WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

CHLORFENAPYR

4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-1*H*-pyrrole-3-carbonitrile

World Health Organization

TABLE OF CONTENTS

Disclaimer 3

Introduction 4

Part One: Specifications 5

Chlorfenapyr Information 6
Chlorfenapyr Technical Material 7
Chlorfenapyr Suspension Concentrate 8

Part Two: Evaluation Reports 10

FAO/WHO Evaluation Report 570/2024.2 11

Supporting Information 13
Annex 1: Hazard Summary Provided by the Proposer 15
Annex 2: References 16

FAO/WHO Evaluation Report 570/2024.1 17

Supporting Information 19
Annex 1: Hazard Summary Provided by the Proposer 20
Annex 2: References 22

WHO Evaluation Report 570/2022.3 23

FAO/WHO Evaluation Report 570/2022.2 24

Supporting Information 27
Annex 1: Hazard Summary Provided by the Proposer 28
Annex 2: References 30

FAO/WHO Evaluation Report 570/2022.1 31

Supporting Information 35
Annex 1: Hazard Summary Provided by the Proposer 36
Annex 2: References 38

FAO/WHO Evaluation Report 570/2021 39

Annex 1: References 41

FAO/WHO Evaluation Report 570/2017 42

Annex 1: References 43

FAO/WHO Evaluation Report 570/2014 44

Supporting Information 46
Annex 1: Hazard Summary Provided by the Proposer 50
Annex 2: References 62

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.

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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[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 chemical pesticides." This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS).

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

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

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual and supported by other information sources. 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 Internet under the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/prequal/vector-control-products

PART ONE: SPECIFICATIONS

CHLORFENAPYR

Page

Chlorfenapyr Information 6
Chlorfenapyr Technical Material 7
Chlorfenapyr Suspension Concentrate 8

Chlorfenapyr Information

ISO common name

Chlorfenapyr (ISO 1750 approved)

Synonyms

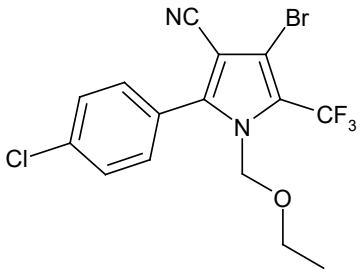
None

Chemical names

IUPAC 4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-*1H*-pyrrole-3-carbonitrile

CA 4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-*1H*-pyrrole-3-carbonitrile

Structural formula



Molecular formula

$C_{15}H_{11}BrClF_3N_2O$

Relative molecular mass

407.6

CAS Registry number

122453-73-0

CIPAC number

570

Identity tests

HPLC retention time, IR spectrum, mass spectrum, UV spectrum, ^{1}H-NMR spectrum.

Chlorfenapyr Technical Material

WHO specification 570/TC (December 2024∗)

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 (570/2014, 570/2017, 570/2022.1, 570/2022.2, 570/2022.3, 570/2024.1, 570/2024.2). 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 (570/2014, 570/2017, 570/2022.1, 570/2022.2, 570/2022.3, 570/2024.1, 570/2024.2), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of chlorfenapyr together with related manufacturing impurities and shall be an off-white to tan halide-smelling solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 Identity tests (570/TC/M/2, CIPAC Handbook O, p.23, 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 Chlorfenapyr content (570/TC/M/3, CIPAC Handbook O, p.23, 2017)

The chlorfenapyr content shall be declared (not less than 940 g/kg), and, when determined, the average measured content shall not be lower than the declared minimum content.

∗ 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

Chlorfenapyr Suspension Concentrate

WHO specification 570/SC (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 (570/2014, 570/2017, 570/2021). This specification should be applicable to relevant products of these manufacturers 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 (570/2014, 570/2017, 570/2021), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical chlorfenapyr, complying with the requirements of WHO specification 570/TC, in the form of off-white to tan, mildly sweet smelling liquid, in an aqueous phase together with suitable formulants. After gentle agitation, the material shall be homogeneous (Note 1) and suitable for further dilution in water.

2 Active ingredient

2.1 Identity tests (570/SC/M/2, CIPAC Handbook O, p.26, 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 Chlorfenapyr content (570/SC/M/3, CIPAC Handbook O, p.26, 2017)

The chlorfenapyr content shall be declared (240 g/l at 20 ± 2ºC, Note 2), and when determined, the average measured content shall not differ from that declared by more than ± 6%.

3 Physical properties

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

Maximum "residue": 5%.

3.2 Spontaneity of dispersion (MT 160, CIPAC Handbook F, p.391, 1995) (Note 3)

Minimum: 80% after 5 min in CIPAC Standard Water D at 30 ± 2°C.

3.3 Suspensibility (MT 184.1, CIPAC Handbook P, p.245, 2021 and 570/SC/M/4, CIPAC Handbook O, p.27, 2017) (Note 3)

Minimum: 70% after 30 minutes in CIPAC Standard Water D at 25 ± 5°C

3.4 Wet sieve test (MT 185, CIPAC Handbook K, p.149, 2003) (Note 4)

Maximum: 2% of the formulation shall be retained on a 75 µm test sieve.

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

*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

Maximum: 50 ml after 1 min.

4 Storage stability

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

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clauses for:

- suspensibility (3.3)
- wet sieve test (3.4).

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 6), and the formulation shall continue to comply with the clauses for:

- pourability (3.1)
- spontaneity of dispersion (3.2)
- suspensibility (3.3)
- wet sieve test (3.4).

Note 1 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Note 2 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 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 results equal to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Note 4 This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials, which could cause blockage of spray nozzles or filters in the spray tank.

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

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

PART TWO: EVALUATION REPORTS

CHLORFENAPYR

		Page
2024.2	**FAO/WHO evaluation report** based on submission of data from Shivalik Rasayan Limited (TC)	**11**
	Supporting information	**13**
	Annex 1: Hazard summary provided by the proposer	**15**
	Annex 2: References	**16**
2024.1	**FAO/WHO evaluation report** based on submission of data from Tagros Chemicals India Pvt. Ltd. (TC)	**17**
	Supporting information	**19**
	Annex 1: Hazard summary provided by the proposer	**20**
	Annex 2: References	**22**
2022.3	**WHO evaluation report** based on submission of data from BASF for additional manufacturing sites (TC)	**23**
2022.2	**FAO/WHO evaluation report** based on submission of data from Shandong Weifang Shuangxing Pesticide Co. Ltd. (TC)	**24**
	Supporting information	**27**
	Annex 1: Hazard summary provided by the proposer	**28**
	Annex 2: References	**30**
2022.1	**FAO/WHO evaluation report** based on submission of data from Shijiazhuang Richem Co., Ltd. (TC)	**31**
	Supporting information	**35**
	Annex 1: Hazard summary provided by the proposer	**36**
	Annex 2: References	**38**
2021	**FAO/WHO evaluation report** based on submission of data from Tianjin Yorkool International Trading Co., Ltd (SC)	**39**
	Annex 1: References	**41**
2017	**FAO/WHO evaluation report** based on submission of data from BASF (TC, SC)	**42**
	Annex 1: References	**43**
2014	**FAO/WHO evaluation report** based on submission of data from BASF (TC, SC)	**44**
	Supporting information	**46**
	Annex 1: Hazard summary provided by the proposer	**50**
	Annex 2: References	**62**

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2024.2

Recommendations

The Meeting recommended the following:

(i) The chlorfenapyr TC as proposed by Shivalik Rasayan Limited should be accepted as equivalent to the chlorfenapyr reference profile.

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

(iii) The existing WHO specification for chlorfenapyr TC should be extended to encompass the technical material produced by Shivalik Rasayan Limited.

Appraisal

The Meeting considered data and information submitted by Shivalik Rasayan Limited in 2023 and 2024 in support of the extension of the existing FAO and WHO specifications for chlorfenapyr TC (FAO Specification 570/TC 2014; WHO Specification 570/TC September 2022).

The data submitted met the requirements of the Manual on development and use of FAO and WHO specifications for chemical pesticides (2022 – Second Edition).

The manufacturer submitted confidential data on the manufacturing process and five batch analysis data on all detectable impurities present at or above 1 g/kg, and their manufacturing limits in the TC. Mass balances ranged from 99.79% – 98.86% in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and are statistically justified. The proposer declared the minimum purity of the chlorfenapyr TC as 970 g/kg which is statistically justified (mean value-3 standard deviation = 982 g/kg) and is higher than the minimum purity in the FAO/WHO reference specification. The 5-batch analysis study report indicates that no other significant impurities (each at or above 1 g/kg) were found in any of the 5 batches.

