| 267-2-11-7054 | A.H. Patel | 2014 | Preliminary screening of five representative production batches of bifenthrin technical grade active ingredient (TGAI) and its associated impurities. Study No. 267-2-11-7054. GLP. Jai Research Foundation. Unpublished. |
| 227-2-12-8134 | A.H. Patel | 2014 | Preliminary analyses of five representative production batches of bifenthrin technical grade active ingredient (TGAI) to determine % bifenthrin and to quantify its associated impurities. Study No. 227-2-12-8134. GLP. Jai Research Foundation. Unpublished. |
| 227-2-12-8134 | A.H. Patel | 2014 | Validation of analytical method for determination of bifenthrin content and its associated impurities, Appendix 3, Study No. 227-2-12-8134. GLP. Jai Research Foundation. Unpublished. |
| - | UPL | 2019 | Percent Purity Analysis of UPL source Bifenthrin; Comparison of results between JRF HPLC Method and AOAC GLC Method. UPL. |
| - | UPL | 2021 | Justification for E-Isomer content and Z:E Ratio in bifenthrin technical. UPL. |
| - | S.S. Gaikwad | 2014 | Bacterial Reverse Mutation Test of bifenthrin technical using *Salmonella Typhimurium*. Study No. 481-1-06-6554. GLP. Jai Research Foundation. Unpublished. |

**BIFENTHRIN**

**FAO/WHO Evaluation Report 415/2016**

## Recommendations

The Meeting recommended that:

(i) The FAO and WHO specifications for bifenthrin TC should be extended to encompass the product of Bharat Rasayan Limited.

## Appraisal

The data for bifenthrin technical material were submitted in 2012 by Bharat Rasayan Limited, India (Bharat Rasayan) and evaluated in support of extension of the existing FAO and WHO specifications for bifenthrin TC.

The Meeting was provided with commercially confidential information on the manufacturing process, together with five batch analysis data and manufacturing specification for purity and impurities present at or above 1 g/kg. Mass balances ranged from 998.5 to 999.2 g/kg.

At the beginning of the evaluation, differences in the declared minimum purity registered in India (920 g/kg) with that declared for JMPS (970 g/kg) and in the manufacturing specifications became apparent. The company explained that the specification of the bifenthrin TC submitted in India had recently been updated to 970 g/kg after improving the manufacturing process. The Indian pesticide registration authority (Dr.B.S. Phogat, 2015) confirmed the update and the similarity of the confidential data packages submitted to the Indian authority and to JMPS.

The manufacturing process developed by Bharat Rasayan is different from that used by the proposer of the reference profile. The minimum purity of bifenthrin is 970 g/kg and complies with the existing specification. The *Z/E* ratio was equivalent to that in the reference profile. The *cis/trans* ratio was reported as two different results, which were 99.92/0.08 and 100:0 in 2 different reports both using un-validated methods. A new report submitted in 2016 using the collaboratively tested AOAC method showed the *cis/trans* ratio in Bharat Rasayan's products to be ≥ 999:1, which is in equivalence with the reference profile.

One impurity in the manufacturing specification, when compared with the limit in the reference profile, exceeded the threshold of 50% higher as compared to the maximum level in the reference profile as set out in the Manual. No toxicity/ecotoxicity data on this impurity has been found.

However, the molecular structure of the impurity does not indicate a toxicological alert, and the compound is also known as a mammalian metabolite of bifenthrin. The Meeting concluded that, based on the structural considerations, this impurity at its higher level should not be considered as relevant, so that the manufacturing specifications can be considered as equivalent on Tier-1.

Two new impurities were reported and specified, including one residual solvent which is controlled at 5 g/kg or below; the other was not detected above the limit of quantitation (0.02 g/kg) in all 5 batches, and their low concentrations render them non-relevant impurities. The later however would be treated as relevant if the content would exceed 0.1 g/kg.

The analytical method for the active ingredient (including identity tests) is Bharat Rasayan's in house validated method. The bifenthrin content was determined by capillary GC, using a HP-5 (30 m length, 0.25 µm film thickness, 0.25 mm diameter) capillary column and a FID detector, and quantified using n-octacosane as internal standard. The proposer submitted a bridging study for the in-house and a modified AOAC method. The results of the two methods showed a good agreement for all batches, except the ratio of *cis* and *trans* isomers not being determined as the AOAC method did.

Alternatively, the company determined the ratio of bifenthrin *cis/trans* isomers using a normal phase HPLC method for separation, and identified each peak based on its elution pattern and molecular structure. The *cis/trans* isomer ratio was determined based on an area normalization. Since no standards of *cis/trans* isomers were used for identification, the quantitative analysis or method was not available either. A reverse phase HPLC method for separation of a starting material related to the acid part of the molecule was also provided by the supplier of the intermediate. However, no isomer standards were used either. In 2014, the meeting requested the company to use an acceptable method for determination of the *cis/trans* isomer ratio.

Two new reports were submitted for the determination of the ratio of *cis/trans* isomers by using chiral HPLC and AOAC methods separately, and bifenthrin *Z-cis* standard (purity: 98.6%) and bifenthrin *E-trans* standard (purity: 56.5% *E-trans*-isomer, 41.2% *Z-cis*-isomer) were used in the two methods. When using chiral HPLC method, it was observed that the enantiomeric peaks of the *E-trans* isomer was not detectable in any of the technical samples of bifenthrin, and only 2 enantiomers peaks of *Z-cis* isomers were obtained. The virtual absence of the *E-trans isomer* was verified by fortifying the bifenthrin technical samples with standard solution of bifenthrin *E-trans* isomer to get extra peaks of 2 enantiomers of *E-trans* isomer. When using AOAC method, only one peak for bifenthrin *Z-cis* isomer was observed, and *E*-trans isomer peak was absent in all technical samples. Based on the above findings, the proposer confirmed that its product does not contain detectable amounts of the *E-trans* isomer of bifenthrin, that is, the ratio of *cis/trans* would be 100:0 (but *Z-trans* was not determined at all). The meeting noted that the new result is not consistent with the result of 99.868/0.132 in an earlier report, in which normal HPLC method were used based on % area normalization. No validation data for the in-house HPLC method was available.

The company stated that they did not use the HPLC method any more. Subsequently in 2016, a new report was submitted, in which the AOAC method was verified, and the *cis/trans* ratio was determined using *Z-cis* and *Z-trans* isomer standards by GC method. The AOAC method for *cis/trans* ratio was verified for linearity, specificity, accuracy, precision and LOQ. The Meeting concluded that based on these studies the minimum purity in the technical material produced by Bharat Rasayan is justified.

The batches used in genotoxicity studies were different from those used in 5 batch study. The proposer stated that the batches were from the same commercial manufacturing process as those used in the 5 batch study, and submitted a CoA for each batch, in which the content of active ingredient was determined, but not those of impurities.

The Meeting therefore concluded that the bifenthrin TC produced by Bharat Rasayan is equivalent to the reference profile by Tier-1.

**Supporting Information**
**for**
**Evaluation Report 415/2016**

## Physico-chemical properties of bifenthrin

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

| | | | | |
|---|---|---|---|---|
| Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data | | Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.85 to 99.92 % and percentages of unknowns were 0.08 to 0.15 %. | | |
| Declared minimum bifenthrin content | | 970 g/kg | | |
| Relevant impurities ≥ 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 | | |
| Parameter | Value and conditions | Purity % | Method reference | Study number |
| Melting temperature range of the TC | 63.3-64.0°C | 98.35 | EEC A.1, OECD 102, USEPA OPPTS 830.7200 | 12150 |

## Formulations and co-formulated active ingredients

Bharat Rasayan did not propose a formulation specification.

## Methods of analysis and testing

The method for determination of bifenthrin content in TC was a modified AOAC method published in 2011. The bifenthrin content was determined by GC, using a HP-5 MS column (30 m x 0.25 mm (i.d.) x 0.25 µm film thickness) and with FID detection, and n-octacosane as internal standard.

The method to determine the cis/trans ratio is an in-house validated method. It was determined by GC, using a 50% trifluoropropyl-methylpolysiloxane (30 m length, 1 µm film thickness, 0.53 mm diameter).

The methods for determination of impurities are based on GC-MS and GC and external standardization.

## Containers and packaging

No special requirements for containers and packaging have been identified.

## Expression of the active ingredient

The bifenthrin content is expressed as bifenthrin.

## 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 bifenthrin 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.

**Table A. Mutagenicity profile of technical bifenthrin based on *in vitro* test**

| Species | Test | Purity % | Duration and conditions or Guideline adopted | Result | Study number |
|---|---|---|---|---|---|
| *Salmonella typhimurium* | OECD 471 | 98.35 | OECD Guideline 471 and US-EPA-OPPTS-870.5100 1998. 0.156, 0.313, 0.625, 1.25 and 2.5 mg/plate, both in presence (+S9) and in absence (-S9) of metabolic activation (S9 mix). Strains: *Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102. | Does not induce gene mutations by base pair changes or frameshifts in the genome of the strains used. | 3550 |

## Annex 2: References


| Study number | Author(s) | Year | Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study. |
|---|---|---|---|
| R&D/BRL/BFT-ISOMEER-022016 | | 2016 | Analysis of Bifenthrin Isomers Contents in Representative Production Batches of Bifenthrin Technical Using AOAC Validated Gas Chromatographic Method. Research and Development Centre Bharat Rasayan Limited Bahadurgarh, India. Non-GLP. |
| Dr.B.S.Phogat, 2015 | | 2015 | E-mail from Dr.B.S.Phogat, APPA & Secretary (CIB&RC) , Ministry of Agriculture, Government of India sent 18 May 2015 to Mr Chen Tiechun, ICAMA, confirming the similarity of confidential data submitted for registration of Bharat's Bifenthrin in India with the data submitted to JMPS. |
| | FAO/WHO | 2010 | Manual on development and use of FAO and WHO specifications for pesticides. February 2009 Revision of First Edition. FAO Plant Production and Protection Paper. Revised. |
| R&D/BRL/BFT-ISO-092013 | | 2013 | Title: Separation and Analysis of *cis/trans* and *Z/E* isomers ratio in Bifenthrin Technical Samples and Lambda-Cyhalothrin Acid Using HPLC. Research and Development Centre Bharat Rasayan Limited Bahadurgarh, India. Non-GLP. |
| R&D/BRL/BFT-IMP-062013 | | 2013 | Title: Analysis of Bifenthrin Associated Impurities in Representative Production Batches of Bifenthrin Technical Grade Active Ingredient (TGAI) Using Gas Chromatographic Method. Research and Development Centre Bharat Rasayan Limited Bahadurgarh, India. Non-GLP. |
| | | 2013 | Title：Test Certificate (Bifenthrin-GPC Analysis Report). Shriram Institute for Industrial Research, India Non-GLP. |
| R&D/BRL/BFT-TC-012013 | | 2013 | Title: Analysis of Bifenthrin Content in Representative Production Batches of Bifenthrin Technical Grade Active Ingredient (TGAI) Using AOAC Gas Chromatographic Method. Research and Development Centre Bharat Rasayan Limited Bahadurgarh, India. Non-GLP. |
| R&D/BRL/BFT-ENTM-122014 | Mr.R K Srivastava | 2014 | Title: Bifenthrin c*is/trans* Enantiomers Analysis Using Chiral HPLC. Research and Development Centre Bharat Rasayan Limited Bahadurgarh, India. Non-GLP. |
| 232-2-12-1801 | | 2011 | Analysis of Bifenthrin Active Ingredient Content in Five Representative Production Batches of Bifenthrin Technical by Gas Chromatography. Jai Research Foundation (JRF), India. GLP. |
| 227-2-12-1800 | | 2011 | Preliminary Analyses of Five Representative Production Batches of Bifenthrin Technical Grade Active Ingredient (TGAI) to Determine % Bifenthrin and to Quantify its Associated Impurities. Jai Research Foundation (JRF), India. GLP. |
| 12150 | | 2012 | Title: Bifenthrin Technical: Laboratory Study of Melting point. International Institute of Biotechnology and Toxicology (IIBAT), India. GLP. |
| 12155 | | 2012 | Title: Bifenthrin Technical: Determination of Active Ingredient Content. International Institute of Biotechnology and Toxicology (IIBAT), India. GLP. |
| 12156 | | 2012 | Title: Bifenthrin Technical: Laboratory Study of Solubility in Organic Solvents. International Institute of Biotechnology and Toxicology (IIBAT), India. GLP. |

