WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

TRANSFLUTHRIN

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

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 be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

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

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

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

INTRODUCTION

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

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

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

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

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual and supported by other information sources. 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.

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

PART ONE: SPECIFICATIONS

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Transfluthrin Information

ISO common name

Transfluthrin

Synonym

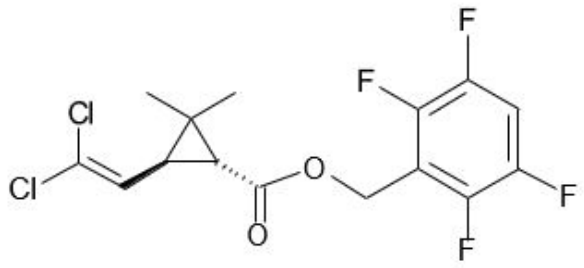
benfluthrin

Chemical names

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

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

Structural formula



Empirical formula

$C_{15}H_{12}Cl_2F_4O_2$

Relative molecular mass

371.16

CAS Registry number

118712-89-3

CIPAC number

741

Identity tests

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

Transfluthrin Technical Material

WHO specification 741/TC (November 2021*)

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 (741/2002, 741/2006, 741/2015, 741/2018, 741/2019, 741/2021, 741/2023). The 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 (741/2002, 741/2006, 741/2015, 741/2018, 741/2019, 741/2021, 741/2023), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of transfluthrin, together with related manufacturing impurities, and shall vary from a white to yellow coloured solid to liquid state depending upon the ambient temperature. It can exist in either solid and/or liquid form, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (741/TC/(M)/2, CIPAC Handbook K, p.122, 2003 and 741/TC/M/4, CIPAC Handbook O, p.158, 2017)

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

2.2 **Transfluthrin content** (741/TC/(M)/3, CIPAC Handbook K, p.122, 2003 and 741/TC/M/4, CIPAC Handbook O, p.158, 2017) (Note 1)

The transfluthrin content shall be declared (not less than 985 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities (Note 2)

3.1 1R-trans permethric acid anhydride (741/TC/M/4, CIPAC Handbook P, p.207, 2021

Maximum: 0.1 g/kg.

Note 1 The determination of transfluthrin in transfluthrin TC in the possible presence of other stereoisomers relies on the combined use of the chemical purity method published in CIPAC Handbook K and of the peer validated enantioselective HPLC method for transfluthrin published in Handbook O.

Note 2 Besides permethric acid anhydride (PAA), permethric acid chloride [((1R,3S)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride] could occur as a result of certain manufacturing processes. If this impurity would occur at ≥ 1 g/kg (of transfluthrin) in the products of other manufacturers, it would be designated as a relevant impurity, and a clause would be required to limit its concentration.

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

PART TWO: EVALUATION REPORTS

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FAO/WHO Evaluation Report 741/2023

Summary of Action

In October 2022, WHO was notified that in the frame of the implementation of the divestment of Environmental Science business by Bayer, the ownership of the data package of Transfluthrin TC, previously submitted by Bayer Crop Science, was transferred to Envu (Environmental Science US. LLC.).

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FAO/WHO Evaluation Report 741/2021

Recommendations

The Meeting recommended that:

I. The transfluthrin TC as proposed by Jiangsu Yangnong Chemical Co., Ltd should be accepted as equivalent to the transfluthrin reference profile.

II. The existing WHO specification for transfluthrin TC should be extended to encompass the technical material produced by Jiangsu Yangnong Chemical Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in October 2019 by Jiangsu Yangnong Chemical Co., Ltd (Yangnong) in support of extension of the existing WHO specification for transfluthrin TC (WHO specification 741/TC). The data submitted were in accordance with the requirements of the "Manual for development and use of FAO and WHO specifications for pesticides" (2016, third revision of the First Edition).

Transfluthrin has two chiral centres and therefore has four possible stereoisomers. The transfluthrin active substance is the 1*R*-*trans* configuration, and the other three isomers (1*S*-*trans*, 1*S*-*cis* and 1*R*-*cis*) are considered impurities. The CIPAC chiral (HPLC-UV) identity test (741/TC/M/4) published in CIPAC Handbook O enables the separation of all four stereoisomers, and along with the achiral CIPAC method 741/TC/(M)/3 (GC-FID) published in CIPAC Handbook K, allows the determination of 1*R*-trans and 1*S*-*trans* enantiomer content by calculation.

The Meeting was provided with a detailed description of the manufacturing process of the technical grade active ingredient, the description of the raw materials, the 5-batch analysis data for transfluthrin TC and all detectable impurities at or above 1g/kg and their manufacturing limits in the TC. The 5-batch analysis study was performed according to GLP guidelines.

The manufacturing process utilizes two reaction steps, as does the process of the reference profile. The Yangnong manufacturing process was supported by the 5-batch data.

Mass balances in the 5-batch analysis data were in the range from 993.4 g/kg to 994.7 g/kg (batches manufactured from end of December 2018 to beginning of February 2019), and no unidentified impurities greater than 1 g/kg were reported. The minimum purity of transfluthrin (1*R*-*trans* isomer) in the TC is 985 g/kg and complies with the existing WHO specification. The percentage of unknowns ranged from 5.3 to 6.6 g/kg. This was considered acceptable by the Meeting.

The specified maximum limit for the potentially relevant impurity permethric acid anhydride [(1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic anhydride)] is the same as the maximum limit (0.1 g/kg) of the current WHO specification for transfluthrin TC. The transfluthrin TC proposed by Yangnong contains a new impurity. At the request of the Meeting, Yangnong provided QSAR (Quantitative Structure Activity Relationships) analysis data that demonstrated there were no

additional hazards compared to transfluthrin, and the Meeting therefore concluded that this impurity can be regarded as non-relevant.

The Meeting noted that the batches included in the 5-batch analysis were manufactured over a short period of time (all manufactured in a period of approximately 1.5 months). The manufacturer confirmed that these batches were representative of the quality of their material.

The proposer submitted a “Certificate for Pesticide Registration” that confirmed that Yangnong’s transfluthrin TC has been registered in China with a declared minimum purity of 98.5% (ICAMA), which is consistent with the declared minimum purity in the data submitted to WHO.

The transfluthrin (1*R-trans* isomer) content in the 5-batch study has been determined by the GC-FID CIPAC method 741/TC/(M)/3 (CIPAC Handbook K) in combination with the HPLC-UV CIPAC method 741/TC/M/4 (CIPAC Handbook O). Both methods have been revalidated by Yangnong in regard to precision, linearity of response and accuracy.

The transfluthrin manufacturing impurities were determined by GC-FID, except for the potentially relevant impurity permethric acid anhydride that was determined by the CIPAC method 741/TC/M/4 published in Handbook P and using HPLC-UV and external standardization. All the analytical methods used in the 5-batch analysis study for the organic impurities were fully validated for their specificity, linearity of response, repeatability, accuracy, limit of detection and quantification. Water was determined by the internationally accepted Karl Fischer method. The identity of transfluthrin in the five batches of Yangnong’s transfluthrin TC was confirmed by mass spectrometry (GC-MS), FTIR and ^{1}H-NMR. The impurities in the 5 batches, as declared by Yangnong, were confirmed by GC-MS and ^{1}H-NMR.