Shivalik Rasayan Limited stated that their chlorfenapyr TC has been registered in Australia and India. A notice of approval has been received for Australia (APVMA, December 2024) and a notice for manufacture for export for India (F.No.434360-Export/9(3)2023, July, 2023). The applicant for APVMA's notice of approval is Opal Pharmaceuticals Pty Ltd., a subsidiary of Shivalik Rasayan Limited.
The batch analysis study was performed according to the principles of GLP. The CIPAC method (570/TC/M/3) was not used for the determination of chlorfenapyr in the batch analysis study; instead, a fully validated in-house method based on the CIPAC method was used.

Impurities were determined by fully validated in-house methods using HPLC-DAD, GC-FID, or by CIPAC MT methods.

All the analytical methods used in the batch analysis study were adequately validated with their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

Process reagents were sought in the batches and were not detected. Consideration of the potential relevance of the process reagents was provided by JMPS toxicologists. The Meeting concluded that the process reagents could be considered as non-relevant.

A bacterial reverse mutation test (OECD 471) was submitted. The results of the study show that Chlorfenapyr TC produced by Shivalik Rasayan Limited does not show mutagenicity in *in vitro* bacterial assays under the conditions of this study.

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

TC melting point test report was submitted. Data on temperature of decomposition, vapour pressure, octanol/water partition coefficient, solubility in water and solubility in organic solvents of technical chlorfenapyr were as well provided. These physical-chemical properties were in agreement with the reference material.

On the basis of Tier-1 data provided by Shivalik Rasayan Limited (manufacturing process, purity/impurity profile, batch analysis data, mutagenicity profile), the Meeting concluded that chlorfenapyr TC from Shivalik Rasayan Limited should be considered as equivalent to the reference profile supporting the existing FAO Specification 570/TC 2014; WHO Specification 570/TC September 2022.

Supporting Information
for
Evaluation Report 570/2024

Table 1. Physico-chemical properties of pure chlorfenapyr

No data provided. Instead, data were provided for the TC.

Table 2. Chemical composition and properties of Chlorfenapyr 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 or WHO. "Mass balances were 98.86% (988.61g/Kg) to 99.79% (997.94 g/Kg) and percentages of unknowns were 1.14% (11.39 g/Kg) to 0.21% (2.06 g/Kg)."
Declared minimum chlorfenapyr 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	101.3 ± 0.58 °C	98.4	OECD 102	2023-08-015
Temperature of decomposition	188 °C	98.4	OECD 102	23511
Vapour pressure	8.6×10^{-6} Pa at 20 °C 9.3×10^{-6} Pa at 40 °C	98.4	OECD 104 (Gas saturation method)	2023-08-009
Octanol/water partition coefficient	log P_{OW} =4.4 (pH 5.0) log P_{OW} =4.4 (pH 7.0) log P_{OW} =4.4 (pH 9.0)	98.4	OECD 117 (HPLC method)	2023-08-012
Solubility in water	At 20 ± 0.5 °C: 0.000126 g/l (pH 5.0) 0.000123 g/l (pH 7.0) 0.000135 g/l (pH 9.0)	98.4	OECD 105 (Shake flask)	2023-08-011
Solubility in organic solvents	At 30.5 ˚C: n-heptane: 7.20 g/l p-Xylene: 319.57 g/l 1,2-dichloroethane: 404.35 g/l methanol: 56.56 g/l acetone: 536.43 g/l ethyl acetate: 311.77 g/l	98.4	OECD 105 CIPAC MT 181 (Shake flask)	2023-08-010

Annex 1: Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from chlorfenapyr having impurity profiles similar to those referred to in the table above.

(ii) (ii) The conclusions expressed in the summary below are those of the proposer unless otherwise specified.

Table A. Mutagenicity profile of chlorfenapyr technical material based on in vitro tests

Species	Test	Purity %	Guideline, duration, doses, and conditions	Result	Study number
Salmonella typhimurium Strains *TA98,* *TA100,* *TA102* *TA1535* *TA1537*	Bacterial Reverse Mutation Test	98.4	OECD 471. Doses: 3.12, 6.25, 12.5 25 and 50 µg/plate in DMSO with and without metabolic activation	Non-Mutagenic	23418

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
2023-07-010	Mr. Sachin Tambe	2023	Five Batch analysis of Chlorfenapyr Technical. Study No. 2023-07-010. GLP. M/s NACL Industries Limited, India. Unpublished
2023-08-015	Yadav A.	2023	Determination of melting point of Chlorfenapyr Technical. Study No. 2023-08-015. GLP. M/s NACL Industries Limited, India. Unpublished
2023-08-010	Yadav A.	2023	Determination Solubility in Organic Solvents of Chlorfenapyr Technical. Study No. 2023-08-010. GLP. M/s NACL Industries Limited, India. Unpublished
2023-08-011	Yadav A.	2023	Determination Solubility in Water of Chlorfenapyr Technical. Study No. 2023-08-011. GLP. M/s NACL Industries Limited, India. Unpublished
2023-08-009	Yadav A.	2023	Determination of Vapour Pressure of Chlorfenapyr Technical. Study No. 2023-08-009. GLP. M/s NACL Industries Limited, India. Unpublished
2023-08-012	Yadav A.	2023	Determination of Partition Coefficient of Chlorfenapyr Technical. Study No. 2023-08-012. GLP. M/s NACL Industries Limited, India. Unpublished
23511	Arthi K.	2023	Determination of Decomposition Temperature of Chlorfenapyr Technical. Study No. 23511. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
23418	Magesh V.	2023	Reverse Mutation (in vitro) of Chlorfenapyr Technical. Study No. 23418. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
23476	Mohamed Assalam S.	2023	Method Validation for AMES of Chlorfenapyr Technical. Study No. 23476. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
-	APVMA	2024	Notice of Approval for Chlorfenapyr Technical produced by Shivalik Rasayan Limited

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2024.1

Recommendations

The Meeting recommended the following:

(i) The chlorfenapyr TC as proposed by Tagros Chemicals India Pvt. Ltd. should be accepted as equivalent to the chlorfenapyr reference profile.

(ii) The existing WHO chlorfenapyr TC specification should be extended to encompass the technical material produced by Tagros Chemicals India Pvt. Ltd.

Appraisal

The Meeting considered data and information submitted in 2023 and 2024 by Tagros Chemicals India Pvt. Ltd. (Tagros) in support of an extension of the existing WHO specification for chlorfenapyr TC.

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

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

Tagros stated that their chlorfenapyr TC has been registered in Australia. A notice of approval has been received (APVMA, May 2024).

The batches analysed in the 5-batch study were produced over 5 months in 2023. The mass balance in the 5 batches ranged from 988.39 to 992.38 g/kg. The specified minimum purity of chlorfenapyr in the TC is 970 g/kg, which is higher than the limit of 940 g/kg specified in the published TC specification. Two new organic impurities not found in the reference source were detected in Tagros TC. The maximum limits for the impurities were supported by the 5-batch data and are statistically justified. The 5-batch analysis study report indicates that no other significant impurities (each at or above 1 g/kg) were found in any of the 5 batches.

The potential relevance of one of the new impurities was assessed based on its structural similarity with chlorfenapyr and *in silico* prediction of toxicity (Derek Nexus v 6.3.0). The Meeting concluded that this new impurity should be considered as non-relevant at the specified limit.

The other new impurity, a residual solvent, was also considered for its potential relevance. Based on available toxicological information and the criteria of the Manual, the Meeting concluded that this new impurity should be considered as non-relevant at the specified limit.

The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 570/TC/M/3 (HPLC on a reversed phase column with UV detection and external standardization) was used for the determination of chlorfenapyr in the technical material. In-house methods (HPLC with UV detection, or GC with flame ionization detection) were used for the determination of organic manufacturing

impurities. Water was determined using the CIPAC method MT 30.6 (Karl Fischer titration). All the analytical methods used in the 5-batch analysis study were adequately validated with their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

Chlorfenapyr TC test reports on solubility in organic solvents (CIPAC MT 181) and on melting point (OECD 102, CIPAC MT2) were submitted.

A bacterial reverse mutation test (Ames test, OECD 471) using the *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 was submitted. The results of the study showed that the chlorfenapyr TC produced by Tagros does not induce bacterial reverse mutations under the conditions of this study.

On basis of Tier-1 data provided by Tagros (manufacturing process, purity/impurity profile, 5-batch analysis data, mutagenicity profile), the Meeting concluded that the chlorfenapyr TC from Tagros should be considered as equivalent to the reference profile supporting the existing WHO specification 570/TC.