| | | | |
|---|---|---|---|
| 12157 | | 2012 | Title: Bifenthrin Technical: Laboratory Study of Physical state, COLOUR AND ODOR. International Institute of Biotechnology and Toxicology (IIBAT), India. GLP. |
| RCC 3550 | | 2012 | Title: Bacterial Reverse Mutation Assay with Bifenthrin Technical. RCC Laboratories India Private Limited, Hyderabad, India. GLP. |
| BIO-TX280 | | 2013 | Title: Skin Sensitisation Study of Bifenthrin Technical in Guinea Pigs. Bioneeds, India. GLP |
| | FAO/WHO | 2009 | FAO/WHO specifications and Evaluations for Public Health Pesticides - Bifenthrin, FAO/WHO Evaluation Report 415/2009. |
| | FAO/WHO | 2010 | FAO/WHO specifications and Evaluations for Public Health Pesticides - Bifenthrin, FAO/WHO Evaluation Report 415/2010. |

**BIFENTHRIN**

**FAO/WHO Evaluation Report 415/2014**

## Recommendations

The Meeting recommended that:

(i) The existing FAO specification for bifenthrin TC should be extended to encompass the product of Jiangsu Yangnong Chemical Co., Ltd., manufactured by Youth Chemical Co., Ltd., China.

(ii) The existing WHO specification for bifenthrin TC should be extended to encompass the product of Jiangsu Yangnong Chemical Co., Ltd., manufactured by Youth Chemical Co., Ltd., China.

## Appraisal

The data for bifenthrin were submitted in 2013 by Jiangsu Yangnong Chemical Co. (Yangnong) and evaluated in support of extension of existing FAO and WHO specifications 415/TC (2012).

The Meeting was provided with confidential information on the manufacturing process, together with 5-batch analytical data and manufacturing specification for purity and impurities present at levels ≥1 g/kg. Mass balances were in the range of 989.4 - 993.0 g/kg.

The purity and impurity profile submitted by Yangnong to JMPS was consistent with that submitted to the pesticide registration authority in China (Zhao Yonghui, 2014).

The manufacturing process provided by Yangnong is similar to that supporting the existing FAO and WHO specification for bifenthrin TC. The Meeting noted, that Yangnong's process description also included information on the manufacturing of some starting materials. The minimum purity of bifenthrin in the TC is 980 g/kg and complies with the existing specification. The *cis/trans* and *Z/E* isomer ratios were similar to those in the reference profile.

The declared manufacturing limits for the impurities identified in the technical material were comparable to the limits in the reference profile and did not exceed the tolerances as set in the FAO/WHO Manual. No new impurities related to bifenthrin were identified. However, the Meeting questioned the completeness of the manufacturing specification with regard to the possible presence of residues of certain solvents and reagents used in the manufacturing process. The company subsequently provided additional data that led to the conclusion that the control limits of residual solvents and reagents in the proposer’s product are much lower than those in the reference profile.

The Meeting concluded that the solvents and reagents used in the manufacturing process are sufficiently removed so their low concentrations render them non-relevant impurities. These compounds were determined by a GC-FID method using external standard, properly validated for linearity of response, accuracy and repeatability.

Initially, the analytical methods for the active ingredient (including identity tests) were in- house methods, as at the time of elaboration of the data on 5 typical batches the AOAC method was not yet published. The bifenthrin content was determined by reversed phase HPLC with UV detection. The *cis/trans* isomer ratio was determined by GC-FID according to the area ratio by using peak area normalization method. The

possible *trans* isomer peak was confirmed according to the MS spectra from test item after excluding the peak of active ingredient and the *E* isomer.

The Meeting requested the company to carry out a bridging study for the in-house and AOAC methods for the determination of bifenthrin content and *cis/trans* ratio. The comparison of the results of the two methods (AOAC method and Yangnong in-house method) showed a good agreement for all batches.

The batches used for the determination of the *cis/trans* ratio were different from that used for the 5-batch report, and were analyzed for the content of the active ingredient and significant impurities. The results were consistent with those in 5-batch report.

The genotoxicity data were provided following the OECD guideline 471 with the exception, that only *S. typhimurium* and no *E. coli* had been included in the tests. The tests were performed in compliance with GLP, and the results led to the conclusion that the bifenthrin TC from Yangnong did not show genotoxicity *in vitro* under the conditions of the test.

The batches used in genotoxicity studies, identification studies, physical chemical property studies were all different from those used in 5 batch study. The proposer stated that:

(i) The data provided have been generated from the proposer's material.

(ii) All toxicological data generated from batches of material which were not specially purified, and in which the impurity concentrations complied with the limits.

(iii) Current production complies with the limits of active ingredient and impurities.

The analytical details were provided to JMPS to establish the links between the hazard and purity/impurity profile data submitted. The analytical results showed that the concentrations of bifenthrin and all impurites in all the above batches complied with the manufacturing limits.

The Meeting therefore concluded that the bifenthrin TC produced by Yangnong is equivalent to the reference profile by Tier-1.

The Meeting agreed also to update in the specification for bifenthrin WP the CIPAC method for persistent foam (MT 47.3 instead of MT 47.2) to be in line with the current CIPAC method.

**Supporting Information**
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## Physico-chemical properties of bifenthrin

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

| | | | | |
|---|---|---|---|---|
| Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data | Confidential information supplied and held on file by FAO and WHO. Mass balances were 98.94 - 99.30 % and percentages of unknowns were 1.06-0.70 %. | | | |
| Declared minimum bifenthrin content | 980 g/kg | | | |
| Relevant impurities ≥ 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 | | | |
| Parameter | Value and conditions | Purity % | Method reference | Study number |
| Melting temperature range of the TC | 69.4~70.0 °C | 98.3 | OECD 102 | 3513080006 |
| Solubility in organic solvents | 80-100 g/l n-heptane at 25 °C<br>> 250 g/l p-xylene at 25 °C<br>> 250 g/l 1,2-dichloro-ethane at 25 °C<br>< 10 g/l propane-2-ol at 25 °C<br>> 250 g/l acetone at 25 °C<br>> 250 g/l ethyl acetate at 25 °C | 98.3 | CIPAC MT 181 | 3513080008 |

## Formulations and co-formulated active ingredients

Yangnong did not propose a formulation specification.

## Methods of analysis and testing

The AOAC method for determination of bifenthrin content in TC and WP was published in 2011, whereas the Yangnong 5-batch study report was completed in 2009. The analytical method for the active ingredient (including identity tests) was developed and adequately validated by the test facility under the US EPA guidelines (OPPTS 830.1700 and 830.1800). The bifenthrin content is determined in the TC by reverse phase HPLC, using UV detection at 245 nm and external standardization.

The method to determine the Z/E ratio is an in-house validated method. It was determined by HPLC, using a ZORBAX SB-C8 (250 x 4.6 mm, 5 □m particle size) column and UV detection at 210 nm.

The method(s) for determination of impurities are based on reverse phase HPLC, using UV detection at 210 nm and external standardization.

## Containers and packaging

No special requirements for containers and packaging have been identified.

## Expression of the active ingredient

The bifenthrin content is expressed as bifenthrin.

## 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 bifenthrin 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.

**Table A. Mutagenicity profile of bifenthrin technical material based on *in vitro* test**

| Species | Test | Purity % | Guideline, duration, doses and conditions | Result | Study number |
|---|---|---|---|---|---|
| *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102 and TA1535 | Bacterial reverse mutation | 98.3 | OECD 471<br>128, 320, 800, 2000, 5000 µg/plate (with and without S-9 mix)<br>37°C for 48 hours | Not mutagenic | 2014-165-01-01 |

The results of the study lead to the conclusion that bifenthrin TC produced by Yangnong does not induce mutation under the conditions of the study.

## Annex 2: References

| Study number | Author(s) | Year | Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study. |
|---|---|---|---|
| Zhao Y., 2014 | | 2014 | E-mail from Mr Zhao Yonghui, deputy director of Registration Division of ICAMA sent 12 June 2014 to Mr Chen Tiechun, ICAMA, confirming the similarity of confidential data submitted for registration of Yangnong's bifenthrin in China with the data submitted to JMPS. |
| NC-2011-042 | | 2011 | Determination of cis/trans ratio (Active Ingredient/trans-isomers ratio) in 5 batch bifenthrin TGAI. NC-2011-042. GLP. Nutrichem Laboratory Co. Ltd., China. |
| NC-2008-022 | | 2009 | Preliminary Analysis and Enforcement Analytical Method of bifenthrin TGAI. NC-2008-022. GLP. Nutrichem Laboratory Co. Ltd., China. |
| NC-2013-098 | | 2014 | Determination of 3D spectra, Identification of Active Ingredient and Impurities for 5 Batches of Bifenthrin TGAI as amendment to study NC-2008-022. NC-2013-098. GLP. Nutrichem Laboratory Co. Ltd., China. |
| 3513080006 | | 2013 | Determination of the Melting Point/Melting Range of 97% bifenthrin Technical. 3513080006. GLP. Shanghai Research Institute of Chemical Industry Testing Centre, China. |
| 3513080008 | | 2013 | Determination of the Solubility in Organic Solvents of 97% bifenthrin Technical. 3513080008. GLP. Shanghai Research Institute of Chemical Industry Testing Centre, China. |
| 2014-165-01-01 | | 2014 | Bacterium Reverse Mutation Test for Bifenthrin. 2014-165-01-01. GLP. |

**BIFENTHRIN**

**FAO/WHO Evaluation Report 415/2010**

## Recommendations

The Meeting recommended the following.

(i) The specifications proposed by FMC for bifenthrin TC and WP as amended should be adopted by WHO and FAO, taking into account that the collaboratively tested analytical method is now published and a method for the chemical assay of the active ingredient in the suspensibility assay has been provided.

## Appraisal

The analytical method for determination of bifenthrin in TC and WP was published in the Journal of AOAC INTERNATIONAL, Volume: 94 and is also available on the AOAC INTERNATIONAL website. Furthermore, the company provided an addendum to the analytical method for the determination of the remaining 10% in the cylinder in the CIPAC MT 184, suspensibility method.