The proposer provided mutagenicity data according to OECD 471 guidelines. The mutagenicity study was conducted on one batch of transfluthrin TC from the 5-batch analysis study using TA98, TA100, TA102, TA1535 and TA1537 strains of *Salmonella typhimurium*. The results of the GLP study demonstrated that the test item was not mutagenic.

Yangnong provided data on physical and chemical properties of transfluthrin TC with a purity of 98.85% (solubility in water, solubility in organic solvents, n-octanol/water partition coefficient, dissociation characteristics). Based on the studies submitted by the proposer, it can be concluded that transfluthrin has a water solubility of <1.13 mg/L at 20°C in distilled water. Its n-octanol/water partition coefficient (log P_{ow}) is 5.5 and shows a tendency to bioaccumulation. Transfluthrin is readily soluble in most organic solvents (heptane, p-xylene, 1.2 dichloroethane, methanol, acetone and ethyl acetate). The melting temperature was in the range 30.8–32.9°C (purity of 98,5%), which is consistent with the reference profile (32°C).

The Meeting concluded that the purity/impurity and mutagenicity profiles of the transfluthrin TC produced by Jiangsu Yangnong Chemical Co., Ltd, as well as toxicity QSAR data indicated Tier 2 equivalence with the reference profile supporting the existing FAO/WHO specifications (evaluation report 741/2018).

Additional Action Proposed by the Meeting

The Meeting recommended to update the specification for transfluthrin TC to reference the latest version of the CIPAC method for 1*R-trans* permethric acid anhydride (741/TC/M/4) as published in CIPAC Handbook P.

Supporting Information
for
Evaluation Report 741/2021

Physico-chemical properties of transfluthrin

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.34 – 99.47 % and percentages of unknowns were 0.53 – 0.66 %.
Declared minimum transfluthin content	985 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them	Permethric acid anhydride, 0.1 g/kg
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	30.8-32.9°C	98.85	OECD 102	YN-2019-004
Solubility in water	<1.13 mg/L at 20°C	98.85	OECD 105	YN-2019-004
Octanol/water partition coefficient	log K_{OW} = 5.479	98.85	OECD 117,HPLC method	YN-2019-004
Solubility in organic solvents	> 250g/L in heptane at 25°C; > 250g/L in p-xylene at 25°C; > 250g/L in 1,2-dichloroethane at 25°C; > 250g/L in methanol at 25°C; > 250g/L in acetone at 25°C; > 250g/L in ethyl acetate at 25°C	98.85	CIPAC MT 181	YN-2019-004

Formulations and co-formulated active ingredients

The main formulation types available are mosquito coils (MC) and liquid vaporizers (LV). These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

The analytical methods for the active ingredient (including identity tests) are 741/TC/(M)/3 published in CIPAC Handbook K and 741/TC/M/4 published in CIPAC Handbook O. Transfluthrin is determined by GC-FID and internal standardization. This method, in combination with the new chiral identity test, enables the determination of 1*R-trans* and 1*S-trans* enantiomer content.

The analytical method for the relevant impurity permethric acid anhydride is the CIPAC method 741/TC/M/4 published in CIPAC Handbook P.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and CIPAC as indicated in the specification.

Containers and packaging

The technical material may be stored in glass containers, plastic containers or steel drums with appropriate plastic bags.

Expression of the active ingredient

The active ingredient content is expressed as transfluthrin in g/kg.

Annex 1: Hazard Summary Provided by the Proposer

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from transfluthrin 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 transfluthrin technical material based on bacterial in vitro tests

Species	Test	Purity %	Conditions and guideline	Result	Reference
Salmonella typhimurium strains TA1535, TA1537, TA98, TA100 and TA102	Ames Test	98.5	OECD 471 0.0125, 0.0369, 0.1252, 0.3956 and 1.25 mg/plate mixed in DMSO (with and without S9 mix) 37 ± 2°C for 48 hours	Not mutagenic	8982

Annex 2: References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
YN-2019-002	Ms. Chunyan Sun	2019	Validation of Analytical Methodology for the Assay of Active Ingredient and Related Significant Impurities and Subsequent 5-batch Qualitative and Quantitative Analysis of Transfluthrin TC. Study Number YN-2019-002. GLP. Yangnong GLP Laboratory.
8982	S. Srilatha	2019	Bacterial Reverse Mutation Assay with Transfluthrin TC. RCC Study Number 8982. GLP. RCC Laboratories India Private Limited
YN-2019-004	Yuan Zhou	2019	The Determination of Color, Odor, Physical State, pH Values, Solubility in Organic Solvents, Melting Point, Partition Coefficient (n-octanol / water) and Water Solubility for Transfluthrin TC. Study Number YN-2019-004. GLP. Yangnong GLP Laboratory.
JQC-2021-0008	Max Liu	2021	QSAR Prediction Report. Project Number JQC-2021-0008. Hangzhou Jireh Standard Co., Ltd.

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FAO/WHO Evaluation Report 741/2019

Recommendations

The Meeting recommended the following:

(i) The transfluthrin TC from Tagros Chemicals India Private Limited should still be accepted as equivalent to the transfluthrin TC (revised) from Bayer CropScience.
(ii) The revised WHO specification for transfluthrin TC (2018) should be extended to encompass the TC from Tagros Chemicals India Private Limited.

Appraisal

The Meeting considered data for transfluthrin TC submitted in 2019 by Tagros Chemicals India Private Limited.

The data were evaluated to support continuing equivalence with the revised (2018) FAO/WHO specification 741/TC.

The reference specification and supporting data were provided by Bayer CropScience, published and revised in 2018.

In the revised specification (2018 BCS) an additional CIPAC enantioselective analytical method was introduced, which clearly separates transfluthrin (1*R-trans*) from its enantiomer (1*S-trans*) and other stereoisomers (1*S*-cis and 1*R*-cis). This method is published in the CIPAC Handbook O. Bayer CropScience had also previously presented the method for determination of the relevant impurity 1*R-trans* permethric acid anhydride (PAA) in the TC at the CIPAC meeting in 2018, and the method was accepted. This method (CIPAC/5105/m) is available on the CIPAC website. Bayer CropScience had provided a 5-batch analysis report using this new chiral CIPAC method for 1*R*-trans and the new CIPAC method for PAA.

As the revised transfluthrin TC specification will be again the reference specification, the 2018 Meeting recommended that companies having hitherto equivalent TC specifications submit 5-batch data (non-GLP) using these new CIPAC methods to demonstrate, that their material still complies with the revised specification.

The data submitted by Tagros using this enantioselective method clearly prove that the content of 1*R*-trans transfluthrin is above the minimum purity of 985 g/kg. The impurity PAA was not detected in the Tagros TC material at a LOD well lower than the specified limit of 0.1 g/kg. The Meeting regarded this as sufficient, as other parameters like manufacturing process or impurity profile had already been evaluated in the original evaluations and had not changed since then.

As the original batches were not available for any of the equivalent products, Tagros used new batches for the analysis, and this was considered acceptable by the Meeting.

Based on the data submitted the existing Tagros equivalence for transfluthrin TC should be regarded as valid also for the revised specification.