Supporting Information
for
Evaluation Report 570/2024

Physico-chemical properties of chlorfenapyr

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

Manufacturing process, maximum limits for impurities ³ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO or WHO. Mass balances were 98.84-99.24 % and percentages of unknowns were <0.1 %.
Declared minimum chlorfenapyr content	970 g/kg
Relevant impurities ³ 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 of the TC and/or TK	98.5-99.8 °C mean: 99.7 °C	98.32	OECD 102, CIPAC MT2	AG-G3962
Solubility in organic solvents	Temperature: 20 ± 0.5 °C methanol: 57-67 g/L dichloromethane: >250 g/L acetone: >250 g/L ethyl acetate: >250 g/L toluene: >250 g/L *n*-heptane: <10 g/L	98.32	CIPAC MT181	AG-G3963

Annex 1: Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

(i) The proposer has confirmed that the toxicological and ecotoxicological data included in the summary below were derived from chlorfenapyr having impurity profiles similar to that referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 1. Mutagenicity profile of the chlorfenapyr technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium test strains: TA98, TA100, TA102, TA1535, TA1537	Bacterial reverse mutation	98.22	OECD No. 471 (2020) in triplicate at 5, 2.5, 1.25, 0.625, 0.313 mg/plate (in both the presence and absence of S9 mix) 37±1 °C for 66 hours	Not mutagenic	ERF/G01778

Annex 2: References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [If GLP]. Company conducting the study.
AG-G2254	Adya P.	2023	Five Batch Analysis of Chlorfenapyr Technical, GLP compliant, conducted by Eurofins Advinus Agrosciences Services India Private Limited, India
ERF/G01778	N.V.N. Mayuri	2023	Bacterial Reverse Mutation Test of Chlorfenapyr Technical Using *Salmonella Typhimurium*, GLP compliant, conducted by Edara Research Foundation, India
AG-G3962	Yajna	2024	Determination of Melting Range and Melting Point of Chlorfenapyr Technical, GLP compliant, conducted by Eurofins Advinus Agrosciences Services India Private Limited, India
AG-G3963	Yajna	2024	Determination of Solubility of Chlorfenapyr Technical in Organic Solvents, GLP compliant, conducted by Eurofins Advinus Agrosciences Services India Private Limited, India
-	APVMA	2024	Notice of Approval for Chlorfenapyr Technical produced by Tagros

CHLORFENAPYR

WHO Evaluation Report 570/2022.3

Recommendations

The Meeting recommended the following:

(i) The two new sites identified by BASF for the production of chlorfenapyr TC should be accepted as equivalent to the current production of chlorfenapyr TC by BASF.

Appraisal

The Meeting considered data and supporting information submitted by BASF in 2022 in support of the proposed inclusion of two additional manufacturing sites for the production of the established BASF chlorfenapyr TC for public health uses. BASF submitted information so as to present the substantial similarity of the manufacturing process and resulting batch production at the new sites as compared to the production based on which the compliance with the WHO specification was established.

The production at the two new sites relies upon a similar manufacturing process and the same internal manufacturing limits as the original site.

The Meeting concluded that the chlorfenapyr TC from two new sites identified by BASF should be considered as equivalent to the reference profile supporting the existing WHO specification 570/TC.

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2022.2

Recommendations

The Meeting recommended the following:

(i) The chlorfenapyr TC, as proposed by Shandong Weifang Shuangxing Pesticide Co. Ltd., should be accepted as equivalent to the chlorfenapyr reference profile.

(ii) The existing FAO specification for chlorfenapyr TC should be extended to encompass the technical material produced by Shandong Weifang Shuangxing Pesticide Co. Ltd.

(iii) The existing WHO specification for chlorfenapyr TC should be extended to encompass the technical material produced by Shandong Weifang Shuangxing Pesticide Co. Ltd.

Appraisal

The Meeting considered data and supporting information submitted by Shandong Weifang Shuangxing Pesticide Co. Ltd. (Shandong Weifang) in 2019 in support of extension of the existing FAO and WHO specifications for chlorfenapyr TC (FAO/WHO specifications 570/TC). The data submitted were in accordance with the requirements of the Manual on the development and use of FAO and WHO specifications for pesticides (2016 third revision of the first edition).

The reference specification and supporting data for chlorfenapyr TC had been provided by BASF, and the FAO specification was published in 2014. The FAO specification was then extended to WHO for use of chlorfenapyr in public health, and the WHO specification for chlorfenapyr TC was published in 2017.

The Meeting was provided with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for chlorfenapyr and all detectable impurities at or above 1 g/kg.

The manufacturing process used for the chlorfenapyr TC of the proposer differs somewhat from the process used to produce the material of the reference specification, although the intermediates and the ultimate product are the same. The Shandong Weifang manufacturing process includes four steps as for the reference technical material.

Mass balances ranged from 995.4 to 1002.7 g/kg in the 5-batch data. The declared minimum active ingredient content is 980 g/kg, higher than that of the reference FAO/WHO specification (940 g/kg), and therefore complies with the existing specification.

Four impurities, three organic impurities plus water, were identified, together with material insoluble in acetone. The manufacturing limits for the three organic impurities and water, respectively, were declared to be at or above 1 g/kg and were statistically supported by the batch analysis data. The manufacturing limits for the impurities commonly occurring both in the reference profile and in the material under consideration did not exceed the limits in the reference profile. A new impurity not found in the reference source occurred at slightly above 1 g/kg in only

one of the batches of the Shandong Weifang's chlorfenapyr TC. The quality control data further provided by the proposer showed the same impurity to be present at 1 g/kg or above in 4 out of 20 batches, implying that this impurity occurred at or above 1 g/kg in approximately 20% of batches. The manufacturing limit of this new impurity is maximum 2 g/kg.

The potential relevance of the new impurity was assessed based on its structural similarity with chlorfenapyr and *in silico* predictions of toxicity (Derek Nexus v 6.0.1, VEGA v 1.2.4 and Toxtree v 2.6.13) as well as by conducting a bacterial reverse mutation assay (Ames Test). The *in silico* predictions of toxicity did not give rise to additional structural alerts for the impurity compared to chlorfenapyr. Both chlorfenapyr and the impurity fired the identical structural alerts for skin sensitization and for carcinogenicity. Based on read-across, the impurity is considered like chlorfenapyr non-carcinogenic and non-skin-sensitizing. The outcome of the Ames test showed an absence of mutagenicity. The Meeting concluded that the new impurity should be considered as non-relevant.

The company stated that the confidential data presented to FAO/WHO are identical to those submitted for registration in Brazil, Argentina, Paraguay, Mexico, Indonesia and Egypt. The company also provided a letter of access to confidential data submitted to the Chinese registration authority and a certificate of registration of their chlorfenapyr TC in China. The Meeting noted a difference in the minimum purity declared to FAO/WHO (≥ 980 g/kg) and this declared to the Chinese authorities (≥ 950 g/kg). The company explained that the minimum purity of 950 g/kg meets the Chinese market but that their TC complies with the minimum purity of 980 g/kg, which was confirmed by the data package submitted to FAO/WHO.

The determination of the active ingredient content in the chlorfenapyr TC was done by a validated in-house method using reversed phase liquid chromatography with UV detection and external standard calibration. The collaboratively validated CIPAC method published in Handbook O in 2017 was not used. The proposer clarified that they conducted the 5-batch study during 2012 and 2013, while the CIPAC method for chlorfenapyr TC was published in 2017. As the CIPAC method is the reference method of the FAO/WHO specification, the Meeting requested the company to provide an analytical bridging study between the in-house and the CIPAC methods. The study submitted by the company on 3 batches of chlorfenapyr TC analysed both by the in-house and the CIPAC methods showed that the results for chlorfenapyr content are in good agreement.

The identity of chlorfenapyr in the 5-batch analysis data was confirmed by mass spectrometry (GC-EI-MS), ultraviolet spectrophotometry (UV) and nuclear magnetic resonance of proton (^{1}H-NMR). The organic impurities were determined by liquid chromatography with UV detection. OECD test methods were used for determination of physical-chemical properties of the technical active ingredient.

Shandong Weifang provided data on the melting point and solubility in some organic solvents of their chlorfenapyr TC (with a purity of 980 g/kg). Although not required, they also provided additional data on physical-chemical properties of chlorfenapyr, including vapour pressure, solubility in water and octanol/water partition coefficient. In order to avoid duplication with similar data evaluated for the reference profile, the Meeting agreed that these physical-chemical data for the pure active ingredient should not be reported in the supporting information.