The draft specifications were essentially in accordance with the requirements of the FAO and WHO Specification Manual, March 2006 revision. A few issues were identified by the Meeting relating to the WP.

<u>WP only</u>

The necessity of limiting water content was discussed by the Meeting. The Meeting accepted that water should be limited in the WP, to minimize to potential for clumping of the powder particles during storage of the formulation. The proposed limit of 30 g/kg was accepted. The Meeting noted the exceptionally long wetting time of 3 minutes, which was explained by the proposer to be due to the hydrophobic nature of the active ingredient.

**BIFENTHRIN**

**FAO/WHO Evaluation Report 415/2009**

## Recommendations

The Meeting recommended the following.

(i) (The specifications proposed by FMC for bifenthrin TC and WP as amended should be adopted by WHO subject to the publication of the analytical method for bifenthrin TC and WP and amendment of the analytical method for WP for determination of the suspensibility. In the meantime, the evaluation report can be published.

(ii) The specifications for bifenthrin TC and WP as amended should be adopted by FAO, subject to the publication of the analytical method for bifenthrin TC and WP and amendment of the analytical method for WP for determination of the suspensibility. In the meantime, the evaluation report can be published.

## Appraisal

The Meeting considered data and supporting information submitted by FMC for the development of new FAO and WHO specifications for bifenthrin TC and WP. 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.

Bifenthrin is a pyrethroid insecticide, which had been the subject of a time-limited WHO interim specification withdrawn in April 2008. A WHOPES recommendation for the use of a 10 % bifenthrin WP in public health for indoor residual spraying for malaria vector control was published in 2001. The toxicology of bifenthrin was evaluated by the FAO/WHO JMPR in 2009. The WHO/IPCS (International Programme on Chemical Safety) has also evaluated bifenthrin in 2002.

The ISO common name, bifenthrin, denotes a compound consisting of the Z 1 R/S *cis* enantiomers of the trifluorochloromethylchrysanthemic acid esterified with the 2-methylbiphenylalcohol, together with small amounts of the respective E and *trans* forms (see below). Bifenthrin has two chiral centres, but as the configuration of the *cis*-trifluorochloromethylchrysanthemic acid is carried forward to the final product, bifenthrin contains predominantly the two *cis* stereoisomers at the cyclopropane moiety, providing the highest insecticidal activity (1). The *cis*/*trans* ratio in technical bifenthrin is higher than 97:3 and the Z/E ratio is higher than 99:1.

Confidential information on the manufacturing process and limits for all impurities occurring at or above 1 g/kg in the TC were provided to the Meeting. The manufacturing specification for minimum bifenthrin content of the TC was 930 g/kg. The limits for content of bifenthrin and impurities were supported by 5 batch analysis data. The manufacturing specification and their data on 5 batches have evolved over time, in the way that, among other, the minimum purity was increased (from initially 890 g/kg to 930 g/kg) and additional manufacturing sites were introduced.

The first impurity profile and specification were elaborated in 1986 for the TC produced in US. In recent years, two more production sites were introduced and the material produced characterized by analysis of 5 typical batches.

Mass balances were in the range of 98.6 to 99.1 and 97.9 to 98.8 % respectively in the batches of the two actual production sites.

The bifenthrin TC produced at the different sites were considered to meet a common manufacturing specification, even though some impurities show a considerable variability in their concentrations in the batches from the two sites analyzed. The questions of equivalence of the TC produced in the different sites was discussed and the Meeting agreed that based on the rules of the Manual on equivalence the TC produced at the different sites can be considered broadly equivalent. The methods to analyze the batches were the same for all samples and full validation was provided.

The information on the manufacturing process and impurities present in the TC was identical to that submitted in support of registration of bifenthrin in Switzerland.

The manufacturer provided information on the materials used in the hazard tests and the Meeting agreed that the hazard data were acceptable. The Meeting noted that the TC with a content of 901 g/kg, tested in the majority of toxicological and ecotoxicological studies (Annex 1, Tables 3-6), was lower than the current manufacturing specification (≥930 g/kg).

The proposer stated that no relevant impurities are present in the technical material, either > 1 g/kg or less than 1 g/kg. The question of the relevance of certain impurities was discussed by the Meeting. The stereoisomers having *trans*- and E configuration at the cyclopropane moiety or the vinyl bond, respectively, being present in technical bifenthrin were considered non-relevant as there was no indication that these stereoisomers would adversely influence the hazard when present at higher concentrations. The Meeting discussed the question of some residual solvents present in the TC – among them toluene – which had been considered relevant in other cases. In bifenthrin TC the amounts detected are so low that they can be considered as non-relevant.

However, based on the rules of the Specifications Manual, one impurity, the anhydride of the 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane carboxylic acid, for brevity called the TFP anhydride[3], was identified as a potentially relevant impurity. Considering the end points of the hazard data provided in Table 3 on acute dermal toxicity in the Buehler and Magnusson-Kligman tests on dermal sensitization and the composition of the technical materials used in these studies, the negative end point in the Buehler test and the positive end point in the Magnusson-Kligmann test were tentatively associated with a low content of TFP anhydride in the material used for the Buehler test and a higher content of TFP anhydride in the material used in the maximization test. The meeting noted, that the latter test is more challenging and tends to show more positive results with the same material used. It remained however unclear whether bifenthrin itself as a pure compound would elicit such a response in the tested animals. In order to elucidate how the residual TFP anhydride was contributing to the dermal sensitization, an additional study was recently undertaken with a low content (0.2 g/kg) of TFP anhydride. The overall result clearly showed that technical bifenthrin with such a low content of anhydride is a sensitizer too. In conclusion, bifenthrin is a sensitizer by itself, which renders the TFP anhydride non-relevant, and hence the Meeting agreed that no limit for this impurity needs to be set.

The method developed by the proposer and collaboratively validated by AOAC International to determine the content of bifenthrin in TC and in formulations (WP, EC, SC) utilizes megabore column gas chromatography with internal standard. This method allows the separation of the *cis* and *trans* isomers of bifenthrin and to the determination of the total bifenthrin content (expressed as sum of *cis* and *trans*-

[3] The IUPAC chemical name of the TFP anhydride is 3-[(1*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylic anhydride.

bifenthrin) as well as to the measurement of the ratio of *cis*/*trans* isomers present. However, the method for the WP does not yet provide a submethod for the determination of the suspensibility (MT 184, CIPAC Handbook K, p. 142). The suspensibility is an important clause in the specification for solid formulations forming suspensions upon dilution with water as a WP. The assay is preferably done by chemical analysis similar to that for the total content of TC or WP. This submethod which is normally a part of the method for total content in a solid formulation is not yet available.

In addition, the ratio of *cis*/*trans* isomers can be determined by non-enantioselective HPLC using an octadecyl-substituted silica (ODS) column (2). As the *cis*/*trans* isomers have diastereomeric relationship, they can easily be separated by this technique. The ratio of Z and E isomers at the vinyl bond together with the respective *cis*/*trans* isomers is determined using a non-enantioselective HPLC normal phase system (3), which provides full resolution of all *cis*-*trans* and Z/E isomers present in the technical bifenthrin. A validated method for determination of the TFP anhydride based on reversed phase HPLC-UV detection is available. The validation data show that the TFP anhydride can be determined in bifenthrin TC and show acceptable accuracy, reproducibility, and recovery and is capable to determine the impurity in a concentration range of 0.5 g/kg to 50 g/kg. The method is not validated for bifenthrin formulations.

As the AOAC method is not yet publicly available, an essential prerequisite for the publication of the specifications is missing and therefore the evaluation report only is published.

Bifenthrin is almost insoluble in water but moderately to highly soluble in organic solvents, such as hexane, ethanol, acetone, toluene, etc. It has a low volatility. It is stable under normal storage conditions and is only slowly hydrolyzed in water under neutral, acidic and basic pH conditions. The process of direct photolysis in water is slow, but in natural freshwater systems indirect photolysis may contribute significantly to the dissipation of the compound (cited after 4). Bifenthrin is strongly adsorbed on soil particles and is degraded with half-lives of typically 65 to 125 days (cited after Ref. 9). Despite this somewhat higher stability of bifenthrin in soil and water as compared to other pyrethroids, residues of bifenthrin are not expected to accumulate in soil and sediment, taking into consideration the low amounts applied and the moderate degradation rates in soil and water.

The toxicology data were elaborated using the technical active ingredient complying with the criteria given above (e.g. with a bifenthrin content of 901 g/kg, *cis*/*trans* ratio > 97.3, and Z/E 99: 1). Exceptions are data on skin sensitization (batch from 2004 with purity indicated) and in aquatic ecotoxicology testing, where biphenyl U-$^{14}$C-labelled material having a comparable *cis*/*trans* ratio as the unlabelled material was used.

Bifenthrin generally shows moderate acute mammalian toxicity. The European Union, in the conclusion document on bifenthrin, also concluded that this compound is a sensitizer in the maximization test according to Magnusson and Kligman. The JMPR concluded that the results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that bifenthrin is unlikely to pose a mutagenic and teratogenic hazard to humans. An ADI of 0–0.01 mg/kg bw was set based on a NOAEL of 1.0 mg/kg bw per day in a study of developmental toxicity in rats and using a safety factor of 100. The JMPR Meeting also established an ARfD of 0.01 mg/kg bw based on a threshold dose of 1.3 mg/kg bw for motor activity in a study of acute toxicity in male rats treated by gavage and using a safety factor of 100.

The test battery for the assessment of mutagenicity yielded again mixed results. Whereas some tests were clearly negative (such as the Ames test on different strains of *Salmonella typhimurium* with and without activation, respectively), other tests showed weak positive response or yielded inconclusive results with technical bifenthrin, such as the Mouse Lymphoma Mutagenesis Assay or the unscheduled DNA synthesis test with rat hepatocytes. The overall conclusion, as shared with the JMPR evaluation (2), was that bifenthrin does not pose a significant hazard to humans with respect to mutagenicity.

A considerable data package on ecotoxicological effects of bifenthrin was presented. Aquatic organisms like Daphnia magna, mysid shrimp and several fish species were found to be very sensitive to low levels of the compound. These levels, often in the sub-ng/l range, were determined using $^{14}$C-labelled bifenthrin (*cis*/*trans* ratio 98:2). The compound has been shown to bioaccumulate in fish (BCF 1060 at a concentration of less than 0.1 ng/l in a flowthrough system). Bifenthrin is therefore highly toxic to aquatic organisms except algae, where no effect concentrations in the ppm-range clearly above water solubilility were observed.

Non-target predatory insects and mites such as *Chrysoperla carnea* or *Typhlodromus pyri* showed a high mortality at the somewhat exaggerated field rates corresponding to 60 g a.i. per ha (recommended field rate in Switzerland in agriculture: 20 – 40 g/ha). The same holds for the honey bee, *Apis mellifera*. The spray deposits being dried up, the risk for honey bees is clearly reduced. In contrast, birds are not sensitive to the intake of bifenthrin, with acute toxicity (8 day feeding study) in the range of 1250 to 4450 mg/kg ($LC_{50}$).

Bifenthrin is used both in agriculture to control sucking and biting insects like aphids, white fly, colorado beetle in various crops and in public health applications (mainly as emulsifiable concentrates or wettable powder), against mosquitoes, houseflies, cockroaches.