Annex 1. References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
--	P. Gopi M. Sc	2019	Method validation and quantification of 1*R*-trans permethric acid anhydride content in five batches of transfluthrin technical. GLP. Tagros Chemicals India Private Limited. Unpublished.
--	P. Gopi M. Sc	2019	Method validation and quantification of transfluthrin and enantiomer (1*S*-trans) content in five batches of transfluthrin technical. Tagros Chemicals India Private Limited. Unpublished.

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FAO/WHO Evaluation Report 741/2018

Recommendations

The Meeting recommended the following:

(i) The existing specification for transfluthrin TC should be withdrawn.
(ii) The revised specification for transfluthrin TC, proposed by Bayer CropScience, and as amended by the Meeting, should be adopted by WHO as a new reference specification.

Appraisal

A draft specification and supporting data were provided by Bayer CropScience (BCS), Germany in 2016 and evaluated by the Meeting in support of revising the WHO specification for transfluthrin TC.

Transfluthrin is a fast acting pyrethroid insecticide. It is used in household and hygiene products, mainly against flying insects, such as mosquitoes and flies, but also against material pests, such as moths. Transfluthrin is not under patent. Transfluthrin was previously evaluated by WHO in 2002, 2006 and 2015.

Transfluthrin was also evaluated by the European Commission in 2010. Transfluthrin was included in Annex I of Directive 98/8/EC in 2014 with a minimum purity of 965 g/kg. Transfluthrin has two chiral centres and therefore has 4 possible stereoisomers. The active substance is the 1*R-trans* isomer using Rothamsted nomenclature, and all other isomers are considered impurities. CIPAC adopted a new chiral identity test in 2014. This new enantioselective identity test which is now published in the Handbook O (741/TC/M/4) replaces the previous chiral identity test (CIPAC 741/TC/M/3.2, CIPAC Handbook L). A revised reference specification was requested by the proposer on the basis of the availability of the new chiral identity test. The new chiral identity test enables the separation of all 4 stereoisomers. In combination with the achiral CIPAC method 741/TC/(M)/3 from Handbook K, the new chiral identity test also allows the determination of 1*R-trans* and 1*S-trans* enantiomer content by calculation.

The Meeting was provided with commercially confidential information in relation to the proposed technical specification, the manufacturing process and the supporting 5-batch analysis. Mass balances were between 99.4 - 99.7% w/w in the 5-batch data and no unidentified impurities greater than ≥1 g/kg were reported. There are no relevant impurities in the technical material as manufactured in the reference source of the TC. However there is the potential to form 1*R-trans* permethric acid anhydride (PAA) under certain conditions. PAA is known to be highly sensitizing and consequently a maximum limit of 0.1 g/kg is justified according to GHS criteria. The proposer has developed, validated and peer validated a method capable to quantify such maximum limit (0.1 g/kg). The method utilizes high performance liquid chromatography (HPLC) with UV detection and external standard calibration.

The proposer presented the PAA analytical method at the CIPAC meeting in 2018 and the method was accepted. The method (CIPAC/5105/m) is now available on the CIPAC website. The proposer also provided a 5-batch analysis report using the new method for PAA, and the impurity was not detected in the represented batches.

The Meeting considered the revision proposals from BCS in relation to description, identity and minimum purity of the active substance (1*R-trans* isomer). The current minimum specification value (965 g/kg) is based on the sum of 1*R-trans* and 1*S-trans* isomers. The new chiral method was used in the 5-batch analysis and the new minimum specification of 985 g/kg 1*R-trans* was discussed and accepted by the Meeting as in line with the ISO definition. The Meeting noted that the maximum specification limits for impurities included in the original reference specification have decreased or are no longer included in the revised specification. BCS has confirmed that there are no significant changes in the manufacturing process compared to their 2006 WHO submission and that there has been no change in plant location. The company suggested that the change in impurity specification is due to improved quality of starting materials. The meeting also noted that the change in impurity specified values are also due to progress in analytical methodology, and application of statistical considerations (e.g. mean ± 3 SD) to the supporting 5-batch analysis. It was noted that the batches included in the 5-batch analysis were manufactured over a short time period (all manufactured in a period of less than one month), however BCS confirmed that these batches were representative of the quality of their material.

The proposer confirmed that the methods of analysis used for analysis of impurities in the GLP 5-batch analysis were validated according to EU standards. It was noted that the proposer did not analyse for a certain catalyst of interest in the manufacturing process, however the company gave a reasonable explanation to not include the catalyst in the supporting 5-batch analysis based on high analytical closure and clean up steps used in the manufacturing process.

The Meeting noted that BCS has submitted their new 5-batch analysis to the Australian national regulatory authority and that a letter of access was issued to APVMA to allow a comparison of confidential data submitted to the APVMA and WHO. The confidential data on the manufacturing process, declaration of composition, and 5-batch analysis submitted to the WHO were essentially the same as those submitted to the APVMA for national registration.

As the revised transfluthrin TC specification will again be the reference specification, the Meeting recommended that companies having hitherto equivalent TC specifications are requested to submit data packages to demonstrate that their material also complies with the new reference. In the meantime the revised specification should be published.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
M-420775-02-1	S. Dörner-Rieping and H. Junker	2010	Amendment No 1 to: Validation of the GC - method 2201-0342401-02E- Transfluthrin by-products in Transfluthrin technical material by capillary gas chromatography. Study M-420775-02-1. Report PA 11/072. GLP. Bayer CropScience AG, Germany. Unpublished.
M-437186-03-1	S. Dörner-Rieping and H. Junker	2015	Analytical method - Determination of the enantiomeric purity of Transfluthrin (AE 0035474) in technical grade and pure materials by high performance liquid chromatography (HPLC).Study M-437186-03-1. Report AM032712FP3, Bayer CropScience AG, Germany. Unpublished.
M-437198-01-1	S. Dörner-Rieping and C. Perez-Diaz	2012	Validation of the HPLC - method AM032712FP1 - Determination of the enantiomeric purity of Transfluthrin (AE 0035474) in technical grade and pure materials by high performance liquid chromatography (HPLC). Study M-437198-01-1. Report PA12/012. GLP. Bayer CropScience AG, Germany. Unpublished.
M-493872-02-1	S. Dörner-Rieping and H. Junker	2015	Amendement No 1 to: Validation of analytical GC method AM039914FP1- Determination of the chemical purity of Transfluthrin and its enantiomer in technical grade and pure active substance by gas chromatography (GC). Study M-493872-02-1. Report PA14/10. GLP. Bayer CropScience AG, Germany. Unpublished.
M-493873-02-1	S. Dörner-Rieping and H. Junker	2015	Determination of the chemical purity of Transfluthrin and its enantiomer in technical grade and pure active substance by gas chromatography (GC). Study 493873-02-1. Report AM039914FP2. Bayer CropScience AG, Germany. Unpublished.
M-494450-02-1	S. Dörner-Rieping and H. Junker	2015	Determination of organic impurities in technical grade and pure Transfluthrin (AE 0035474) by gas chromatography (GC). Study M-494450-02-1. Report AM039814FP2. Bayer CropScience AG, Germany. Unpublished. *AM043615FP2 is a revised version of method 2201-0342401-02E*
M-527927-01-1	S. Dörner-Rieping and H. Junker	2015	Validation of GC-method AM039814FP2 - Determination of organic impurities in technical grade and pure Transfluthrin (AE 0035474) by gas chromatography (GC). Study M-527927-01-1. Report PA 15/051. GLP. Bayer CropScience AG, Germany. Unpublished.
M-528647-01-1	S. Dörner-Rieping and H. Junker	2015	Material accountability of technical Transfluthrin (AE 0035474). Study M-528647-01-1. Report PA15/056. GLP. Bayer CropScience AG, Germany. Unpublished.
M-549618-01-1	J.Ph. Bascou	2016	Transfluthrin (BCS-AB72848, AE 0035474, NAK 4455) Description of the Manufacturing Process for the Technical Grade Active Substance manufactured by Bayer at Vapi site (India) (Specification No. 102000008838). Study M-549618-01-1. Bayer CropScience AG, Germany. Unpublished
M-625521-01-1	S. Dörner-Rieping and C. Perez-Diaz	2018	Analysis of BCS-CZ92926 in technical Transfluthrin (AE 0035474). Unpublished.
M-625427-01-1	S. Dörner-Rieping and C. Perez-Diaz	2018	Determination of permethric acid anhydride (BCS-CZ92926) in technical grade or pure Transfluthrin (AE 0035474) by high performance liquid chromatography (HPLC). Unpublished.