The proposer provided mutagenicity data on chlorfenapyr TC (bacterial reverse mutation assay, Ames test, according to OECD 471). The proposer and the Meeting agreed that the Shandong Weifang's chlorfenapyr TC is considered as being non-mutagenic under the conditions of this test. However, the Meeting raised an issue with this study, as the top concentration tested did not elicit cytotoxicity. This is a deviation from the test guideline, which states that soluble test substances which are cytotoxic already below 5 mg/plate should be tested up to a cytotoxic concentration. Nevertheless, the bacterial reverse mutation assay (Ames test) performed on the new impurity showed that it was not mutagenic – see hereunder. In addition, the proposer provided a skin sensitization test (guinea pig maximisation test, GPMT) on chlorfenapyr TC, which demonstrated that it is non-sensitizing to skin under the conditions of this test. Despite deviations from the OECD test guideline 406, the Meeting considered the study acceptable as supporting evidence that chlorfenapyr TC from Shandong Weifang and the new impurity are non-mutagenic.

The proposer also provided the Meeting with toxicity data of their chlorfenapyr TC (acute oral, dermal and inhalation toxicity, skin and eye irritation). These data were not further considered by the Meeting as they are not requested by the FAO/WHO Manual for equivalence assessment in Tier-1.

On basis of Tier-1 data provided by the company (manufacturing process, purity/impurity profile, 5-batch analysis data, mutagenicity profile), the Meeting concluded that the chlorfenapyr TC from Shandong Weifang Shuangxing Pesticide Co. Ltd. should be considered as equivalent to the reference profile supporting the existing FAO and WHO specifications 570/TC.

Supporting Information
for
Evaluation Report 570/2022.2

Physico-chemical properties of chlorfenapyr

Table 1. Chemical composition and properties of chlorfenapyr 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/WHO. Mass balances were 99.54 – 100.27% and percentages of unknowns were <0.1%.
Declared minimum chlorfenapyr 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	100.9 - 101.9°C	98.0	OECD 102,1995	6580.005.012.12
Solubility in organic solvents	1032.0 g/L in acetone at 20 ± 0.5°C 78.4 g/L in methanol at 20 ± 0.5°C	98.0	OECD 105, 1995	6580.008.037.12

Annex 1: Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from chlorfenapyr 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 chlorfenapyr technical material, based on sensitization

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Guinea Pigs (female)	Skin sensitisation	98.4	OECD 406; 48 hours under occlusion with the test item at 50% one week after the intradermal induction;1% dilution of the test item;	Non-sensitizing	1298

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

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium Strains TA1535, TA1537, TA98, TA100 and TA102	Bacterial reverse mutation assay	99.0	OECD 471; 48 hours; 0.156, 0.313, 0.625, 1.25 and 2.5 mg/plate; after solidification the plates were incubated upside down at 37 ± 2°C, both in presence (+S9) and in absence (-S9) of metabolic activation	Does not induce gene mutations either by base pair substitution or by frameshifts in the genome of the strains used under the conditions of the assay with and without metabolic activation.	3750

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
006580.030.010.12	Marcela Fernandes Terni	2013	Qualitative and Quantitative Profile of the test substance CHLORFENAPYR (Five Batch Analysis). Study No. 006580.030.010.12. GLP. BIOAGRI Laboratórios Ltda
6580.008.037.12	Reinaldo R. O. Zen	2012	Solubility in water and organic solvents of CHLORFENAPYR. Study No. 6580.008.037.12. GLP. BIOAGRI Laboratories Ltda.
6580.005.012.12	Reinaldo R. O. Zen	2012	Melting point and range of CHLORFENAPYR. Study No. 6580.005.012.12. GLP. BIOAGRI Laboratories Ltda.
3750	Mr. D. Narayanasamy	2013	Bacterial Reverse Mutation Assay with Chlorfenapyr Technical. Study No. 3750. GLP. RCC Laboratories India Private Limited.
-	Shandong Weifang	2019	Letter of access to confidential data submitted to the Chinese registration authority (ICAMA).
-	Ministry of agriculture, china	2019	Certificate of registration by ICAMA of chlorfenapyr TC from Shandong Weifang Shuangxing Pesticide Co. Ltd.
-	Shandong Weifang	2022	Statement from Shandong Weifang Shuangxing Pesticide Co. Ltd. on why different 5 batch analysis were submitted to FAO/WHO and ICAMA.
1298	Mr. G. Ilamurugan	2010	Contact Hypersensitivity in Albino Guinea Pigs, Maximization Test (Magnusson and Kligman Method) with Chlorfenapyr Tech. Study No. 12698. GLP. RCC Laboratories India Private Limited.
NC-2022-071	Jing Zhang	2022	Analytical testing of Chlorfenapyr TC : Content of Active Ingredient. Study No. NC-2022-071. GLP. Nutrichem Laboratory Co., Ltd.

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2022.1

Recommendations

The Meeting recommended the following:

(i) The chlorfenapyr TC, as proposed by Shijiazhuang Richem Co., Ltd., should be accepted as equivalent to the chlorfenapyr reference profile.

(ii) The existing FAO specification for chlorfenapyr TC should be extended to encompass the technical material produced by Shijiazhuang Richem Co. Ltd.

(iii) The existing WHO specification for chlorfenapyr TC should be extended to encompass the technical material produced by Shijiazhuang Richem Co. Ltd.

Appraisal

The Meeting considered data and supporting information submitted by Shijiazhuang Richem Co., Ltd. (Shijiazhuang Richem) in 2019 in support of extension of the existing FAO and WHO specifications for chlorfenapyr TC (FAO/WHO specification 570/TC). The data submitted were in accordance with the requirements of the Manual on the development and use of FAO and WHO specifications for pesticides (2016 third revision of the first edition).

The reference specification and supporting data for chlorfenapyr TC had been provided by BASF, and the FAO specification was published in 2014. The FAO specification was then extended to WHO for use of chlorfenapyr in public health, and the WHO specification for chlorfenapyr TC was published in 2017.

The Meeting was provided with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for chlorfenapyr and all detectable impurities at or above 1 g/kg.

The manufacturing process used for the chlorfenapyr TC of the proposer differs somewhat from the process used to produce the material of the reference specification, although the intermediates and the ultimate product are the same. The Shijiazhuang Richem's manufacturing process consists of three reaction steps, whereas there are four reaction steps in the manufacture of the reference technical material. A more in-depth consideration of the processes reveals that the proposer has effectively combined the first two steps of the four-step manufacturing process utilized to produce the reference TC into a single step.

Mass balances ranged from 990.5 to 991.4 g/kg in the 5-batch data. The declared minimum active ingredient content is 980 g/kg, higher than that of the published FAO/WHO specification (940 g/kg), and therefore complies with the existing specification.

The Shijiazhuang Richem's chlorfenapyr TC contains fewer impurities than the reference profile. Four impurities were identified and quantified in the 5-batch analysis data, whose three impurities are shared with the reference profile. A new impurity is present in the Shijiazhuang Richem's chlorfenapyr TC. The maximum limits for all the impurities were adequately supported by the 5-batch data. The structure of the new impurity was screened with computational methods to predict

its toxicity (using "R" and “Package 'bestglm' version 0.37.1”, Derek Nexus: 6.1.0, Nexus: 2.3.0 and Sarah: Sarah Nexus: 3.1.0). This new impurity did not fire any additional alert compared to chlorfenapyr (DEREK model) and is not considered mutagenic in bacteria (DEREK and SARAH models). According to the results of the model developed in “R”, the impurity is not more acutely toxic by the oral route compared with chlorfenapyr. The Meeting concluded that this impurity should be considered as non-relevant. The manufacturing limit for another commonly occurring impurity exceeded the manufacturing limit of the reference profile. However, the limit was not increased by more than 50% (relative to the maximum level in the reference profile), nor by more than 3 g/kg, and it was therefore considered acceptable by the Meeting.

The company stated that the confidential data presented to FAO/WHO are identical to those submitted for registration in China, South Korea and Malaysia. Certificates of registration were provided from the Chinese and Korean registration authorities, reflecting the minimum purity of 980 g/kg.

The active ingredient content in the chlorfenapyr TC was performed by a validated in-house method using reversed phase liquid chromatography coupled to UV detection with external standard calibration. The proposer clarified that the 5-batch analysis was carried out for the purpose of registration in Brazil, where the use of CIPAC methods is not compulsory, and that the method used was a reliable and validated analytical method that complied with generally accepted criteria. The proposer also stated that the principle of the method used is the same as the CIPAC method 570/TC/M/3 published in 2017 in Handbook O. The CIPAC method uses high performance liquid chromatography on a reversed phase column (isocratic elution with flush gradient) with UV detection and external standardization. The Meeting noted that the 5-batch analysis data was performed in 2017 on batches manufactured in 2015. As the CIPAC method is the reference method of the FAO/WHO specification, the Meeting requested the company to provide an analytical bridging study between the in-house and the CIPAC methods. The study submitted by the company on 3 batches of chlorfenapyr TC analysed both by the in-house and the CIPAC methods showed that the results for chlorfenapyr content are in good agreement with the criteria set out in Appendix J of the Manual.