Test methods for determination of physical-chemical properties of the technical active ingredient were OECD or EC, while those for the formulations were AOAC International and CIPAC methods, as indicated in the specifications.

The Meeting considered the proposed specifications were broadly in accordance with the requirements of the specification manual (FAO/WHO 2006) and thus certain clauses in the existing specifications, e.g. melting point and flash point, had been omitted and did not require further consideration.

## References for the appraisal


| Ref. Nr. | Authors | Year | Title |
|---|---|---|---|
| 1 | Chamberlain K, Matsuo N, Kanoko H and Khambay B P S | 1998 | Pyrethroids, in “Chirality in Agrochemicals”, Ed. Norio Kurihara and Juhshi Miyamoto, Wiley, p. 32 |
| 2 | Anon. | 1987 | FMC Test Method ACG 88, High Performance Liquid Chromatographic Analysis of FMC 54800 (“Reversed Phase”) |
| 3 | Anon. | no date | FMC Corporation, Test Method ACG 89, High Performance Liquid Chromatographic Analysis of FMC 54800 (“Normal Phase”) |
| 4 | Roberts T and Hutson D | 1988 | Metabolic Pathways of Agrochemicals, Part Two, Insecticides and Fungicides, “Bifenthrin”, p. 594 to 596. The Royal Society of Chemistry |

**Supporting Information**
**for**
**Evaluation Report 415/2009**

## Explanation

The data for bifenthrin were evaluated in support of new FAO/WHO specifications.

Bifenthrin is not under patent.

Bifenthrin was first registered in the US and Europe in 1985. Bifenthrin was evaluated by the FAO/WHO JMPR in 1992 and 2009 and there are currently 27 approved CODEX maximum residue limits (MRLs) for bifenthrin. The WHO/IPCS (International Programme on Chemical Safety) has also evaluated bifenthrin (WHO Recommended Classification of Pesticides by Hazard, 2000-2002). The bifenthrin dossier was submitted to the European Commission in November 2003 in compliance with the EC Directive 91/414. Recently, EFSA published its conclusion on bifenthrin (available through http://www.efsa.europa.eu).

The draft specification and the supporting data were provided by FMC Corporation in 2001.

## Uses

Bifenthrin is a fourth generation pyrethroid insecticide and acaricide that affects the nervous systems of target pests. It is used in horticulture and public health against (including but not limited to) caterpillars, grasshoppers, fleas, ants, cockroaches, moths, beetles, mites, aphids, thrips, scales, termites, mosquitoes, scorpions, wasps, and spiders.

## Identity of the active ingredient

*ISO common name*

Bifenthrin (ISO 1750 published)

*Chemical name(s)*

IUPAC 2-methylbiphenyl-3-ylmethyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

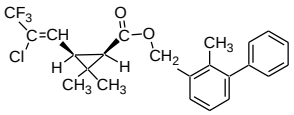
CA (2-methyl[1,1'-biphenyl]-3-yl)methyl 3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate

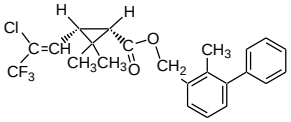
*Synonyms*

FMC 54800

*Structural formulae*

(*Z*)-(1*R*)-*cis*-





(*Z*)-(1*S*)-*cis*-

*Molecular formula*

$C_{23}H_{22}ClF_3O_2$

*Relative molecular mass*

423.0

*CAS Registry number*

82657-04-3

*CIPAC number*

415

*Identity tests*

GC relative retention time, IR spectrum, electron ionization mass spectrum (from GC-MS)

## Physico-chemical properties of bifenthrin

**Table 1. Physico-chemical properties of pure bifenthrin**

| Parameter | Value(s) and conditions | Purity % | Method reference (and technique if the reference gives more than one) | Reference |
|---|---|---|---|---|
| Vapour pressure | $2.4 \times 10^{-5}$ Pa at 25°C | 98.9 | Gas Saturation Method | CGP-83-1 |
| Melting point, boiling point and/or temperature of decomposition | Melting point: 65-70°C<br>Bifenthrin vaporizes intact in the 215-225°C temperature range | 98.5 | DSC<br>TGA-IR | P-2544 |
| Solubility in water | Less than 0.1 micrograms per litre at pH = 2, 7, and 11 (approximately 14 ppt) | 96.6 | Column generator method | P-17-99-45 |
| Octanol/water partition coefficient | Log $P_{OW}$ > 6 The extremely low water solubility of bifenthrin makes a more precise measurement of the partition coefficient nearly impossible and unnecessary. | 96.5 | Shake flask partitioning with HPLC analysis | P-0698 |
| Hydrolysis characteristics | No hydrolysis was detected over a study period of 22 days at pH = 5, 7, and 9 | 96.5 | Hydrolysis solutions stored in glass at 25°C. Analysis by HPLC | P-0701 |
| Photolysis characteristics | This study estimates a DT50 of 24.4 to 24.8 days in the summer at 40° N and 50° N, respectively, and demonstrates that there is a pathway for the degradation of bifenthrin in water. Major transformation product-biphenyl alcohol.<br>Quantum yield: $7.00 \times 10^{-6}$. | Radiolabeled bifenthrin (98.3%) | Acetonitrile (30%) in water was used as a co-solvent due to low solubility of bifenthnin. Analyses were carried out by HPLC. | P-3837 |
| Dissociation characteristics | Bifenthrin contains no functionalities subject to reversible dissociation. | Not applicable | Not applicable | Not applicable |

**Table 2. Chemical composition and properties of bifenthrin technical material**

| | |
|---|---|
| Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data | Confidential information supplied and held on file by FAO and WHO. Mass balances were 95.79 –98.54 % and percentages of unknowns were 4.21 – 1.46 %. |
| Declared minimum bifenthrin content | 930 g/kg |
| Relevant impurities ≥ 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 temperature range | 65-70 °C, bifenthrin vaporizes intact at temperatures between 215-225°C |

## Hazard summary

Bifenthrin has been evaluated by the WHO IPCS [2000-2002, Report No. WHO/PCS/01.5] and by the FAO/WHO JMPR in 1992 and 2009. The JMPR concluded that the results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that bifenthrin is unlikely to pose a carcinogenic hazard to humans. An ADI was allocated on the basis of the NOAEL of 0 to 0.01 mg/kg/bw/day using a 100-fold safety factor. This result was supported by the same NOEL in the rat teratology study, although in the latter study gavage, rather than dietary administration, was used.

The IPCS hazard classification of bifenthrin is moderately hazardous, class II.

## Formulations

The main formulation types available are WP (wettable powder), EC (emulsifiable concentrate), GR (granules), UL (ultra-low volume liquid), SC (suspension concentrate) and ME (micro emulsion).

These formulations are registered and sold in many countries throughout the world.

## Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is a AOAC collaboratively validated analytical method. The bifenthrin content is determined by capillary GC with FID and internal standardisation with octacosane. Validation includes TC and WP, whereas EC and SC were tested but the validation results did not meet the acceptance criteria. The method was published in the Journal of AOAC INTERNATIONAL, Volume: 94, beginning of 2011. Furthermore, an addendum to CIPAC MT 184 (suspensibility) for the chemical assay of the remaining 10% in the cylinder was provided by the company (see Note 5, WP specification).

Test methods for determination of physico-chemical properties of the technical active ingredient were based on accepted procedures during the time period bifenthrin was under development, while those for the formulations were based on CIPAC methods as indicated in the specifications.

## Physical properties

The physical properties, the methods for testing them and the limits proposed for the WP formulation, comply with the requirements of the FAO/WHO Manual (March 2006

version of the first edition). One exception is that the material was subjected to 3 minutes wetting time instead of the 1 minute specified. The wetting time specification reported as part of the “Bifenthrin Wettable Powder” report for the FAO/WHO Specification was determined by the CIPAC method MT 53.3 (CIPAC Handbook F, p. 164). Bifenthrin 10 WP shall be completely wetted in 3 minutes without swirling. This value reflected the actual production values obtained from the Bifenthrin 10 WP 2003 campaign in Middleport, NY. The longer wetting time is probably due to the hydrophobic nature of the active ingredient, bifenthrin. Even though this value is higher than 1 minute, no adverse impact during application is expected. This product has been in commercial use for a decade without any significant performance issues.

**Containers and packaging**

No special requirements for containers and packaging have been identified.

**Expression of the active ingredient**

The bifenthrin is expressed as bifenthrin.

## Annex 1: Hazard Summary Provided by the Proposer

Notes:

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from bifenthrin 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.

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

| Species | Test | Duration and conditions or guideline adopted | Result | Batch/Purity | Reference |
|---|---|---|---|---|---|
| Rat (M/F) | Oral | EPA 81-1<br>10% Corn oil.<br>Single dose / 14 day observation<br>67, 55, 48, 44, 40 and 34 mg/kg b.w | $LD_{50}$ 55.5 mg/kg male<br>54.5 mg/kg combined<br>53.4 mg/kg female | E1276-140/ 92% | A82-756 |
| Mouse (M/F) | Oral | EPA 81-1<br>10% Corn oil.<br>Single dose / 14 day observations<br>50.0, 42.0, 35.0 and 25.0 mg/kg b.w | $LD_{50}$ 43.5 mg/kg male<br>42.5 mg/kg female | E2425-145/ 91.4% | A83-837 |
| Rat (M/F) | Oral | EPA 81-1<br>10% Corn oil.<br>Single dose / 14 day observation<br>males : 20, 40, 60, 80, 90 or 100 mg/kg b.w<br>females : 40, 60, 80 or 100 mg/kg b.w | $LD_{50}$ 70.1 mg/kg male<br>56.7 mg/kg combined<br>53.8 mg/kg female | 151A/ 91.4% | A83-859 |
| Rat (M/F) | Oral | EPA 81-1, OECD 401 and EC method, part B1.14 day, undiluted, single dose, 14-day observation.<br>males : 100, 150, 200 and 300 mg/kg b.w<br>females : 75, 100, 200 or 300 mg/kg b.w | $LD_{50}$ 168.4 mg/kg male<br>186.1 mg/kg combined<br>210.4 mg/kg female | PL97-592/ 93.7% | A97-4681 |

| Species | Test | Duration and conditions or guideline adopted | Result | Batch/Purity | Reference |
|---|---|---|---|---|---|
| Rabbit (M/F) | Dermal | EPA 81-2<br>14 day observations<br>24 hour exposure<br>2000 mg/kg | LD50 > 2000 mg/kg | E2392-105/<br>88.35% | A83-1032 |
| Rat (M/F) | Dermal | EPA 81-2<br>24 hour exposure<br>2000 mg/kg | $LD_{50}$ > 2000 mg/kg<br>Practically non-toxic | E2392-105/<br>88.35% | A85-1924 |
| Rat (M/F) | Inha-lation | OPPTS 870-1300, OECD 403, EC B2<br>Nose-only.<br>14 day observations<br>4 hour exposure<br>0.56, 0.99, and 2.3 mg/l. | $LC_{50}$ 1.10 mg/L males<br>1.01 mg/L combined<br>0.8 mg/L females | PL02-0477/<br>94.8% | A2003-5589 |
| Rabbit (M/F) | Primary Eye Irritation | EPA 81-4<br>48 hour observations; 0.1 mL administered | Unwashed / Washed – Practically non-irritating | E2392-105/<br>88.35% | A83-1034 |
| Rabbit (M/F) | Primary Skin Irritation | EPA 81-5<br>4 hour exposure<br>0.5 ml (undiluted) | Non-irritating (PII = 0.0) | E2392-105/<br>88.35% | A83-1033 |
| Guinea Pig (M) | Skin Sensitiz ation | Buehler method<br>EPA 81-6 | Non-sensitizing | E2392-105/<br>88.35% | A83-1035 |
| Guinea Pig (F) | Skin Sensitiz ation | Maximization method<br>OECD 406 and Method B6 (Directive 96/54/EEC) | Positive | PL02-0477/<br>94.8%<br>TFP anhydride content 35 g/kg | A2002-5588 |
| Guinea Pig (F) | Skin Sensitiz ation | Maximization method<br>OECD 406 and Method B6 (Directive 96/54/EEC) | Positive | G3042:140/<br>96.2%<br>TFP anhydride content 0.2 g/kg | A2009-6770 |