M-625428-01-1	S. Dörner-Rieping and C. Perez-Diaz	2018	Validation of analytical method AM051418FP1 -Determination of BCS-CZ92926 in technical grade or pure Transfluthrin (AE 0035474) by high performance liquid chromatography (HPLC) Unpublished.

TRANSFLUTHRIN

FAO/WHO Evaluation Report 741/2015

Recommendations

The Meeting recommended the following:

(i) The transfluthrin TC as proposed by Tagros Chemicals India Limited should be accepted as equivalent to the Bayer CropScience reference profile.
(ii) The existing WHO specification for transfluthrin TC should be extended to encompass the corresponding product of Tagros Chemicals India Limited.

Appraisal

The Meeting considered data and information submitted by Tagros chemicals India Limited in support of extension of the existing WHO specification for transfluthrin TC. The data submitted by Tagros chemicals India Limited were largely in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010 - second revision of the First Edition) (Section 3.2).

The Meeting was provided by Tagros chemicals India Limited with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for transfluthrin and all detectable impurities. The manufacturing process provided by Tagros chemicals India Limited is not the same as the one from the reference process and therefore leading to a difference in potential impurities.

The confidential information (manufacturing process, purity and impurity profile) submitted to WHO was confirmed by the Australian Authorities (APVMA) as being identical to that submitted for registration in Australia, and was evaluated and considered acceptable by the APVMA.

The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 741/TC/(M)/3 (GC-FID) was used for determination of transfluthrin content and the capillary GC-FID CIPAC method was used for isomer ratio. The only slight deviation was the use of helium instead of nitrogen as carrier gas in the case of the chiral method. The transfluthrin manufacturing impurities were determined by reverse phase HPLC-UV or GC-FID, except water and acetone insoluble which were determined using the appropriate CIPAC methods. All the analytical methods used in the 5-batch analysis study were fully validated with respect to their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

The minimum purity of transfluthrin in the TC is 965 g/kg and complies with the existing WHO specification. Mass balances are very high (98.9 - 100.2%), with no unknowns detected, and similar to those of the reference profile of Bayer CropScience (99.2 - 99.8%). A number of additional impurities were found in the new source of technical material, however none of these impurities were considered to be relevant.

Tagros provided the Meeting with mutagenicity data (supported by GLP studies) on *Salmonella typhimurium* (reverse mutation Ames test) showing that no mutagenic effect nor induction of chromosomal damages could be observed.

Equivalence could not be determined on the basis of Tier 1.

Tagros provided the Meeting with acute toxicity, irritation and sensitization data, however they provided no physico-chemical properties of pure transfluthrin (vapour pressure, melting point, solubility in water and in organic solvents, octanol / water partition coefficient). These additional Tier-2 data indicated equivalence of the Tagros TC with the reference profile supporting the existing WHO specification.

Supporting Information
for
Evaluation Report 741/2015

Physico-chemical properties of transfluthrin

Table 1. Chemical composition and properties of transfluthrin 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 98.9-100.2% with no unknowns.
Declared minimum transfluthrin content	965 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilizers or other additives and maximum limits for them	None

Methods of analysis and testing

Transfluthrin content is determined by the CIPAC method 741/TC/(M/)3 - gas chromatography with internal standardisation and flame ionisation detection. Identity is confirmed by GC retention time, IR spectrum (CIPAC Handbook K, p.121, 2003) and enantioselective GC (CIPAC Handbook L, p.128, 2005).

The methods for determination of impurities are based on analysis by reverse phase HPLC using UV detection and quantification by external standard.

Annex 1: Hazard Summary Provided by the Proposer

Note:

(i) Tagros Chemicals India Limited confirmed that the toxicological data included in the summary below were derived from transfluthrin 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. Toxicology profile of transfluthrin technical material, based on acute toxicity, irritation, and sensitization

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Rat (F)	Oral	97.81%	OCED 423, 14 days, 2000 mg/kg bw, acute	LD_{50} > 2000 - 5000 mg/kg bw	14_14_076
Rat (M & F)	Dermal	97.81%	OECD 402, 14 days, 2000 mg/kg, acute	LD_{50} > 2000 mg/kg bw	14_14_078
Rat (M & F)	Inhalation	97.81%	OECD 403, 14 days, 1.88 - 3.22 - 5.07 mg/l, acute	LC_{50} = 4.57 mg/l	14_14_079
Rabbit (M)	Skin Irritation	97.81%	OECD 404, 72 hours, 0.5 g	Non-irritant	14_14_077
Rabbit (M)	Eye Irritation	97.81%	OECD 405, 72 hours, 0.1 g	Non-irritant	14_14_081
Guinea pig (M)	Skin sensitizatio n	97.81%	OECD 406, 24 days, 25-50-75-100 mg, Semi-Occlusive (Buehler Test)	Non-sensitizer	14_14_080

Table B. Mutagenicity profile of transfluthrin technical material based on in vitro tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Salmonella typhimurium	Ames test, *in vitro*	97.81	OCDE 471	Negative	14_14_071

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
G10110	B. Jagadish	2015	Five batch analysis of Transfluthrin technical. Study identification number: Not Available. Report identification number: G10110. GLP, Unpublished, Advinus Therapeutics limited. Confidential.
14_14_071	M. Reddi Nagesh B. Tech	2014	Bacterial reverse mutation test of Transfluthrin technical in salmonella Typhimurium tester strains. Study identification number: Not Available. Report identification number: 14_14_071. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_076		2015	Acute Oral toxicity study of Transfluthrin technical in rats. Study identification number: Not Available. Report identification number: 14_14_076. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_078		2014	Acute Dermal toxicity study of Transfluthrin technical in rats. Study identification number: Not Available. Report identification number: 14_14_078. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_079		2015	Acute Inhalation toxicity study of Transfluthrin technical in Wistar rats. Study identification number: Not Available. Report identification number: 14_14_079. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_077		2014	Acute Dermal Irritation/Corrosion study of Transfluthrin technical in rabbits. Study identification number: Not Available. Report identification number: 14_14_077. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_081		2015	Acute Eye Irritation/Corrosion study of Transfluthrin technical in rabbits. Study identification number: Not Available. Report identification number: 14_14_081. GLP, Unpublished, Sa-Ford. Non confidential.
14_14_080		2015	Skin Sensitization maximization study of Transfluthrin technical in Guinea pigs. Study identification number: Not Available. Report identification number: 14_14_080. GLP, Unpublished, Sa-Ford. Non confidential.