The identity of chlorfenapyr in the 5-batch analysis data was confirmed by mass spectrometry (GC-EI-MS), ultraviolet spectrophotometry (UV) and nuclear magnetic resonance of proton (^{1}H-NMR). The organic impurities were determined by liquid chromatography with UV detection. The method was fully validated as regards its specificity, selectivity, linearity of response, accuracy (recoveries), repeatability, intermediate precision and limits of detection (LOD) and quantification (LOQ). The identity of impurities was confirmed by ultraviolet spectrophotometry, mass spectrometry and nuclear magnetic resonance.

Test methods for determination of physical-chemical properties of the technical active ingredient were mainly OECD and, for one test, OPPTS/ASTM.

Shijiazhuang Richem provided data on the melting point and solubility in organic solvents of their chlorfenapyr TC (with a purity of 985.3 g/kg). Although not required, they also provided additional data on physical-chemical properties of chlorfenapyr, including vapour pressure, solubility in water, octanol/water partition coefficient, hydrolysis and photolysis characteristics. In order to avoid duplication

with similar data evaluated for the reference profile, the Meeting agreed that these physical-chemical data for the pure active ingredient should not be reported in the supporting information.

The proposer provided mutagenicity data on chlorfenapyr TC (bacterial reverse mutation assay, Ames test, according to OECD 471). The Meeting raised an issue with this study as the highest concentration tested did not comply with the guideline provisions, the tested top concentration was too low. At the request of the Meeting, the company provided a new Ames test in which the top concentration was adequately selected. Under the conditions of test, the Shijiazhuang Richem's chlorfenapyr TC is considered non-mutagenic.

The proposer also provided a micro-nucleus mutagenicity test according to OECD 474 as well as studies on the acute toxicity by the oral, dermal and inhalation route, skin and eye irritation and a study on skin sensitization potential of chlorfenapyr TC. These data were not further considered by the Meeting as they are not requested by the FAO/WHO Manual for equivalence assessment in Tier-1.

On basis of Tier-1 data provided by the company (manufacturing process, purity/impurity profile, 5-batch analysis data, mutagenicity profile), the Meeting concluded that the chlorfenapyr TC from Shijiazhuang Richem Co., Ltd should be considered as equivalent to the reference profile supporting the existing FAO and WHO specifications 570/TC.

The company also provided the Meeting with summary data on the toxicology profile of their TC on repeated administration (sub-acute to chromic), as well as summary data on the ecotoxicology profile. These data were not further considered by the Meeting as they are not requested by the FAO/WHO Manual for equivalence assessment in Tier-1.

Supporting Information
for
Evaluation Report 570/2022.1

Physico-chemical properties of chlorfenapyr

Table 1. Chemical composition and properties of chlorfenapyr 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/WHO. Mass balances were 99.05 – 99.14% and percentages of unknowns were <0.1%.
Declared minimum chlorfenapyr 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	101.2 - 102.0℃	98.53	OECD 102,1995	RF.6553.005.058.14
Solubility in organic solvents	Temperature: 20°C Methanol: 55.819 g/L Acetone: 727.507 g/L	98.53	OECD 105, 1995	RF-6553.008.099.14

Annex 1: Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

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

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium Strains TA97a, TA98, TA100, TA102 and TA1535	Bacterial reverse mutation assay	98.6	OECD 471 Doses: 52, 104, 208, 416, 833 and 1667 µg/plate, both in presence (+S9) and in absence (-S9) of metabolic activation.	Non-mutagenic up to the acceptable precipitation test concentration of 1667 µg/plate	RLL Study Number 3597
Mouse (m, f)	Micro-nucleus Test	98.14	OECD 474 Doses: 24 h preparation interval: 7.81, 15.63 and 31.25 mg/kg body weight 48h preparation interval: 31.25 mg/kg body weight.	No induction of micronuclei in the bone marrow cells of the mouse. Non-clastogenic.	RCC Study Number 6084

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
6553.030.058.14	Camila G. Gyuricza Silva	2015	Melting point and range of chlorfenapyr. Study No. 6553.030.058.14. GLP. BIOAGRI Laboratórios Ltda.
6553.008.099.14	Márcio José Liberale	2015	Solubility in water and organic solvents of Chlorfenapyr. Study No. 6553.008.099.14. GLP. BIOAGRI Laboratórios Ltda.
6084	Srinivasa Rao Kandula	2016	Micronucleus Test in Bone Marrow Cells of Mouse with Chlorfenapyr Technical. Study No. 6084. GLP. RCC Laboratories India Private Limited.
6553.030.050.14	Lahys de G. Caetano Tomaz	2017	Qualitative and Quantitative Profile of the test substance Chlorfenapyr (Five Batch Analysis). Study No. 6553.030.050.14. GLP. BIOAGRI Laboratórios Ltda.
6553.030.050.14	Lahys de G. Caetano Tomaz	2017	Qualitative and Quantitative Profile of the test substance Chlorfenapyr (Five Batch Analysis). Study No. 6553.030.050.14. Amendment to the final report. GLP. BIOAGRI Laboratórios Ltda.
2634	Jun Lu	2019	Study on the physico-chemical properties of chlorfenapyr technical. Study No. 2634. GLP. Rotam Research Laboratory (RRL).
NC-2021-052	Jing Zhang	2021	Analytical testing of Chlorfenapyr Technical : Content of Active Ingredient. Study No. NC-2021-052. GLP. Nutrichem Laboratory Co., Ltd.
-	Shijiazhuang Richem	2019	Letter of access to confidential data submitted to the Chinese registration authority (ICAMA).
-	Ministry of agriculture, china	2019	Certificate of registration by ICAMA of chlorfenapyr TC from Shijiazhuang Richem.
LMD-QU45-31-PREV	Ravinanth Gogineni	2022	QSAR model for the prediction of three impurities related to chlorfenapyr. Analisis Quimico Computational S.A.S.
3597	Jasmine Zhang	2022	*Salmonella Typhimurium* reverse mutation assay (Ames Test) with chlorphenapyr technical. Study No. 3597. GLP. RRL Global Services.

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2021

Recommendations

The Meeting recommended that the existing WHO specification for chlorfenapyr SC should be extended to encompass the corresponding product of Tianjin Yorkool International Trading Co., Ltd.

Appraisal

The Meeting considered data and information submitted in 2021 by Tianjin Yorkool International Trading Co., Ltd (Tianjin Yorkool) to support the extension of the existing WHO specification 570/SC for chlorfenapyr suspension concentrate (SC). The data submitted were in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (2016, third revision of the first edition).

FAO specifications for chlorfenapyr TC and SC were developed in 2014 based on submission of data from BASF (FAO/WHO evaluation report 570/2014). The FAO specifications were extended to WHO in 2017 for use of chlorfenapyr in public health (FAO/WHO evaluation report 570/2017).

Tianjin Yorkool provided data on physical-chemical properties of their chlorfenapyr 240 SC formulation, including active ingredient identity and content, persistent foam, wet sieve test, suspensibility, spontaneity of dispersion, pourability, accelerated storage stability testing at 54°C ± 2°C for 14 days and storage stability at 0 ± 2°C for 7 days. Tianjin Yorkool indicated that the specification is representative of the quality of their chlorfenapyr 240 SC by providing GLP study reports for all physical-chemical parameters tested for three different batches.

Tianjin Yorkool tested their chlorfenapyr SC for all physical-chemical properties using the most recent CIPAC methods, except for suspensibility where the method MT 184 was used instead of the revised MT 184.1 and the accelerated storage stability test where the MT 46.3 was used instead of the revised MT 46.4. The Meeting agreed that it is acceptable as the updated methods published in Handbook P are considered to provide equivalent results with the previous versions.

Tianjin Yorkool used the official CIPAC method 570/SC/M/3 published in Handbook O for the determination of chlorfenapyr content in the SC formulation (before and after storage at 54ºC). According to this method, chlorfenapyr is determined by reversed phase HPLC using UV detection at 300 nm and external standardization.

The stability of the SC in the accelerated storage test was demonstrated to be acceptable, and no significant deterioration was observed in terms of active ingredient content, suspensibility, spontaneity of dispersion, pourability and residues after sieving. After storage at 0 ± 2°C for 7 days (MT 39.3), the formulation continues to comply with the clauses for active ingredient content, suspensibility, and wet sieve test.

The Meeting concluded that Tianjin Yorkool could demonstrate that their chlorfenapyr SC fully comply with the existing WHO specification 570/SC.