**Table 4. Toxicology profile of technical bifenthrin based on repeated administration (subacute to chronic)**

| Species | Test | Duration and conditions or guideline adopted | Result | Batch/purity | Reference |
|---|---|---|---|---|---|
| Dog (M/F) | 13-week feeding – Repeated dose | Dir. 87/302/EEC, Part B<br>Gelatine capsules<br>0, 2.5, 5.0 , 10.0 and 20.0 mg/kg bodyweight/day | NOEL = 2.5 mg/kg/day | E2392-105/ 88.35% | A83-820 |
| Rat (M/F) | 28-day feeding – Repeated dose | Dietary Range-finding<br>0, 50, 100, 200, 300 and 400 ppm | Death at ≥ 300 ppm<br>Tremors at 200 ppm<br>NOEL = 100 ppm | E2425-145/ 91.4% | A83-817 |
| Mouse (M/F) | 28-day feeding – Repeated dose | Dietary Range-finding<br>study A83-839 : 50 (500), 100, 200, 300 ppm<br>study A83-839A : 500, 600, 750 and 1000 ppm | NOEL = 300 ppm<br>LOEL = 500 ppm | E2392-105/ 88.35% | A83-839 |
| Rat (M/F) | 90-day Feeding - Repeated dose | Dietary Range-finding<br>0, 12, 50, 100 and 200 ppm | NOEL = 100 ppm | E2425-145/ 91.4% | A83-818 |
| Dog (M/F) | 1-year Feeding – Chronic | Dir. 87/302/EEC, Part B – chronic toxicity test<br>Gelatin capsule<br>0, 0.75, 1.50, 3.00 and 5.00 mg/kg/day | NOEL = 1.50 mg/kg day<br>LOEL = 3.0 mg/kg/day | E2392-105/ 88.35% | A83-821 |
| Rat (M/F) | Chronic – Oncogenicity | EPA 83-5<br>2 year dietary<br>0, 12, 50, 100 and 200 ppm | NOEL = 50 ppm<br>LOEL = 100 ppm<br>Not carcinogenic | E2392-105/ 88.35% | A83-952 |
| Mouse (M/F) | Chronic – Oncogenicity | EPA 83-2<br>18-month dietary<br>0 , 50, 200, 500 and 600 ppm | NOEL = 50 ppm male<br>200 ppm female<br>Increased incidence of submucosal tumours (hemangiomas) of marginal statistical significance. | E2392-105/ 88.35% | A83-974 |
| Rabbit (M/F) | 21-day Dermal Toxicity (Repeated dose) | EPA 82-2 (1984)<br>6 hours / day<br>0, 25, 50, 100 or 500 mg/kg/day | NOEL = 100 mg/kg/day | E2392-105/ 88.35% | A83-1041 |
| Rat (M/F) | 21-day Dermal Tox (Repeated dose) | EPA 82-2 (1984)<br>6 hours / day<br>5 days / week<br>0, 25, 50, 100, or 1000 mg/kg b.w./day | NOEL = 50 mg/kg/day | G1295-15B/ 93.2% | A2000-5162 |

| Species | Test | Duration and conditions or guideline adopted | Result | Batch/purity | Reference |
|---|---|---|---|---|---|
| Rat (M) | Dermal Absorption | No guideline.<br>Applied as a dilution of a liquid formulation<br>Achieved average dose (mg/kg b.w.) Group I: 0.18; Group II: 1.96; Group III: 19.38 | Dermal absorption 10-hours after administration of test material was 55.4% of the applied dose in animals dosed w/49.2 ug/10.8 sq. cm (4.6 ug/sq. cm) | $^{14}$C-Study<br>Lot 83022/<br>95.49% | PC-0059 |
| Rat (F) | Teratology | EPA - OPPTS 870.3700<br>Dietary<br>0, 30, 60, 90, or 200 ppm (equivalent to 0, 2.5, 5.0, 7.4, and 16.3 mg/kg b.w./day) | Maternal NOEL = 90 ppm (7.4 mg/kg/d) | PL99-0108/<br>95.3% | A2000-5263 |
| Rat (F) | Teratology | EPA 83.3 (1984)<br>Days 6-15 of gestation<br>0 (vehicle), 0.50, 1.0 and 2.0 mg/kg/day<br>Vehicle: corn oil | Not teratogenic at levels up to and including 2.0 mg/kg/day<br><br>NOEL = 1 mg/kg/day | E2392-105/<br>88.35% | A83-1091 |
| Rabbit (F) | Teratology | EPA 83.3 (1984)<br>Days 7-19 of gestation<br>0 (vehicle), 2.67, 4.0 and 8.0 mg/kg/day. Individual doses were adjusted daily in order to compensate for changes in maternal body weights<br>Vehicle: corn oil | Not teratogenic at levels up to and including 8.0 mg/kg/day<br><br>NOEL = 2.67 mg/kg/day | E2392-105/<br>88.35% | A83-1092 |
| Rat (M/F) | 2-Generation Reproduction | Dietary<br>0, 30, 60, or 100 ppm (approximately equivalent to 0, 1.5, 3.0 and 5.0 mg/kg/day) | NOEL toxicity = 60 ppm (3 mg/kg/day); NOEL reproduction 100 ppm (5mg/kg/day) | E2392-105/<br>88.35% | A83-977 |
| Chicken (F) | Acute Delayed Neurotoxicity | 21 day observation | Negative | E2392-105<br>88.35% | A83-1081 |
| Rat (M/F) | Acute Neurotox | Undiluted (gavage), 14 day observation<br>Single oral dose : 0, 10, 35 or 75 mg/kg | NOEL = 35 mg/kg<br><br>FOB and motor activity effects noted in animals receiving 75 mg/kg | PL97-592/<br>93.7% | A97-4643 |

| Species | Test | Duration and conditions or guideline adopted | Result | Batch/purity | Reference |
|---|---|---|---|---|---|
| Rat (M/F) | 28-day Feeding – Repeated dose | Neurotoxicity study rangefinding 0 or 50 ppm (10 animals/sex/group) or 100, 200, or 300 ppm (5 animals/sex/group) | NOEL = 100 ppm<br>LOEL = 200 ppm | PL97-592/ 93.7% | A97-4699 |
| Rat (M/F) | Subchronic Neurotoxicity | 13 weeks, dietary<br>0 or 50 ppm (10 animals/sex/group)or 100, 200, or 300 ppm (5 animals/sex/group) | NOEL = 50 ppm (2.9 mg/kg/day males; 3.7 mg/kg/day females) | PL97-592/ 93.7% | A97-4700 |

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

| Species | Test | Conditions | Result | Batch | Reference |
|---|---|---|---|---|---|
| Salmonella typhimurium | Ames Assay<br>0, 10, 33, 67, 100, 33, 667, 1000, 3.333, 6.667, 10.000 µg/plate in mutation test 1<br>0, 375, 1.875, 3.750 and 7.500 µg/plate in mutation test 2<br>(in both the presence and absence of S-9 mix) | 5 Strains with and without metabolic activation. Microsomes from male and female Swiss Webster mice and male Sprague Dawley rats | Not mutagenic | E2425-145/ 91.4% | A83-838 |
| Mouse Lymphoma Cells | Mouse Lymphoma Mutagenesis Assay<br>0.24, 0.18, 0.13, 0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018 µg/ml without metabolic activation.<br>0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018, 0.03, 0.010, 0.0075 µg/ml with metabolic activation | L5178Y TK+/-<br>Rat liver S-9 | Weak positive results with and without metabolic activation | E2392-105/ 88.35% | A83-978 |
| Rat (M) | In vivo Cytogenetics<br>30, 10 and 3 mg/kg/day for five consecutive days | 5 day exposure<br>oral by gavage | Negative | E2392-105 88.35% | A83-979 |
| Chinese Hamster Ovary (CHO) (F) | In vitro Chromosome Aberration<br>10.00, 30.00, 60.00 and 100.00 µg/mL in DMSO | Tested to 10,000 ug/mL with and without activation | Negative | E2392-105 88.35% | A1989-3099 |
| CHO (F) | HGPRT Assay<br>Test 1 : 2.5, 5.0, 10, 25, 50, 100, 250, 500, 1000 µg/mL<br>Test 2 : 250, 500, 750, 1000 µg/mL (without S9), 20, 30, 40, 50µg/mL (with S9) | With and without metabolic activation | Inconclusive w/metabolic activation | E2392-105/ 88.35% | A83-1144 |
| CHO (F) | In vitro Gene Mutation<br>Preliminary cytotoxicity test : range of 0.10 to 10.000 µg/ml<br>Main study : 100, 500, 1.000, 2.500, 5.000, 10.000 µg/ml in acetone | Tested to 10,000 ug/mL with and without activation | Not mutagenic | E2392-105/ 88.35% | A83-1105 |
| Mouse Lymphoma Cells | HGPRT Gene Mutation<br>Preliminary cytotoxicity test : 1, 5, 10, 30, 100 µg/ml | L5178Y<br>Dosed to the limit of solubility (500 ug/mL) | Not mutagenic | E2392-105/ 88.35% | A86-2059 |

| Species | Test | Conditions | Result | Batch | Reference |
|---|---|---|---|---|---|
| | Main study : 1.0, 30.0, and 60.00 µg/mL in acetone | | | | |
| Rat Hepatocytes | Unscheduled DNA Synthesis<br>Initial cytotoxicity test: ten treatments ranging from 100 to 0.005 µg/ml<br>UDS assay: 0.01, 0.05, 0.1, 0.5, 1.0, 2.0 µg/ml in acetone | Tested at levels up to 100 ug/mL in DMSO | Marginally positive at one highly toxic dose. Two repeat assays yielded negative responses | E2392-105/ 88.35% | A83-985, A83-1043, 175408 |
| Mouse Embryo Cells (BALB/3T3) | Cell Transformation | No metabolic activation<br>3 - 100 µg/mL in DMSO | Negative | E2392-105/ 88.35% | A83-980 |
| Drosophila | Sex Linked Recessive Lethal – Genotox | Concentrations of 50 & 100 ug/mL | Negative | E2392-105/ 88.35% | A83-1104 |
| Chinese Hamster (F) Ovary (CHO) | In vitro Sister Chromatid Exchange | With and without metabolic activation up to 60 ug/mL in DMSO | Negative | E2392-105/ 88.35% | A1989-3016 |