TRANSFLUTHRIN

Evaluation Report 741/2006

Recommendation

The Meeting recommended that the specification for transfluthrin, proposed by Bayer CropScience[1*], should be adopted by WHO.

Appraisal

Data in support of a specification for transfluthrin TC were evaluated by the JMPS in 2002 (evaluation report 741/2002) but, at the request of the manufacturer, the specification was not published. In 2004, following submissions of additional information, the manufacturer stated that new 5-batch analytical data would be generated to support production of the TC at a new site and requested reconsideration of the data and proposed specification by the JMPS. The new data and a revised proposed specification for transfluthrin TC were submitted in 2005-6.

The Meeting was provided with commercially confidential information on:

(i) the comparability of data with those submitted for registration in Australia;
(ii) the manufacturing process at the new site;
(iii) the names, structures and methods of analysis of impurities;
(iv) data from analysis of 5 batches and the manufacturing specification at the new site.

The Australian Pesticides and Veterinary Medicines Authority (APVMA) confirmed that:

(i) the new site manufacturing process described is essentially identical to that described in the data submitted for registration in Australia;
(ii) the new site manufacturing specification for transfluthrin TC is identical to the declaration of composition provided for registration in Australia;
(iii) the new site 5 batch analysis data provided to WHO comply with the declaration of composition provided for registration in Australia.

Material accountability in the 5-batch data from the new site was high (99.4-100.1%). One impurity had a reported limit of quantification (0.08 g/kg) above the stated manufacturing QC limit (0.02 g/kg). The impurity was non-relevant and the manufacturing specification for it was below the 1 g/kg threshold, therefore it was disregarded in considering whether or not the new manufacturing specification was within the earlier one. Nonetheless, the manufacturer explained that the impurity is monitored indirectly by determining the level of its precursor and, if the precursor is

<0.02 g/kg, then the impurity is taken to be within the same limit.

The manufacturing process at the new site was identical to that at the previous site and the 5-batch data and manufacturing specification from the new site were all

[1] The manufacturer informed WHO that, in 2002, all Bayer AG assets related to crop protection and environmental science business, including the supporting data, were transferred to Bayer CropScience, which currently has the ownership.

within the previous manufacturing specification. Thus a formal determination of equivalence by the Meeting was unnecessary.

TRANSFLUTHRIN

Evaluation Report 741/2002[4]

Explanation

The data for transfluthrin were evaluated in support of a new WHO specification.

Transfluthrin is/was under patent in Barbados until 2002; Poland, Czech Republic, Slovakia, South Korea, Libya, Syria, Lebanon, Kuwait, Sri Lanka, China, Dominican Republic and Brazil until 2003; Jordan, Pakistan and Taiwan until 2004; Colombia until 2005; Panama until 2007; Denmark, Norway, Finland, Hungary, Pakistan, Malaysia, South Africa, Nigeria, Turkey, Israel, Ireland, Thailand, South Korea, Japan, USA, Mexico, El Salvador, Argentina, Australia and New Zealand until 2008; Canada until 2010.

Transfluthrin has not been evaluated by the FAO/WHO JMPR and WHO/IPCS.

The WHO hazard classification of transfluthrin is “unlikely to present acute hazard in normal use.”

The draft specification and the supporting data were provided by Bayer AG, Leverkusen[5], in 2001.

Uses

Transfluthrin is a fast acting insecticide. It is used in household and hygiene products, mainly against flying insects, such as mosquitoes and flies, but also against material pests, such as moths (Pflanzenschutz Nachrichten Bayer, Special edition, 1995, Bayer AG, Leverkusen).

Identity

Common name

transfluthrin: E-ISO (published)

Synonyms

benfluthrin (Bayer), NAK 4455[6]

Chemical names

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

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

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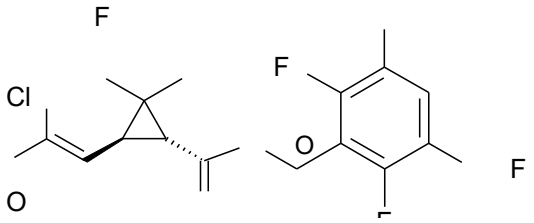
[4] 2006 footnote: minor editorial corrections were introduced in 2006, mainly to clarify the CIPAC status of the analytical method for determination of transfluthrin.

[5] 2006 footnote: the manufacturer informed WHO that, in 2002, all Bayer AG assets related to crop protection and environmental science business, including the supporting data, were transferred to Bayer CropScience, which currently has the ownership.

[6] The development code, NAK 4455, is included because it appears in various references provided by the proposer.

Structural formula



Molecular formula
$C_{15}H_{12}Cl_2F_4O_2$

Relative molecular mass
371.2

CAS Registry number
118712-89-3

CIPAC code number
741

Identity tests
(GC retention time and IR spectrum (CIPAC Handbook K, p. 121, 2003); Enantioselective GC (CIPAC Handbook L, p. 128, 2006))

Physico-chemical properties

Table 1. Physico-chemical properties of pure transfluthrin

Parameter	Value(s) and conditions	Purity %	Method
Vapour pressure	9×10^{-4} Pa at 20°C	97.8	OECD 104
Melting point, boiling point and/or temperature of decomposition	melting point: 32°C boiling point: 242°C decomposition temperature: sublimes at ≥204°C	98	differential scanning calorimetry, OECD 103
Solubility in water	0.057 mg/l at 20°C	97.8	OECD 105
Octanol/water partition coefficient	log K_{OW} = 5.46 at 20°C	97.8	OECD 107
Hydrolysis characteristics	half-life = >1 year at 25°C at pH 5 and pH 7 half-life = 14 days at 25°C at pH 9	min. 94	according to EPA Guideline, Subdivision N, § 161–1 (1982)
Photolysis characteristics	hardly affected by direct photo-degradation but accessible to natural photochemical degradation, through radical-induced oxidation	97.8	not stated
Dissociation characteristics	does not show basic or acidic properties in water	98.4	OECD 112, titration method

Table 2. Chemical composition and properties of transfluthrin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.2 to 99.8%.
Declared minimum [a.i.] content	950 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 or boiling temperature range	32°C melting point, 242°C boiling point