Additional actions proposed by the Meeting

The Meeting recommended to update the FAO and WHO SC specifications to align them with the most recent version of the specification template in the Manual, particularly with the latest versions of CIPAC MT methods for suspensibility (MT 184.1 instead of MT 184) and stability at elevated temperature (MT 46.4 instead of MT 46.3). These updated methods published in CIPAC Handbook P are considered to provide equivalent results with the previous versions. Therefore, all limits in the concerned clauses remain the same as for the previous versions.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
20154	S. Pandiselvi	2020	Active ingredient content, physical properties, and storage stability test for 240 g/L Chlorfenapyr Suspension Concentrate. IIBAT study report 20154. GLP. Unpublished.
20201	S. Pandiselvi	2020	Active ingredient content, physical properties, and storage stability test for 240 g/L Chlorfenapyr Suspension Concentrate – 2nd production. IIBAT study report 20201. GLP. Unpublished.
21044	S. Pandiselvi	2021	Active ingredient content, physical properties, and storage stability test for 240 g/L Chlorfenapyr Suspension Concentrate – 3rd production. IIBAT study report 20201. GLP. Unpublished.

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2017

Recommendations

The Meeting recommended that the specifications for chlorfenapyr TC and SC, proposed by BASF and as amended, should be adopted by WHO.

Appraisal

The FAO specifications for chlorfenapyr TC and SC, based on a data package submitted by BASF, were published in December 2014. BASF had initially requested the development of both FAO and WHO specifications, but WHO specifications could not be published without the successful evaluation of this product by WHOPES. Chlorfenapyr 240 SC was tested and evaluated by WHOPES several times (WHO 2013, WHO 2014, WHO 2017). WHOPES concluded in 2017 that chlorfenapyr 240 SC might have potential for indoor residual spraying in areas with high pyrethroid resistant malaria vectors (i.e. where indoor residual spraying with pyrethroids induced almost no mortality). WHOPES recommended also the use of Interceptor® G2, a polyester net coated with alpha-cypermethrin SC and chlorfenapyr SC, in the prevention and control of malaria (WHO 2017).

The Meeting therefore agreed to publish WHO specifications for chlorfenapyr TC and SC, based on the specifications published by FAO. The WHO specification for the SC was restricted to the formulation containing 240 g/l of chlorfenapyr.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	WHO	2013	Report of the 16th WHOPES Working Group Meeting, WHO/HQ, Geneva, 22-30 July 2013. WHO, Geneva, document ISBN 978 92 4 150630 4 and WHO/HTM/NTD/WHOPES/2013.6.
	WHO	2014	Report of the 17th WHOPES Working Group Meeting, WHO/HQ, Geneva, 15-19 September 2014. WHO, Geneva, document ISBN 978 92 4 150803 2 and WHO/HTM/NTD/WHOPES/2014.3
	WHO	2017	Report of the 20th WHOPES Working Group Meeting, WHO/HQ, Geneva, 20-24 March 2017. Available at : http://www.who.int/whopes/recommendations/wgm/en/

CHLORFENAPYR

FAO/WHO Evaluation Report 570/2014

Recommendations

The Meeting recommended that the specifications for chlorfenapyr TC and SC, proposed by BASF Agro B.V. and as amended, should be adopted by FAO.

Appraisal

The data for chlorfenapyr were evaluated in support of new FAO and WHO specifications for TC and SC. The supporting data and draft specifications were provided by BASF Agro B.V. (BASF) in 2010 and a revised submission in September 2011. As the recommendation of the 16th WHOPES working group meeting on the use of the chlorfenapyr SC formulation in public health was to further evaluate the potential of the product in indoor residual spraying, the Meeting recommended to publish the FAO specification for chlorfenapyr TC and SC formulation.

Chlorfenapyr has not been evaluated by the FAO/WHO JMPR and WHO/IPCS. The US EPA has completed a review of the toxicological data submitted for this compound [EPA 2001].

Chlorfenapyr was evaluated by the European Commission as a Biocidal Product Type 8 (wood preservative), with Portugal as the Rapporteur Member State, and approved for inclusion into Annex I of the Biocidal Products Directive, 98/8/EC. It is currently under evaluation under the Biocidal Products Regulation No.528/2012 as an insecticide active substance (Biocidal Product Type 18). Chlorfenapyr was not included in Annex I of the Council Directive 91/414/EEC [CD, 2001]

The data submitted were in accordance with the requirements of the revised (revision June 2009) 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual] and supported the proposed specifications.

The confidential data provided on the manufacturing process of chlorfenapyr are very similar to the information supplied to EPA OPP. It is however noted that a higher alkylated benzene instead of a related one with lower boiling was specified. The impurities and QC limits for chlorfenapyr TC produced by BASF agree exactly between the information submitted to FAO and to the US EPA, with the exception for the declared minimum content of the active substance which is lower in the US than in the FAO submission (930 g/kg instead of 940 g/kg) [Funk, 2011].

The confidential data submitted by the proposer on the manufacturing process of chlorfenapyr, the data summary in support of the physical-chemical, toxicological and ecotoxicological properties were in accordance with those evaluated by Portugal as part of the European review programme under the Biocide Products Directive 98/8/EC. The only difference is that in the manufacturing process an alkylated aromatic solvent was replaced by a related one with lower boiling point.

Chlorfenapyr is a white to pale yellow solid. It has a low vapour pressure. The compound does not have ionizable groups - therefore, the low water solubility and the octanol/water partition coefficient are not pH dependent. The active ingredient is stable to hydrolysis at pH 4, 7 and 9 at 50°C. In simulated sunlight there is degradation with half-lives of 5-8 days at pH 5, 7 and 9.

The main formulation types available are aqueous suspension concentrates (SC).

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present below or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 98.6 – 99.8 % in the 5-batch data.

Based on JMPS standard estimation of relative toxicity of the impurity and the active ingredient, the impurity CL 303,268 (tralopyril) could be considered as relevant. The Meeting considered, that exposure to even pure chlorfenapyr would actually lead to exposure to tralopyril generated in the metabolism and hence the contribution of tralopyril to the hazard would be covered in the toxicity studies.

The justification was accepted and tralopyril is not considered as a relevant impurity in the technical material.

The identity of chlorfenapyr is confirmed by comparing the retention time in the HPLC method and by IR spectroscopy. The analytical method for the determination of the active ingredient in chlorfenapyr technical and SC formulations is reversed-phase HPLC with UV detection. Impurities were determined by HPLC-UV and HRGC. The LOQs for chlorfenapyr and the impurities were 0.1 g/kg in the TC. Test methods for determination of physical-chemical properties of the technical active ingredient and formulations were OECD, EPA, EC and CIPAC, as indicated in the specifications and supporting data, respectively.

The Meeting recommended amendment of the suspensibility specification clause for chlorfenapyr SC and to replace MT 161 with MT 184 - the harmonization of methods MT 15, MT 161 and MT 168 [CIPAC K].

The Meeting also recommended amendment of the low temperature stability clause for chlorfenapyr SC, and to replace MT 39.2 with MT 39.3 [CIPAC J].

Supporting Information
for
Evaluation Report 570/2014

Uses

Chlorfenapyr is a broad-spectrum insecticide and acaricide acting through ingestion and by contact. It is used in agriculture against leafminers, thrips, mites and other pests, and in non-crop and public health against termites, cockroaches, ants, bedbugs, flies, spiders, centipedes and other insect pests.

BASF chlorfenapyr is currently registered in Brazil [since 1997], Australia [since 1998], Japan [since 1996], Mexico [since 1997] and the USA [since 2001], as well as in several other countries, for agricultural and/or non-crop uses.