**Table 6. Ecotoxicology profile of technical bifenthrin**

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| *Daphnia magna* (water flea) | OECD 202<br>Acute toxicity flow- through | 48 hrs exposure in a flow-through system, to five concentrations of bifenthrin (10, 5.0, 2.5, 1.2 and 0.6 µg/L), control dilution water and solvent control dilution water (dimethyl formamide). | $LC_{50}$:<br>(24hrs) - >10 µg/L<br>(48hrs) - 1.6 µg/L<br>NOEC < 0.60 µg/L<br>Bifenthrin technical (purity - 88.35%, composition - 98 % cis/2% trans isomer) | E-2392-105/ | BW-83-8-1444 |
| *Daphnia magna* (water flea) | OECD 202<br>Acute toxicity flow-through | 48 hrs exposure in a flow-through system, to five concentrations of bifenthrin (0.025, 0.064, 0.12, 0.2 and 0.48 µg/L), control dilution water and solvent control dilution water (dimethyl formamide). | $LC_{50}$ (24hrs) >0.48µg/L<br>(48hrs) - 0.11µg/L<br>NOEC < 0.025 µg/L<br>purity - 88.35%, composition - 98 % cis/2% trans isomer) | Path 830222-142<br>($^{14}$C-) | BW-85-2-1731 |
| *Daphnia magna*, *Cerodaphnia dubia*, *Thamnocephales platyurus*, *Hexagenia sp.* (larvae), *Caddis fly sp.* (larvae), and *Gammarus pulex*. | OECD 202<br>Static acute toxicity tests | *Daphnia*: 48hrs exposure, concentrations: 0.018; 0.056; 0.18; 0.56, 1.8 & 5.6 mg/L<br>*Cerodaphnia dubia:* 24hrs exposure, concentrations: 0.056; 0.18; 0.56, 1.8 & 5.6 mg/L<br>*Thamnocephales platyurus:* 24hrs exposure, concentrations: 0.032; 0.056; 0.18; 0.56; 1.8 and 5.6 mg/L<br>*Hexagenia sp:* 48hrs exposure, concentrations: 0.056; 0.18; 0.56, 1.8 and 5.6 mg/L<br>*Caddis fly sp:* 48hrs exposure, concentrations: 0.056; 0.18; 0.56, 1.8 & 5.6 mg/L<br>*Gammarus pulex:* 48hrs exposure, concentrations: 0.0032; 0.01; 0.032; 0.1; 0.32 & 1.0 mg/L | *Daphnia*:<br>$EC_{50}$(48hrs) - 0.37 µg/L<br>NOEC - 0.056 µg/L<br>*Cerodaphnia dubia* $EC_{50}$(24hrs) - 0.31 µg/L<br>NOEC- 0.043 µg/L<br>*Thamnocephales platyurus*<br>$EC_{50}$(24hrs) - 5.7 µg/L<br>NOEC - 0.032 µg/L<br>*Hexagenia sp*<br>$EC_{50}$(48hrs) - 0.39 µg/L<br>NOEC - 0.039 µg/L<br>*Caddis fly sp* $EC_{50}$(48hrs) - 0.12 µg/L<br>NOEC - 0.031 µg/L<br>*Gammarus pulex*<br>$EC_{50}$(48hrs) - 0.11 µg/L<br>NOEC - 0.032 µg/L<br>Bifenthrin technical (purity 93.8%) | PL00-0082,<br>Batch B00-07 | 01-2424/01 |
| *Daphnia magna* (water flea) | OECD 202<br>Chronic toxicity | Flow-through, 21-day life cycle toxicity test Groups of 40 daphnids (10 per replicate beaker) exposed to one of five nominal concentrations (0.6, 1.2, 2.5, 5.0 and 10 | MATC > 0.0013 < 0.0029 µg/L<br><br>NOEC - 0.0013 µg/L | E2823-2<br>($^{14}$C) | ABC36980 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | ng/L in water, to 50 µL/L acetone (solvent control) or to water alone.<br>Mean measured concentrations determined by liquid scintillation counting were 0.30, 0.76, 1.3, 2.9 and 7.6 ng/L. | $^{14}$C-labelled bifenthrin (purity 96.2 %) | | |
| *Mysidopsis bahia* (mysid) | OECD 202<br>Life cycle toxicity | Flow-through, 28-day life cycle toxicity<br>Groups of 40 mysids (5 per replicate test chamber) in 20% seawater, to 0.1 mL/L acetone (solvent control) or to seawater alone (control).<br>Nominal concentrations of bifenthrin were: 0.00, 0.79, 1.4, 2.8, 5.6 and 11.3 ng/L.<br>Mean measured concentrations were: 0.98 (control and solvent control), 1.2, 1.3, 1.6, 2.5 and 4.7 ng/L. | MATC - 0.00125µg/L<br>NOEC - 0.0012µg/L<br>$^{14}$C-labelled bifenthrin technical (Phenyl-$^{14}$C, purity 96.5 %) | Path 83022-142 ($^{14}$C) | A90-3318 |
| *Chlorella pyrenoidosa (green algae)*<br>*Scenedesmus acutus (fresh water algae)* | Acute toxicity | Two test species exposed to five concentrations of bifenthrin, ranging from 0.05 ppb to 50 ppm in 0.1% acetone.<br>Culture medium according to guideline protocol, 25°C, continuous light, 100 µE/m$^2$/s, 50 mL of medium in 125 mL. | *Chlorella pyrenoidosa* NOEC > 50 ppm<br>*Scenedesmus acutus* NOEC> 10 ppm<br>Bifenthrin (purity not specified) | Not recorded | A2010-6981 |
| *Chironomus riparius* (midge) | Acute toxicity | $^{14}$C bifenthrin applied just below the surface of an artificial water/sediment systems at the nominal concentration of 0, 0.1, 1, 10 and 100 µg/l in the rage finding test and 0, 0.1, 0.32, 1.0, 3.2 and 10 µg/l in the definitive test.<br>Six vessels per concentration prepared, appropriate controls - 2 for the measure of the concentrations and 4 containing 20 chironomid larvae. | Mortality:<br>$EC_{50}$ - 3.96 µg/L<br>NOEL - 0.32 µg/L<br>Emergence ratio:<br>$EC_{50}$ - 3.96 µg/L<br>NOEL - 1.06 µg/L<br>Development rate:<br>$EC_{50}$ >10.3 µg/L<br>NOEL - 1.06 µg/L<br>Bifenthrin technical (purity 94.4%) | PL98-0360 | 19781 |
| *Eisenia foetida* (Earthworm) | Acute toxicity | Four replicates of 10 worms per treatment; total of 240 worms.<br>Doses: 0.12 kg a.i./ha and100x (12 kg a.i./ha | $LC_{50}$ - 18.9 ppm a.i.<br>NOEC - 5.7 ppm<br>Bifenthrin technical (purity 88.35%) | E2392-105 | FCC82/85693 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | On days 7 and 14, worms removed for counting. | | | |
| *Apis mellifera* (honey bee) | Acute contact & oral toxicity | Acute contact toxicity: sprayed 20 mL solution containing bifenthrin at 50 ppm on a lot of caged bees. Two lots were tested for the product and two lots served as control. Mortality was noted after 24 hrs.<br>Acute oral toxicity: ingestion was tested by nourishment of lots of bees by means of a micropipette at a constant volume (20µL). The bees were presented a drop of sweet water containing fixed quantities of bifenthrin. One hr after treatment the bees received honey and pure water. Three doses (0.04 µg, 0.1 µg and 0.4 µg) and one control have been tested and mortality was noted after 24 hrs. | Acute contact toxicity: 100% mortality.<br><br>Acute oral toxicity: $LD_{50}$(24hrs)-0.1 µg/bee.<br><br>Bifenthrin (purity not stated) | Not recorded | Ph.L. SD-519-84 |
| *Poecilus cupreus (*carabid beetle) | Assessment of impact | Six adults per container.<br>60 g/ha dose of bifenthrin, the reference (PERFEKTHION (0.85 l/ha) and the control (water and acetone) were applied to 5 replicate test arenas (volume 400 l/ha). Mortality and food consumption were assessed. | Bifenthrin - 90% mortality at the application dose of 60 g/ha.<br>Bifenthrin technical (purity 94.4%) | PL-98-0360 | 19547 |
| *Thyphlodromus pyri (*predatory mite) | Assessment of impact | Bifenthrin: 60 g/ha, the reference (PERFEKTHION (212.5 ml/ha) and the control (water and acetone) were applied on glass plates (volume 200 l/ha) and were allow to dry.<br>Twenty 2 to 3-day old mites (protonymph stage) were placed in each arenas per treatment.<br>Mortality was assessed 24 hrs and 7 days after introduction.<br>Seven day after application, female and male mites were transferred and the fecundity was assessed by counting the | Bifenthrin -100% mortality at the application dose of 60 g/ha<br><br>Bifenthrin technical (purity 94.4%) | PL-98-0360 | 19141 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | number of eggs laid after a further 7-day period. | | | |
| *Chrysoperla carnea (*green lacewing) | Assessment of impact | Bifenthrin: 60 g/ha, the reference (PERFECTKION (212.5 ml/ha) and the control (water and acetone) were applied on glass plates (volume 200 l/ha) and were allowed to dry.<br>One larvae of *Chrysoperla carnea* was then placed on each glass plate and fed with lepidopteran eggs.<br>The mortality was assessed daily.<br>When pupation had occurred pupae were removed and placed in perspex oviposition cages. Adult emergence was measured daily until no adult had emerged for 7 consecutive days. | Bifenthrin - 100% at the application dose of 60 g/ha<br><br>Bifenthrin technical; (purity 94.4%) | PL-98-0360 | 19572 |
| *Aphidius rhopalosiphi (*aphid parasitoid) | Assessment of impact | Bifenthrin: 60 g/ha, the reference (PERFEKTHION (425 ml/ha) and the control (water and acetone) were applied to 8 glass plates (volume 200 l/ha) and were allow to dry.<br>Ten *Aphidius rhopalosiphi* (5 males and 5 females) were introduced into each test arena. | Bifenthrin -100% mortality.<br><br>Bifenthrin technical; (purity 94.4%) | PL-98-0360 | 19545 |
| Sewage sludge | Assessment of impact | Determined the effect of the test item to the respiration rate of activated sludge. The respiration was measured after a contact time of 3 hrs.<br>Two controls without test item were included in the test design.<br>Due to the low water solubility, bifenthrin was added in the mg range. | $EC_{50}$ - >1900 mg/L.<br><br>Bifenthrin<br>(purity 97.8%) | E6788:143 | E-17-99-47 |
| *Salmo gairdneri* (Rainbow trout) | EEC Method C1<br><br>Acute toxicity flow-through | Rainbow trout exposed in duplicate test chambers in a flow-through system to five concentrations for 96 hrs.<br>Test nominal concentrations of 1.5, 0.75, 0.38, 0.19 and 0.094 µg/L bifenthrin maintained by introducing approx. 7 | $LC_{50}$<br>(24 hrs) - 6.2 µg/L<br>(48 hrs) - 0.34 µg/L<br>(72 hrs) - 0.20 µg/L<br>(96 hrs) - 0.15 µg/L<br>(120 hrs) ~0.1 µg/L | E2392-105 | BW-83-8-1446 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | aquarium volumes/day of fresh test solution via modified, proportional diluter apparatus. Total hardness: $CaCO_3$ of 28-30 mg/L, alkalinity as $CaCO_3$ of 24 mg/L, pH 7.2-7.4, specific conductance range of 130-140 µmhos/cm. | NOEC - 0.094 µg/L<br>Bifenthrin technical (purity 88.35% composition 98% cis/ 2% trans isomers) | | |
| *Lepomis macrochirus* (Bluegill sunfish) | EEC Method C1<br>Acute toxicity flow-through | Bluegill exposed in duplicate test chambers in a flow-through system to five concentrations for 96 hrs.<br>Test nominal concentrations of 1.0, 0.65, 0.42, 0.27 and 0,18µg/L bifenthrin maintained by introducing approx. 8.6 aquarium volumes/day of fresh test solution. Test dilution water conditions were representative of a soft water quality. Total hardness: $CaCO_3$ of 28-31 mg/L, alkalinity as $CaCO_3$ of 24-26 mg/L, pH 7.2-7.4, specific conductance range of 120-140 µmhos/cm. | $LC_{50}$<br>(24 hrs) >1.0µg/L<br>(48 hrs) - 0.65µg/L<br>(72 hrs) - 0.44µg/L<br>(96 hrs) - 0.35µg/L<br>(120 hrs) - 0.32µg/L<br>(144 hrs) - 0.30 µg/L<br>NOEC< 0.18 µg/L<br>Bifenthrin technical (purity 88.35%, composition - 98 % cis/2 % trans isomer) | E2392-105 | BW-83-8<br>1445 |