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from transfluthrin having impurity profiles to those referred to in the table above.
(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.
(iii) A summary and references were provided by the proposer. Original reports were not submitted.
(iv) The UK evaluation of transfluthrin (ACP 1997) was considered as part of this evaluation.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat m/f	Oral	Acute, OECD 401	LD_{50} > 5000 mg/kg bw	17160
Mouse m/f	Oral	Acute, OECD 401	LD_{50} = 583-688 mg/kg bw	17156
Rat m/f	Dermal	Acute, OECD 402	LD_{50} >5000 mg/kg bw	17155
Mouse m/f	Dermal	Acute, OECD 402	LD_{50} >= 4000 mg/kg bw	28471
Rat m/f	Inhalation	Acute, OECD 403	LC_{50} >513 mg/m^3	17216
Rabbit	Skin irritation	4 hours, occlusive, OECD 404	Not irritating	15804
Rabbit	Eye irritation	24 hours, OECD 405	Not irritating	15804
Guinea pig	Skin sensitization	Semi-occlusive, OECD 406 (Buehler Test)	Not sensitizing	17920
Guinea pig	Skin sensitization	Semi-occlusive, OECD 406 (M&K)	Not sensitizing	17964

Transfluthrin is of low acute toxicity in the rat, with an LD_{50} of >5000 mg/kg bw via each route of administration and with an acute and dermal NOEL of 100 mg/kg bw/d. The 4 h LC_{50} was >513 mg/m^3 air for male and female rats. The only sign noted during the 14 d observation period was a slight tremor in females for 5 minutes after dosing. Transfluthrin is not a skin or eye irritant, nor a skin sensitizer.

Table 4. Toxicology profile of transfluthrin technical material based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat m/f	Sub-acute oral	Sub-acute, 28 days, OECD 407 0-10-50-250 mg/kg	NOEL = 50 mg/kg bw/d	19187
Rabbit m/f	Sub-acute dermal	Sub-acute, 15 days, OECD 410 0-20-200-2000 mg/kg	NOEL = 1000 mg/kg bw/d	19236
Rat m/f	Sub-acute inhalation	Sub-acute, 4 weeks, OECD 412 0-1.6-6.6-36.6-168.1 mg/m^3 air (6 h/d; 5 d/wk)	NOEL = 36.6 mg/m^3 (≡ 13 mg/kg bw/d)	17588
Dog m/f	Sub-chronic oral diet	Sub-chronic, 13 weeks, OECD 409 0-50-350-2500 ppm	NOEL = 50 ppm (≡ 1.9 mg/kg bw/d)	R4723
Rat m/f	Sub-chronic oral diet	Sub-chronic, 13-18 weeks 0-10-50-500-5000 ppm	NOEL = 50 ppm (≡ 3.5 mg/kg bw/d)	19756
Rat m/f	Sub-chronic inhalation	Sub-chronic, 90 days 0-4.9-46.7-220.2 mg/m^3 air (6 h/d; 5 d/wk)	LOEL = 46.7 mg/m^3 (≡ 17 mg/kg bw/d)	18417
Dog m/f	Chronic oral diet	Chronic, 52 weeks, OECD 452 0-30-300-3,000 ppm	NOEL < 30ppm (≡ 0.75 mg/kg bw/d)	22638
Dog m/f	Chronic oral diet	Chronic, 53 weeks, OECD 452. 0-10 ppm	NOEL = 10ppm (≡ 0.25 mg/kg bw/d)	22678
Rat m/f	Carcinogenicity and Chronic toxicity diet	Chronic, 2 years, OECD 453 0-20-200-2,000 ppm	NOEL = 20 ppm (≡ 1,0 mg/kg) NOEL for carcinogenicity = 200 ppm (≡ 9.9 mg/kg bw/d)	22375
Mouse m/f	Carcinogenicity and chronic toxicity diet	Oral feed, 2 years, OECD 451. 10, 100, and 1000 ppm diet, i.e. 2, 20, and 200 mg/kg bw/d for males, 3, 33 and 280 mg/kg bw/d for females	Males: NOAEL = 100 ppm (≡ 20mg/kg bw/d) Females: NOEL could not be determined as clinical changes were observed at the lowest dose level. Liver adenomas were observed in females at 1000 ppm dose level	22744
Rat m/f	Multi-generation study oral diet	Oral diet, 84 days, OECD 416 0-20-200-1000ppm	NOAEL = 220ppm Parental NOAEL = 200ppm (= 9 to 38 mg/kg) Neonatal NOAEL = 1,000ppm (= 50 mg/kg calculated) Reproductive NOAEL = 1,000 ppm (= 45 to 191 mg/kg)	R5352
Rat f	Developmental toxicity, gavage	10 days 0-25-55-125 mg/kg/d	Maternal NOAEL = 25mg/kg bw/d Developmental NOAEL = 125mg/kg bw/d	MTD0058
Rabbit f	Developmental toxicity, oral feed [gavage]	13 days 0-15-50-150 mg/kg/d	Maternal NOAEL = 15mg/kg bw/d Developmental NOAEL = 150 mg/kg bw/d	18069

In the rat, mortalities and body tremors were seen at 250 mg/kg/d following gavage dosing. There were no mortalities following dietary administration of up 5000 ppm (approximately 40 mg/kg bw/d).

A low incidence of urinary bladder papillomas/carcinomas was observed in rats at a dietary level of 2000 ppm of transfluthrin[7]. In female mice, an increased incidence of liver adenomas, but not of carcinomas, was observed at 1000 ppm, the highest dose level tested. In 2-stage studies on promoting effects in rat liver cells with diethylnitrosamine as the initiator, transfluthrin had no initiating activity but was a weak promotor (22888). Transfluthrin did not induce hepatocyte proliferation or increase mitoses in the liver *in vivo* (R5555).

Developmental studies in both the rat and rabbit provided no evidence of teratogenicity when transfluthrin was administered at doses up to 125 and 150 mg/kg bw/d, respectively. NOELs of 25 and 15 mg/kg bw/d were established for maternal toxicity in the rat and rabbit respectively.

In a dietary multi-generation reproductive toxicity study in the rat, there was no evidence of teratogenicity, foetoxicity or reproductive toxicity in rats administered transfluthrin at doses up to 191 mg/kg bw/d. NOELs of 45 to 191 and 9 to 38 mg/kg bw/d were established for reproductive and parental toxicity, respectively.

Table 5. Mutagenicity profile of the transfluthrin technical material based on in vitro and *in vivo* tests.

Test system	Test object	Concentration	Purity	Results	Reference
In vitro, Point mutation assays					
Salmonella microsome test	*S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537)	20 to 12500 µg/plate, with and without S9 activation	96.0%	negative	15144
Salmonella microsome test	*S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537)	20 to 12500 µg/plate, with and without S9 activation	94.5%	negative	16084
HPRT-test	Chinese hamster ovary (CHO) cells	25 to 100 µg/ml, with and without S9 activation	94.8%	negative	18148
mitotic recombination assay	*Saccharomyces cerevisiae* D7	625 to 10000 µg/ml, with and without S9 activation	94.5%	negative	16083
In vitro, DNA damage assays					
unscheduled DNA synthesis	primary rat hepatocytes	1 to 500 µg/ml	94.9%	negative	21313
sister chromatid exchange	Chinese hamster ovary (CHO) cells	0.0667 to 2000 µg/ml with and without S9 activation	94.8%	negative	R4718
In vivo, DNA damage assays					
unscheduled DNA synthesis	mouse BOR:CFW1 hepatocytes	780 and 5580 mg/kg body weight	95.0%	negative	R3658
In vitro, Chromosomal damage/aberration assays					
cytogenetic study	human lymphocytes	50 to 200 µg/ml, with and without S9 activation	94.8%, 95.0%	negative	18742
In vivo, Chromosomal damage/aberration assays					

[7] The proposer noted that the effect was most likely attributable to a non-genotoxic mechanism of chronic urothelial irritation and regeneration, induced by transfluthrin or one of its metabolites (Cohen & Ellwein 1990; Bayer 1999).