Identity of the active ingredient

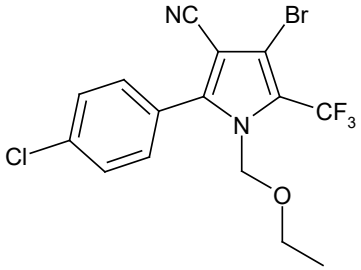
ISO common name
Chlorfenapyr (ISO 1750 approved)

Synonyms
None

Chemical names

IUPAC 4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-*1H*-pyrrole-3-carbonitrile
CA 4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-*1H*-pyrrole-3-carbonitrile

Structural formula



Molecular formula
$C_{15}H_{11}BrClF_3N_2O$

Relative molecular mass
407.6

CAS Registry number
122453-73-0

CIPAC number
570

Identity tests

HPLC retention time, IR spectrum

Physico-chemical properties of chlorfenapyr

Table 1. Physico-chemical properties of pure chlorfenapyr

Parameter	Values and conditions	Purity % Note[3]	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	5.40E-6 Pa at 25 °C (extrapolated from measurements at 60, 70 and 80°C)	99.7	OPPTS 830.7950, EC Annex V method A.4	CK-306-003, 1997/7000836
Melting point.	101.4 - 102.3 °C	99.0	EC Annex V Method A.2, OECD 102	CK-303-002, 1994/7000817
Temperature of decomposition	~183°C	93.6	OPPTS 830.6316	CK-334-001, 1993/7001056
Solubility in water	0.11 mg/l at 20°C, pH=5 0.11 mg/l at 20°C, pH=7 0.14 mg/l at 20°C, pH=9 0.11 mg/l at 10°C, unbuffered deionized water 0.14 mg/l at 20°C, unbuffered deionized water 0.20 mg/l at 30°C, unbuffered deionized water	99.0	EC Annex V method A.6, Shake Flask	CK-311-001, 1994/7000775
Octanol/water partition coefficient	log P_{OW} = 5.28 at 20°C , pH=5 log P_{OW} = 5.21 at 20°C , pH=7 log P_{OW} = 5.24 at 20°C , pH=9 log P_{OW} = 5.28 at 20°C , deionized water	99.0	OECD 107	CK-315-002, 1995/7000648
Hydrolysis characteristics	Half-life = stable at 50 °C at pH 4 Half-life = stable at 50 °C at pH 7 Half-life = stable at 50 °C at pH 9	99.0	EC Annex II section 2.9.1, OECD 111	CK-322-005, 1993/7002659
Photolysis characteristics	Half-lives under conditions that approximate a summer day in Princeton, NJ, USA (40.3°N) were 5 to 8 days Predicted half-lives for Central Europe (52ºN), using the method of Frank and Klöpffer, were 2.3 hours in June and 1.0 day in December	97.0 99.7	US EPA 161-2 BBA Guideline IV, 6-1, July 1990	CK-630-003, 1994/7000719 CK-630-006, 1995/7000721
Dissociation characteristics	The active substance does not contain any ionisable groups	-	Waiver	CK-322-001, 1994/7001669
Solubility in organic solvents	Temperature: 20°C (mg/L) hexane: 6850 methanol: 50600 acetonitirile: 394000 toluene: 490000 acetone: 697000 dichloro-methane: 744000 ethyl acetate: 514000	99.0	EC Annex V, A.6	CK-311-001, 1994/7000775

[3] Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Table 2. Chemical composition and properties of chlorfenapyr technical material

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 98.6 – 99.8 % and percentages of unknowns were < 0.1 %.
Declared minimum chlorfenapyr content	940 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 of the TC	100 - 101°C (98.8%)

Hazard summary

Chlorfenapyr has not been evaluated by the WHO IPCS or FAO/WHO JMPR.

The IPCS hazard classification of chlorfenapyr is: moderately hazardous, class II. [WHO, 2009]

EU classification of chlorfenapyr according to Regulation No 1272/2008/EC (Annex VI Table 3.2):

T; R23 Toxic by inhalation.
Xn; R22 Harmful if swallowed.
N; R50-53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Hazard class and category codes (Annex VI Table 3.1):

Acute Tox. 3 H331 Toxic if inhaled
Acute Tox. 4 H302 Harmful if swallowed
Aquatic Acute 1 H400 Very toxic to aquatic life
Aquatic Chronic 1 H410 Very toxic to aquatic life with long lasting effects [CLP, 2009]

Formulations

The main formulation type available is SC.

Methods of analysis and testing

The analytical method for the active ingredient in TC and in SC formulations is a full CIPAC method. Chlorfenapyr is determined by reverse phase HPLC chromatography and UV detection [CIPAC 570].

The method for determination of impurities are based on HPLC and HRGC and are adequately validated.

Test methods for determination of physical-chemical properties of the technical active ingredient were OECD, EPA or EC, while those for the formulations are CIPAC.

Test methods for determination of physical-chemical properties of the technical active ingredient were essentially OECD and EPA methods, while those for the formulations were CIPAC MT, as indicated in the specifications.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the SC formulation, comply with the requirements of the FAO/WHO Manual.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as chlorfenapyr.

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 chlorfenapyr 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 the chlorfenapyr technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
Rat (m, f)	oral	94.5	Single exposure. Study conducted according to U.S. EPA Guideline No: 81-1. Doses: 156.25, 312.5, 625, 1250 and 2500 mg/kg b.w.	LD_{50} ♂: 441 mg/kg b.w. ♀ 1152 mg/kg b.w.	CK-411-001 1993/7001133
Mouse (m, f)	oral	94.5	Single exposure. Study conducted according to JMAFF Guideline No: 59 NohSan No. 4200. Doses: 35, 70 and 140 mg/kg b.w.	LD_{50} ♂ 45 mg/kg b.w. ♀ 78 mg/kg b.w.	CK-411-004 1994/7000707
Rabbit (m, f)	dermal	94.5	Single exposure. Study conducted according to U.S. EPA Guideline No.: 81-2. Dose: 2000 mg/kg b.w.	LD_{50} > 2000 mg/kg b.w.	CK-412-001 1992/7001140
Rat (m, f)	inhalation	94.5	Single 4-hour exposure. Study conducted according to U.S. EPA Guideline No.: 81-3 Doses: 0, 0.34, 0.71, 1.8 and 2.7 mg/L.	LC_{50} ♂: 0.83 mg/L ♀ > 2.7 mg/L	CK-413-001 1993/7001115
Rabbit (m)	skin irritation	94.5	Single exposure, Study conducted according to U.S. EPA Guideline No.: 81-5. Dose: 0.5 g.	Not irritating	CK-415-004 1993/7001137
Rabbit (m)	eye irritation	94.5	Single exposure, Study conducted according to U.S. EPA Guideline No.: 81-4. Dose: 0.1 mg.	Not irritating	CK-415-003 1993/7001138
Guinea pig (f)	skin sensitisation	95.2	Maximisation test. Study conducted according to JMAFF Guideline No: 59 NohSan No. 4200, OECD guideline No.406, 1992, U.S. EPA Guideline No.: 81-6. Doses: 0.05 mL of 2 w/v% suspension in live oil intradermal and 0.2 mL of 10 w/v% suspension in olive oil topical (induction); 0.5 mL of 0.4 w/v% suspension in olive oil topical (challenge).	Not a skin sensitizer	CK-416-002 1999/7000754

Technical chlorfenapyr is moderately toxic in rats via the oral route and inhalation. Mice were found to be more susceptible towards the acute oral effects of chlorfenapyr technical than the rat. Chlorfenapyr has a low magnitude of toxicity by dermal route of exposure. It is not irritating to the skin or eye in rabbits. It does not cause delayed contact hypersensitivity in guinea pigs by testing according to the maximisation test.

[4] Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat (m, f)	Oral dietary	98.4	28-day study conducted according to OECD Method 407. Doses: 0, 600, 900, 1200, 1600, 2000 ppm. (approx. 0, 72, 108, 139, 185, 246 mg/kg b.w./day).	NOAEL < 71.6 mg/kg b.w./day.	CK-420-003, 1991/7001094
Mouse (m, f)	Oral dietary	98.4	28-day study conducted according to OECD Method 407. Doses: 0, 160, 240, 320, 480, 640 ppm. (approx. 0, 32, 51, 67, 112, 144 mg/kg b.w./day).	NOAEL < 32 mg/kg b.w./day.	CK-420-004, 1991/7001093
Rat (m, f)	Oral dietary	93.6	90-day study conducted according to U.S. EPA Guideline No.: 82-1. Doses: 0, 150, 300, 600, 900, 1200 ppm. (approx. 0, 12, 24, 48, 73, 98 mg/kg b.w./day).	NOAEL = 11.7 mg/kg b.w./day.	CK-425-002, 1993/7001148
Mouse (m, f)	Oral dietary	93.6	90-day study conducted according to U.S. EPA Guideline No.: 82-1. Doses: 0, 40, 80, 160, 320 ppm. (approx. 0, 8, 17, 34, 70 mg/kg b.w./day).	NOAEL = 8.2 mg/kg b.w./day.	CK-425-003, 1994/7000836
Dog, Beagle (m, f)	Oral dietary	94.5	90-day study conducted according to U.S. EPA Guideline No.: 82-1. Doses: 60, 120, 300 ppm. (approx. 0, 2, 4, 4/6/7 mg/kg b.w./day for males and 0, 2, 5, 6/6/7 mg/kg b.w./day for females).	NOAEL = 4.2 mg/kg b.m/day	CK-425-001, 1993/7001149
Dog, Beagle (m, f)	One year dietary toxicity	94.5	12-month study conducted according to U.S. EPA Guideline No.: 83-1. Doses: 0, 60, 120, 240 ppm. (approx. 0, 2, 4, 9 mg/kg b.w./day for males and 0, 2, 5, 10 mg/kg b.w./day for females).	NOAEL = ♂: 4.0 mg/kg b.m/day ♀: 4.5 mg/kg b.m/day	CK-427-004, 1994/7000794
Rat (m, f)	Chronic dietary toxicity and carcinogenicity	94.5	24-month study conducted according to U.S. EPA. Guideline No.: 83-5 Doses: 60, 300, 600 ppm in the feed. (approx. 0, 3, 15, 31 mg/kg b.w./day for males and 0, 4, 19, 37 mg/kg b.w./day for females)	organ x, type of tumour incidences were generally low, no significant differences between control and treated groups of animals other effects: At 200 ppm, decreases in body weight and body weight gain, decreases in albumin/globulin ratios, increases in total cholesterol and hepatocellular	CK-427-002, 1994/7000797