| *Salmo gairdneri* (Rainbow trout) | OECD 210<br>Toxicity to embryos and larvae | Flow-through with nominal test concentrations were 0.070, 0.035, 0.018, 0.0088 and 0.0044 µg/l.<br>Unfertilised rainbow trout eggs and sperm were received individually and mixed for fertilization.<br>50 embryos were distributed to each of 28 incubation cups.<br>Embryos development was observed daily. Percentage hatch calculations were based on the number of live larvae per cup after hatching compared to the number of viable embryos per cup on test day 20.<br>To initiate the 48-hrs larvae exposure, incubation cups within each aquarium were combined on day 28, and the larvae were placed into their respective aquaria.<br>Behaviour and appearance of larvae were observed daily and larvae were counted twice weekly. | NOEC 0.012 µg/L<br>$^{14}C$-bifenthrin (52 mCi/mM phenyl ring label, Hexane solution 10.36% a.i.) | $^{14}C$<br>Path 830222-142 | BW-85-4-1766 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | At 48 days post hatch (30 days post swim-up), the larvae were anaesthetised, and percentage survival, mean total length, and average wet weight were determined. | | | |
| *Pimephales promela*) (Fathead minnow) | EPA 72.5<br>Full life cycle toxicity | Flow –through full life cycle study with nominal water concentrations of 0.0050, 0.0090, 0.019, 0.038, 0.075 µg/l.<br>140 healthy embryos per test concentration used at the start of the test, and place in incubation cups.<br>Number of embryos hatched in each cup recorded daily until hatching completed.<br>Daily observations taken on eggs, embryos, and fry.<br>Day 30, survival and standard length of live fish determined.<br>Day 77, fish reduced to 15 fish per replicate.<br>At 92 and 120 days post hatch fry anesthetised, measure weighted and revived in their respective test chambers.<br>At 121 days post hatching, 20 fish randomly selected and placed in duplicate spawning chambers of each aquarium along with 5 spawning tiles. All other fish were retained in growth chamber or frozen for residue analysis.<br>At 150 and 151 days post hatching, fish were sexed and reduced to 5 males and 12 females in all spawning chambers.<br>On day 198 post hatching (study day 204), fish were reduced to 4 males and 6 females.<br>Tiles were checked for the presence of eggs. Eggs were then placed in a separate container of the appropriate test solution.<br>Spawns of < 50 eggs were removed from the tiles and frozen for residue analysis.<br>Spawn of > 50 eggs were placed into a growth chamber. | $LC_{50}$ (96hr) - 0.21 µg/l (static)<br><br>NOEC - 0.04 µg/l (parent survival)<br><br>NOEC > 0.09 µg/l (reproduction)<br><br>$^{14}C$-FMC bifenthrin (96.2% purity) | $^{14}C$<br>E2823-2 | A86-2100 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | Daily observations were done on eggs, embryos and fry.<br>On day 56 post-hatching, the fish were measured and weighted. A part was frozen. | | | |
| *Lepomis macrochirus (Bluegill sunfish)* | OECD 305 E<br>Bio-accumulation | Lepomis macrochirus were exposed to 2 concentrations (0.007 µg/L and 0.085 µg/L) of 14C-radiolabeled bifenthrin for 60 days to aqueous solutions of bifenthrin under semi-static conditions with a 2-day renewal interval. The depuration phase was performed for 60 days under flow-through conditions, resulting in a total in-life assessment phase of 120 days.<br>Semi-static, two day renewal interval, four replicates per test group, twenty fish per replicate, aeration to prevent oxygen depletion, addition of application solution between renewal days in order to compensate for uptake by fish and adsorption to test vessel walls, daily feeding.<br>Depuration period: Flow-through, started with 4 replicates per test group, with 13 fish per replicate, 50 L stainless steel vessels, 10 volume exchanges per day.<br>Sampling: Water samples were taken twice daily in order to determine the total radioactive residue in the test solutions by LSC during the uptake phase and the first 8 days of the depuration phase.The samples | The concentrations in whole fish increased relatively fast at both treatment levels during the first 28 days of exposure. Thereafter, steady state was reached. 7.9 and 168.8 ± 25.5 µg TRR/kg.<br>During the depuration period, the concentrations of the total radioactive residue in whole fish declined with time.<br>The whole fish BCF based on the total radioactive residue at steady state, i.e., the BCFSS, was 1,494 ± 229 at 0.007 µg a.i./L and 1,622 ± 218 at 0.085 µg a.i./L.<br>The bifenthrin BCFSS of whole fish was 1,362 ± 219 at 0.007 µg a.i./L and 1,414 ± 204 at 0.085 µg a.i./L whole fish. The depuration rate constants for whole fish were 0.024 day-1 for both treatment levels<br>The elimination DT50 for bifenthrin was 28 and 22 days for the 0.007 and 0.085 µg a.i./L treatment levels, respectively. | 14C<br>QFC14435 | 1084.008.<br>135 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | were quantified for 14C-residues, extracted with hexane and analysed for bifenthrin and degradation products.<br>Fish samples were taken on days 7, 15, 28, 39, 48, and 60 after start of the exposure. During the depuration phase, fish samples were taken on days 1, 2, 4, 8, 14, 30, 42 and 60 after start of the depuration phase, i.e. on days 61, 62, 64, 68, 74, 90, 102, and 120 after start of the exposure.<br>Water conditions: temperature ranged 19.9-24.0 °C, total hardness of 0-56 mg/L as CaCO3, total alkalinity of 327-700 mg/L as CaCO3, TOC <2 mg/L, pH of 7.37-8.46, specific conductivity of 420-800 μS/cm, and dissolved oxygen concentration of 7.92-9.97 mg/L. | Phenyl-ring labelled 14C- bifenthrin radiochemical purity 97.8 %). | | |
| *Cyprinus carpio (carp)* | OECD 305 C<br>Bio-accumulation | Two groups of fish, continuously exposed to nominal concentrations (high exposure level: 0.085 ng/mL, low exposure level: 0.0085 ng/mL) of the test substance.<br>Flow-through system which introduced about 400L of fresh test solution per day.<br>On week 10, the addition of the test substance was terminated and only dilution water was supplied during the next two weeks (depuration phase).<br>Concentrations of the test substance in water and whole fish were measured periodically. | Bioconcentration factor<br>Exposure - 0.085ng/mL: 1330x<br>Exposure- 0.0085ng/mL:1030x<br>Elimination<br>Exposure -0.085ng/mL: 11 days (50%)<br>Exposure -0.0085ng/mL: 6 days (50%)<br>14C- bifenthrin (FMC (FMC-U14C labeled) radiochemical purity 97 %) | 14C<br>Isotope 195 | 2B479G |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| *Bobwhite quail* | Acute oral toxicity | 60 quails, divided (5/sex) into a control group + 5 treatment groups: 464, 681, 1000, 1470 and 2150 mg/kg.<br>Orally administered via a syringe on test day 0. The control group received only corn oil.<br>Body weight and food consumption were recorded at days 0, 3, 7, 14 and 21.<br>Observations made daily.<br>All birds found dead + 4 arbitrarily selected birds sacrificed from each group on test days 21 were subjected to a gross necropsy. | LD50 - 1800 mg/kg bw<br>bifenthrin<br>(purity 88.35%) | E2392-105 | BLAL83-QD 30 |
| *Mallard duck* | None stated<br>Acute oral toxicity | 30 ducks, divided (5/sex) into a control group and 2 treatment groups: 1470 and 2150 mg/kg.<br>Orally administered via a syringe on test day 0. The control group received only corn oil.<br>BW and food consumption were recorded at days 0 (only body weight), 3, 7,14 and 21.<br>Observations made daily.<br>Four arbitrarily selected birds sacrificed on test day 21 were subjected to a gross necropsy. | LD50 >2150 mg/kg bw<br><br>Bifenthrin<br>(purity 88.35%) | E2392-105 | BLAL 83-DD 23 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| *Bobwhite quail* | OECD 205<br>Short-term (8-day) dietary study | 150 quails, divided into 5 vehicle control groups (10/group; corn oil), 5 positive control groups (10/group, using 10, 21.5, 46.4 68.1 and 100 ppm of dieldrin) and 5 treatment groups (10/group; using 312, 625, 1250, 2500 and 5000 ppm of bifenthrin).<br>Test material incorporated into the diet with corn oil and fed to the birds for 5 days.<br>Following the 5-day test period birds were maintained on plain feed for a 3-day recovery period.<br>Food consumption recorded through-out the study<br>Birds weighed at 0 hr on day 1 and again on day 8.<br>Observations made daily.<br>All birds found dead and 4 arbitrarily selected birds from each group sacrificed at the termination of the study were subjected to a gross necropsy. | LC50 - 4450 ppm for<br><br>bifenthrin technical (purity 88.35%)<br><br><br>LC50 - 23 ppm for dieldrin | E2392-105 | BLAL83-QC34 |
| *Mallard ducks* | Short-term (8-day) dietary study | 150 ducks, divided into 5 vehicle control groups (10/group; corn oil), 5 positive control groups (10/group, using 46.4, 68.1, 100, 147 and 215 ppm of dieldrin) and 5 treatment groups (10/group; using 312, 625, 1250, 2500 and 5000 ppm of bifenthrin technical).<br>Test material incorporated into the diet with corn oil and fed to the birds for 5 days.<br>Following the 5-day test period birds were maintained on plain feed for a 3-day recovery period.<br>Food consumption recorded throughout the study<br>Birds weighed at 0 hr on day 1 and again on day 8.<br>Observations made daily.<br>All birds found dead and 4 arbitrarily selected birds from each group sacrificed at | LC50 - 1280 ppm for<br><br>bifenthrin technical<br>(purity 88.35%)<br><br>LC50 - 64 ppm for dieldrin | E2392-105 | BLAL83-DC34 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| | | the termination of the study were subjected to a gross necropsy. | | | |
| *Bobwhite quail* | OECD 206<br>Reproduction | Dietary effects quail, 3 groups of 20 replicates (1 male and 1 female per replicate)<br>Dose levels of 25, 50 and 75 ppm.<br>Diet given over a 24-week period – 12 weeks prior to the start of egg production and 12 weeks during egg production.<br>All eggs laid were collected over a 12-week period from the beginning of week 13 until the end of week 24. | No evidence of any adverse effects on the reproduction.<br>Bifenthrin<br>(purity 88.35%) | E2392-105 | FCC57A/ 851423 |

| Species | Test | Duration and conditions | Result [(isomer/form)] (purity) | Batch | Reference |
|---|---|---|---|---|---|
| *Mallard duck* | OECD 206<br>Reproduction | Dietary effects quail, 3 groups of 6 replicates (2 male and 5 females per replicate<br>Dose levels of 25, 50 and 75 ppm.<br>Diet given over a 24-week period – 12 weeks prior to the start of egg production and 12 weeks during egg production.<br>All eggs laid were collected over a 12-week period from the beginning of week 13 until the end of week 24. | No evidence of any adverse effects on the reproduction.<br>Bifenthrin<br>(purity 88.35%) | E2392-105 | FCC58A/ 851430 |