Test system	Test object	Concentration	Purity	Results	Reference
micronucleus test	male and female NMRI-mouse bone marrow cells	375 mg/kg body weight	95.0%	negative	16912
^{32}P-post-labelling assay for detection of adduct formation	male and female Wistar-rat hepatocytes and urinary bladder cells	7 x 100 and 7 x 250 mg/kg body weight	94.7%	negative	R6335

Transfluthrin was not mutagenic *in vitro* in bacteria, yeast or mammalian cells with or without metabolic activation, neither was the any evidence of mutagenicity from *in vivo* tests on rats and mice.

Table 6. Ecotoxicology profile of transfluthrin technical material.

Species	Test	Duration and conditions	Result	Reference
Colinus virginianus (bobwhite quail)	Acute toxicity	14 days, OECD 401	LD_{50} > 2000 mg/kg NOEL = 2000 mg/kg	VB-003
Serinus canarius (Canary bird)	Acute toxicity	14 days, OECD 401	LD_{50} > 2000 mg/kg NOEL = 2000 mg/kg	VK315
Salmo gairdneri (rainbow trout)	Acute (flow through conditions)	96 hours, OECD 203	LC_{50} = 0.7 µg/l NOEC = 0.5 µg/l *	FF-220
Leuciscus idus melanotus (golden orfe)	Acute (flow through conditions)	96 hours, OECD 203	LC_{50} = 1.25 µg/l NOEC = 0.89 µg/l	F0-1108
Daphnia magna (water flea)	Acute toxicity	48 hours, OECD 202	EC_{50} = 1.2 µg/l NOEC = 0.33 µg/l	1091 A/01 D
Scenedesmus subspicatus (green alga)	Growth inhibition	72 hours, OECD 201	EC_{50} > 0.044mg/l NOEC = 0.017 mg/l	1091 A/01 AI
Eisenia foetida (earthworm)	Acute toxicity	14 days, OECD 207	LC_{50} = 194 mg/kg NOEC = 32 mg/kg	HBF/RG15 2
Activated sludge	Microbial respiration rate inhibition	3 hours, OECD 209	EC_{50} = 10 000 mg/l	1091 A/01 B

* It was unclear why the difference between LC_{50} and NOEC values was so small.

Environmental fate and behaviour

Tests of hydrolysis for transfluthrin at 25°C for 36 d gave a half-life of 14 d at pH 9 and >1 year at pH 7 and 5. Under the test conditions transfluthrin did not readily hydrolyse and, considering the very low water solubility and strong adsorption characteristics of the compound, hydrolysis is expected to play a minor role in the degradation of transfluthrin in the environment.

Transfluthrin underwent photolysis when irradiated with light of wavelengths

> 290 nm with an extrapolated half-life of 17 h[8]. A calculation to determine the rate of degradation of transfluthrin in air estimated the half-life to be 4.1 d.

[8] The UV absorption spectrum of transfluthrin indicates that direct photodegradation should not occur. Indirect photodegradation, by radicals generated coincidentally in the surrounding medium, was responsible for an extrapolated half-life of 17 h. In a more recent study, the half-life of indirect photodegradation was determined as 26 h (3467).

Hazard summary

Environmental toxicity tests showed that transfluthrin is of low toxicity to algae, earthworms and birds but is highly toxic to fish and daphnia. If classified using the criteria laid out in the Globally Harmonized System for classification and labelling of chemicals (UN, 2003), transfluthrin would be classified in the category Acute I, in its lower band.

Transfluthrin has not been evaluated by the WHO IPCS but the IPCS hazard classification based on acute toxicity of transfluthrin is "*unlikely to present acute hazard in normal use*" (WHO, 2002).

The FAO/WHO JMPR has not evaluated transfluthrin but the UK evaluation of the compound (ACP, 1997) was considered as part of this evaluation. The Australian Therapeutic Goods Administration of the Commonwealth Department of Health and Ageing has set an ADI of 0 to 0.003 mg/kg/d, based on the NOEL of 0.25 mg/kg bw/d for chronic dietary intake by dogs (TGA 2001).

Formulations

The main formulation types available are mosquito coils (MC) and liquid vaporizers (LV), which are registered and sold in many countries throughout the world.

Methods of analysis and testing

The analytical methods for determination of transfluthrin (including identity tests) in the TC. SL and LV are full CIPAC methods (CIPAC 2003, CIPAC 2006). Transfluthrin is determined by capillary gas chromatography with internal standardization (dipentylphthalate) and flame ionization detection.

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

Physical properties

The limits proposed for physical properties (acidity and alkalinity) of the technical material and the methods for testing them comply with the requirements of the FAO/WHO Manual (FAO/WHO, 2002).

Containers and packaging

The technical active may be stored in glass containers, plastic containers or steel drums with appropriate plastic bags.

Expression of the active ingredient

The active ingredient content is expressed as transfluthrin in g/kg.

Appraisal

There is currently no WHO specification for transfluthrin and this was a new application by Bayer AG, Leverkusen.

Transfluthrin is a synthetic pyrethroid insecticide used in household and hygiene products, mainly for the control of flying insects such as mosquitoes and flies. It has been approved for use in about 50 countries worldwide. The main formulation types

available are mosquito coils and aerosols. Evaluation of specifications for public health use was restricted to the TC.

Transfluthrin is of low acute and dermal toxicity and is classified as unlikely to present acute toxicity in normal use by the IPCS. It is not a skin or eye irritant, nor a skin sensitizer.

In a dietary multi-generation reproductive toxicity study in the rat, there was no evidence of teratogenicity, foetoxicity or reproductive toxicity in rats administered transfluthrin at doses up to 191 mg/kg bw/d.

Transfluthrin induced a low frequency of urinary bladder adenomas/carcinomas in rats at high doses – the NOEL for non-cancer endpoints was 20 ppm, for cancer, 200 ppm, and the urinary tumours were observed at a level of 2000 ppm diet. It also induced adenomas in female mice at a high dose level. Transfluthrin had no initiating activity, but was a weak promotor of carcinogenicity. Transfluthrin was consistently negative in mutagenicity studies in vitro and in vivo; it is concluded that the tumours induced at high dose in rats and female mice are probably not produced by a genotoxic mechanism. Field and laboratory tests showed that transfluthrin is of low toxicity to algae, birds and earthworms but it is highly toxic to fish and aquatic invertebrates such as daphnia.

If classified according to the Globally Harmonized System for classification and labelling of chemicals, transfluthrin would be classified in category Acute I, lower band.

The FAO/WHO JMPR has not evaluated transfluthrin. However, the Australian authorities have set an ADI of 0 to 0.003 mg/kg bw/d (TGA 2001).