## Annex 2: References

| FMC or other document number | Year | Title |
|---|---|---|
| 19141 | 2001 | Technical bifenthrin: an extended laboratory evaluation of the side effects of technical bifenthrin on the predatory mite *Thyphlodromus pyrii* |
| 19545 | 2001 | Technical bifenthrin: an extended laboratory evaluation of the side effects of technical bifenthrin on the aphid parasitoid *Aphidius rhopalosiphi* |
| 19547 | 2001 | Technical bifenthrin: an extended laboratory evaluation of the side effects of technical bifenthrin on the carabid beetle *Poecilius cupreus* |
| 19572 | 2001 | Technical bifenthrin: an extended laboratory evaluation of the side effects of technical bifenthrin on the green lacewing *Chrysoperla carnea* |
| 19781 | 2002 | $^{14}$C-bifenthrin:determination of acute toxicity (EC50) to *Chironomus riparius* (28 days, static) |
| 175408 | 1990 | Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats *in vitro* with bifenthrin |
| 01-2424/01 | 2002 | Static acute toxicity tests with the insecticide bifenthrin technical and 6 arthropod species |
| 1084.008.135 | 2006 | Bifenthrin:Bioconcentration study with bluegill sunfish (Lepomis macrochirus) under semi-static conditions |
| 2B479G | 1993 | Bioaccumulation study of FMC 54800 with carp (*Cyprinus carpio)* |
| A1989-3016 | 1989 | Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) cells *in vitro* with bifenthrin |
| A1989-3099 | 1989 | Gene Mutation Assay in Chinese Hamster Ovary (CHO) cells *in vitro* with bifenthrin |
| A2000-5162 | 2000 | Bifenthrin technical: 21 day repeated dose dermal toxicity study in rat |
| A2000-5263 | 2000 | Bifenthrin technical: Prenatal Developmental Toxicity Study in Rat |
| A2002-5588 | 2003 | Bifenthrin Technical: Contact Hypersensitivity in Albino Guinea-Pigs, Maximisation Test |
| A2003-5589 | 2003 | Acute nose-only inhalation toxicity study of bifenthrin technical in albino rats |
| A2009-6770 | 2009 | (Bifenthrin) Guinea Pig Sensitization - Maximization Test |
| A2010-6981 | 1985 | Bifenthrin toxicity to algae |
| A82-756 | 1982 | Acute Oral Toxicity Study in Rats, FMC 54800 |
| A83-1032 | 1983 | Acute Dermal Toxicity of FMC 54800 Technical in Rabbits. |
| A83-1033 | 1983 | Primary Skin Irritation of FMC 54800 Technical in Rabbits. |
| A83-1034 | 1983 | Primary Eye Irritation of FMC 54800 Technical in Rabbits. |
| A83-1035 | 1983 | Skin Sensitization of FMC 54800, Technical in Guinea Pigs. |
| A83-1041 | 1983 | (Bifenthrin) Guinea Pig Sensitization - Maximization Test |
| A83-1043 | 1983 | Unscheduled DNA Synthesis in Rat Primary Hepatocytes |
| A83-1081 | 1984 | The Acute Oral Toxicity (LD50) and Neurotoxic Effects of FMC 54800 Technical to the Domestic Hen |
| A83-1091 | 1984 | Teratology Study in Rats with FMC 54800 Technical |
| A83-1092 | 1984 | Multi-Generation Reproduction Study with FMC 54800 Technical in Rats. |
| A83-1104 | 1984 | Mutagenicity Evaluation of FMC 54800 Technical, Notebook No. E-3292-105, FMC Study No. A83/1104 in the Sex-Linked Recessive Lethal Test in *Drosophila Melanogaster* |

| FMC or other document number | Year | Title |
|---|---|---|
| A83-1105 | 1984 | Chromosome Aberrations in Chinese Hamster (CHO) Cells |
| A83-1144 | 1984 | CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation |
| A83-817 | 1983 | Twenty Eight Day Range Finding in Rats with FMC 54800 Technical |
| A83-818 | 1983 | Ninety Day Range Finding in Rats with FMC 54800 Technical |
| A83-820 | 1984 | 13-Week Sub-chronic Oral Toxicity Study in Dogs with FMC 54800 Technical |
| A83-821 | 1985 | 52-Week Chronic Oral Toxicity in Dogs |
| A83-837 | 1983 | Acute Oral Toxicity of FMC 54800 in Mice |
| A83-838 | 1983 | *Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (AMES Test) |
| A83-839 | 1983 | Twenty Eight Day Range Finding in Mice with FMC 54800 Technical |
| A83-952 | 1986 | Combined chronic oral toxicity and oncogenicity study of FMC 54800: 2-year feeding study in albino rats |
| A83-959 | 1983 | Acute Oral Toxicity of FMC 54800 in Rat |
| A83-974 | 1991 | FMC 54800 Technical – Oncogenicity Lifetime Feeding Study in Albino Mice Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder |
| A83-977 | 1986 | Multi-Generation Reproduction Study with FMC 54800 Technical in Rats. |
| A83-978 | 1983 | L5178Y TH+/- Mouse Lymphoma Mutagenisis Assay |
| A83-979 | 1983 | Activity of FMC 54800 technical in the sub-chronic *in vivo* cytogenetics assay in Sprague-Dawley rats |
| A83-980 | 1983 | Activity of FMC 54800 technical in the Morphological Transformation of BALB/3T3 Mouse Embryo Cells in the Absence of Metabolic Activation |
| A83-985 | 1983 | Unscheduled DNA Synthesis in Rat Primary Hepatocytes |
| A85-1923 | 1986 | Acute Intraperitoneal Toxicity of FMC 54800 Technical in Rats |
| A85-1924 | 1985 | Acute Dermal Toxicity of FMC 54800 Technical in Rats. |
| A86-2059 | 1986 | Study to Determine the Ability of FMC 54800 to Induce Mutations to 6-Thioguanine Resistance in Mouse Lymphoma L5178Y Cells Using a Fluctuation Assay |
| A86-2100 | 1988 | Full life cycle toxicity of $^{14}$C-FMC 54800 to fathead minnow (*Pimephales promelas*) in a flow-through system |
| A90-3318 | 1991 | Life cycle toxicity of bifenthrin (FMC 54800) to the mysid, *Mysidopsis bahia* |
| A97-4643 | 1998 | FMC 54800 Technical-Acute Neurotoxicity in Rats |
| A97-4681 | 1997 | FMC 54800 technical: Acute Oral Toxicity Study in Rats |
| A97-4699 | 1998 | FMC 54800 Technical-Twenty-Eight Day Neurotoxicity Range-Finding Study in Rats |
| A97-4700 | 1998 | FMC 54800 Technical – Subchronic Neurotoxicity Screen in Rats |
| ABC 34846 | 1988 | Full life cycle toxicity of $^{14}$C FMC 54800 to fathead minnow (*Pimephales promelas*) in a flow-through system |
| ABC 36980 | 1989 | Chronic Toxicity of $^{14}$C-FMC 54800 to *Daphnia magna* under flow-through test conditions |
| BLAL83DC34 | 1983 | 8-day dietary LC50 study with FMC 54800 technical in mallard ducklings |
| BLAL83DD23 | 1983 | Acute oral toxicity study with FMC 54800 technical in mallard ducklings |
| BLAL83QC34 | 1983 | 8-day dietary LC50 study with FMC 54800 technical in bobwhite quail |
| BLAL83QD30 | 1983 | Acute oral toxicity study with FMC 54800 technical in bobwhite quail |
| BW-83-8-1444 | 1983 | Acute Toxicity of FMC 54800 technical to *Daphnia magna* |

| FMC or other document number | Year | Title |
|---|---|---|
| BW-83-8-1445 | 1983 | Acute Toxicity of FMC 54800 technical to bluegill (*Lepomis macrochirus*) |
| BW-83-8-1446 | 1983 | Acute Toxicity of FMC 54800 technical to rainbow trout (*Salmo gairdneri*) |
| BW-85-2-1731 | 1985 | Acute toxicity of $^{14}$C-FMC 54800 to *Daphnia magna* under flow-through conditions |
| BW-85-3-1747 | 1985 | The chronic toxicity of $^{14}$C-FMC 54800 to *Daphnia magna* under flow through conditions |
| BW-85-4-1766 | 1985 | The toxicity of $^{14}$C-FMC 54800 to rainbow trout (*Salmo gairdneri*) embryos and larvae |
| CGP-83-1 | 1983 | Vapor Pressure of FMC 54800 |
| E-17-99-47 | 1999 | Effect of bifenthrin to sewage sludge |
| FCC57A/851423 | 1986 | The effects of dietary inclusion of FMC 54800 on the reproduction in the bobwhite quail |
| FCC58A/851430 | 1986 | The effects of dietary inclusion of FMC 54800 on the reproduction in the mallard duck |
| FCC82/85693 | 1985 | The acute toxicity (LC50) of FMC 54800 to the earthworm *Eisenia foetida* |
| na | 1985 | Bifenthrin toxicity to algae |
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| P-0701 | 1983 | Hydrolysis of bifenthrin |
| P-17-99-45 | 1999 | Water solubility of bifenthrin |
| P-2544 | 1991 | Bifenthrin: physical and chemical characteristics |
| P-3837 | 2006 | Photodegradation of Bifenthrin in Buffered Aqueous Solution at pH 7 by Simulated Sunlight |
| PC-0059 | 1986 | A Dermal Absorption Study in Rats with $^{14}$C-FMC 54800. |
| Ph.L-SD-519-84 | 1984 | Preliminary ecotoxicological tests of FMC 54800 on *Apis mellifera* |