The meeting considered the issue of relevant impurities. WHO/PCS noted that the toxicity studies were all performed using transfluthrin with "similar" impurity profiles and the results showed not only a generally low toxicity but also the absence of unexpected effects. Information provided by the proposer indicated that, at the levels found in the 5 batch analysis, none of the impurities is likely to be associated with important toxic effects. WHO/PCS therefore concluded that none of the impurities was relevant and the meeting concurred with this view.

There were some minor differences in the declared composition of the technical material submitted for registration in the UK and that submitted to the WHO, in that the batch analysis data and manufacturing limits submitted to WHO indicated somewhat lower concentrations of certain impurities. The proposer explained that these were due to improvements in the quality of raw materials used and manufacturing improvements, made as part of the transition from pilot-scale to large- scale production.

CIPAC has adopted the analytical method for determination of the active ingredient in the technical material (including identity tests based on diastereoisomer ratio and stereoisomer ratios and infra-red spectroscopy) and in SL and LV formulations, which renders it acceptable for support of the specification for the TC. Transfluthrin is determined by capillary gas chromatography with internal standardization. The proposer has verified that the analytical method is capable of separation of the diastereoisomers of transfluthrin, i.e. that the corresponding cis-isomers would be separated and detected if present and would not be included in the measurement of transfluthrin (CIPAC, 2003).

Recommendations

The meeting recommended that the proposed specification for the technical material should be adopted by WHO[9].

References

Bayer document number or other reference	Year and title of report or publication details
1091 A/01 AI	2001. NAK 4455 (Bayothrin) - Acute Daphnia toxicity.
1091 A/01 B	2001. NAK 4455 (Bayothrin) Toxicity to bacteria.
1091 A/01 D	2001. NAK 4455 (Bayothrin) - Acute Daphnia toxicity.
15144	1986. NAK 4455, *Salmonella* microsome test to evaluate for point-mutagenic effect.
15804	1987. NAK 4455, study for irritant/corrosive potential for skin and eye (rabbit).
16083	1987. NAK 4455, test on *S. cerevisiae* D7 for the induction of mitotic recombination.
16084	1987. NAK 4455 techn., *Salmonella* microsome test to evaluate for point-mutagenic effect.
16912	1988. NAK 4455, micronucleus test on the mouse to evaluate for clastogenic effects.
17155	1988. NAK 4455 techn., study for acute dermal toxicity to rats.
17156	1988. NAK 4455 techn., study for acute oral toxicity to mice.
17160	1988. NAK 4455 techn., study for acute oral toxicity to rats.
17216	1988. NAK 4455 (c.n.: Benfluthrin, proposed), study for subacute inhalation toxicity to OECD guideline no. 403.
17588	1989. NAK 4455 (c.n.: Benfluthrin, suggested), study for subacute inhalation toxicity to the rat to OECD guideline no. 412.
17920	1989. NAK 4455 techn., study for skin-sensitizing effect on guinea pigs (Buehler test).
17964	1989. NAK 4455 techn., studies for skin-sensitizing effect on guinea-pig (Magnusson and Kligman´s Maximization test).
18069	1989. NAK 4455, study for embryotoxic effects on rabbits after oral administration.
18148	1989. NAK 4455, mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay *in vitro*.
18417	1989. NAK 4455 (c.n.: Benfluthrin , suggested), study for subchronic inhalation toxicity to the rat.
18742	1990. NAK 4455, *in vitro* cytogenetic study with human lymphocytes for the detection of induced clastogenic effects.
19187	1990. NAK 4455, subacute oral study of toxicity to rats.
19236	1990. NAK 4455 techn., subacute dermal study of toxicity to rabbits.
19756	1990. Subchronic toxicological study in rats (administration in the diet for up to 18 weeks).
21313	1992. NAK 4455, mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro.
22375	1993. NAK 4455, study for chronic toxicity and cancerogenicity in Wistar rats (administration in the diet for 2 years).
22638	1993. NAK 4455, chronic toxicity study in dogs (52-week feeding study).
22678	1993. NAK 4455, chronic toxicity study in dogs with oral administration (52-week feeding study).

[9] In 2004, following submissions of additional information and stating that new 5-batch analytical data would be generated to support production of the TC at a new site, the manufacturer requested reconsideration of the data and specification by the JMPS. Therefore the specification recommended for adoption in 2002 was not published.

22744	1993. NAK 4455, study for oncogenicity in B6C3F1 mice after administration in the diet for two years.
22888	1994. NAK 4455, study for possible promotion effect of the liver of male Wistar rats (Administration in diet for approx. 8 weeks).
28471	1999. NAK 4455 (c.n. Transfluthrin (prop.)) – study for acute dermal toxicity in mice.
3467	1991. Experiments concerning the indirect photodegradation of Benfluthrin in aqueous solutions.
ACP 1997	Transfluthrin Use as a Public Hygiene Insecticide – An Evaluation by the Advisory Committee on Pesticides, United Kingdom, September 1997.
Bayer 1999	1999. Transfluthrin evaluation bioassay of carcinogenicity. Expert Opinion.
CIPAC, 2003	Transfluthrin Technical and Transfluthrin SL, CIPAC Handbook K, p. 121
CIPAC, 2006	Transfluthrin Technical, Stereospecific Identity Test and Transfluthrin LV, CIPAC Handbook L, p. 128
Cohen & Ellwein,	S. M. Cohen and L.B. Ellwein. Cell proliferation in carcinogenesis. *Science* 249, 1007-1011, 1990.
F0-1108	1988. Acute toxicity of NAK 4455 to golden orf (*Leuciscus idus melanotus*) in a flow-through-test.
FAO 1999	Manual on Development and Use of FAO and WHO Specifications for Pesticides, 1st Edition, Rome 2002.
FF-220	1988. Acute toxicity of NAK 4455 to rainbow trout (Salmo Gairdneri) in a flow-through-test.
HBF/RG152	1991. Toxicity of NAK 4455 (techn.) to earthworms.
MTD0058	1988. Teratology study in the rat with NAK 4455.
R3658	1986. Influence of NAK 4455 on DNA metabolism.
R4718	1989. Mutagenicity test on NAK 4455 in an in vitro cytogenicity assay measuring sister chromatid exchange frequencies in Chinese hamster ovary (CHO) cells.
R4723	1989. 13-week oral toxicity (feeding) study with NAK 4455 tech. in the dog.
R5352	1991. NAK 4455 technical, multiple generation reproduction study in rats.
R5555	1992. Cell proliferation study in rats treated with NAK 4455.
R6335	1995. ^{32}P post-labelling assay for detection of adduct formation by transfluthrin (NAK 4455) in rat liver and urinary bladder DNA.
TGA 2001	ADI List, Therapeutic Goods Administration, Commonwealth Department of Health and Ageing, Australia. December 2001.
UN 2003	Globally Harmonized System of Classification and Labelling of Chemicals. United Nations, New York and Geneva, 2003.
VB-003	1987. Acute oral LD50 of NAK 4455 to bobwhite quail.
VK315	1987. Acute oral LD50 of NAK 4455 to the canary bird (*Serinus canarius*).
WHO, 2002	The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002, Document WHO/PCS/01.5. WHO, Geneva, 2002.