[5] Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
				enlargement. NOAEL 60 ppm, 2.9 and 3.6 mg/kg b.m./day for males and females, respectively	
Mouse (m, f)	Chronic dietary toxicity and carcinogenicity	94.5	24-month study conducted according to U.S. EPA Guideline No.: 83-2. Doses: 20, 120, 240 ppm in the feed. (approx. 0, 3, 17, 35 mg/kg b.w./day for males and 0, 4, 22, 45 mg/kg b.w./day for females).	organ x, type of tumour no significant differences between control and treated groups of animals other effects: At 240 ppm: Increased mortality, not attributable to any neoplastic changes. At 120 ppm, reduced body weight gain and vacuolization of the white matter of the brain at 120 ppm. NOAEL 20 ppm, 2.8 and 3.7 mg/kg b.m./ day for males and females, respectively	CK-428-002, 1994/7000798
Rat (f)	Oral developmental toxicity (embryo-fetal toxicity/ teratogenicity)	94.5	Study conducted according to U.S. EPA Guideline No.: 83-3 Doses: 0, 25, 75, 225 mg/kg b.w./day from gestation days 6 to 15.	Ovarian, uterine and fetal observations were unaffected at all dose levels. No external, soft tissue or skeletal malformations or variations were attributed to treatment. NOEL for maternal toxicity: 25 mg/kg b.w./day based on reduced maternal body weight gains, food consumption and water consumption. NOEL for fetal/developmental toxicity: 225 mg/kg b.w./day. Not a developmental toxicant nor a teratogenic agent in the rat.	CK-432-001, 1993/7001107
Rabbit (f)	Oral developmental toxicity (embryo-fetal toxicity/ teratogenicity)	94.5	Study conducted according to U.S. EPA Guideline No.: 83-3 Doses: 0, 5, 15, 30 mg/kg b.w./day from gestation days 7 to 19.	NOEL for maternal toxicity: 5 mg/kg b.w./day based on reduced maternal body weight gains nad food consumption. NOEL for fetal/developmental toxicity: 30 mg/kg b.w./day.	CK-432-002, 1993/7001106

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
				Not a developmental toxicant nor a teratogenic agent in the rabbit.	
Rat (m, f)	Two-generation (One-Litter) reproduction study in rat	94.5	Study conducted according to U.S. EPA Guideline No.:83-4. Doses: 0, 60, 300, 600 ppm in the feed (approx. 0, 5, 25, 44 mg/kg b.w./day) for two successive generations (P_1 and F_1).	Parental toxicity (reduced mean body weights and body weight gains) was noted at the 300 and 600 ppm dietary levels. There was no evidence of any parental toxicity at the 60 ppm dietary level. Reproductive performance was not affected at any dietary dose level. No adverse effects at the 60, 300 or 600 ppm dietary levels were evident from reproductive indices, gestation indices or parturition data during either litter interval. The only neonatal parameters significantly affected by treatment were reductions in pup body weights (at the 300 ppm and 600 ppm) and reductions in pup survival (at 600 ppm in the F2 litters from postnatal day 0 to 4). NOEL for general maternal toxicity and toxicity to the offspring = 60 ppm (equivalent to approximately 5 mg/kg b.w./day)	CK-430-002, 1994/7000839
Rat (m, f)	Acute neurotoxicity	94.9	Single exposure. Study conducted according to U.S. EPA Guideline No.:81-8. Doses: 45, 90, 180 mg/kg b.w.	Increased mortality noted at 180 mg/kg b.w. Clinical signs of toxicity (changes in gait, locomotion and arousal, lethargy) noted at 180 and 90 mg/kg b.w. LOAEL = 90 mg/kg b.w. NOAEL = 45 mg/kg b.w. Not considered to be an acute neurotoxicant.	CK-451-001, 1996/7001081
Rat (m, f)	One-year dietary neurotoxicity	94.5	12-month study conducted according to U.S. EPA Guideline No.: 83-1. Doses: 60, 800, 600 ppm in the feed (approx. 0, 3, 15, 30 mg/kg b.w./day)..	Reduced body weights, body weight gains and feed efficiency. Vacuolation and/or myelin sheath swelling of the brain and spinal cord in males at 300 ppm and above. This process was not	CK-451-002, 1994/7000730

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
				associated with any evidence of myelin or axon degeneration and was not evident after the recovery period. LOAEL = 300 ppm NOAEL = 60 ppm (equivalent to daily intake of 2.6 mg/kg b.w./day for males and 3.4 mg/kg b.w./day for females)	

Results observed following long-term dietary administration of chlorfenapyr technical to rats, mice and dogs were similar to those noted following short-term oral administration. The NOAELs for all three species were in the same range, with the lowest NOAEL in rodents: 60 ppm in rats (2.9 and 3.6 mg/kg b.w./ day for males and females, respectively) and 20 ppm in mice (2.8 and 3.7 mg/kg b.w./ day for males and females, respectively). Long-term dietary administration of chlorfenapyr technical resulted in no treatment-related oncogenic findings in either rats or mice.

Results from developmental toxicity studies in rats and rabbits showed that chlorfenapyr technical is neither a teratogen nor a developmental toxicant. The NOAELs for developmental toxicity were the highest doses tested in the respective studies, when tested up to maternally toxic doses (30 and 225 mg/kg b.w./day for rabbits and rats, respectively). The NOAELs for maternal toxicity were 5 and 25 mg/kg b.w./day for rabbits and rats, respectively. Results from a 2-generation reproductive toxicity study in rats showed that chlorfenapyr technical is not selectively toxic to the fertility or the developing offspring. The NOAEL for general maternal toxicity and toxicity to the offspring was 60 ppm (equivalent to approximately 5 mg/kg b.w.).

Results from a one-year neurotoxicity study in rats showed myelin sheath swelling in the spinal nerve roots after 13 weeks of treatment and myelinopathy of the brain and spinal cord after 52 weeks of treatment at doses of 300 and 600 ppm. The NOAEL was 60 ppm (2.6 and 3.4 mg/kg b.m./day for males and females, respectively). The findings were consistent with the neuropathological findings observed in the short-term rodent and long-term mouse studies. The effects were shown to be completely reversible following a 4-month recovery period. The alterations occurred in the absence of direct, degenerative damage to myelin (such as demyelination) or axons (such as axonal degeneration), and were not associated with any clinical behavioral effects (as evidenced by negative findings in the functional observation battery and motor activity tests).

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

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium and *Escherichia coli*	Bacterial Reverse Gene Mutation *in vitro* test	94.5	Study conducted according to U.S. EPA Guideline No.: 84-1 and 84-2. Doses: 0, 0.5, 1, 5, 10, 15, 20 and 25 μg/plate with and without S-9 (3 replicates each).	Does not induce either base-pair substitution or frame-shift mutation in any of the tester bacterial strains. Not mutagenic.	CK-435-001, 1994/7000799
Chinese Hamster lung cell culture	Chromosome aberrations, cytogenic investigation *in vitro* test	93.8	Study conducted according to OECD 473. Doses: 0, 0.9, 1.8, 3.5, 7.0, 14.1, 28.1, 56.3, 112.5, 225, 450, 900 and 1800 μg/ml with and without S-9.	Not clastogenic or polyploidy-inducing agent.	CK-435-007, 1994/7000803
Chinese Hamster Ovary cell culture	Chromosome aberrations, cytogenic investigation *in vitro* test	94.5	Study conducted according to EPA Guideline No.: 84-2. Doses: 0, 6.25, 12.5, 25 and 50 μg/ml with S-9; 0, 12.5, 25, 50 and 100 μg/ml without S-9.	Not clastogenic or polyploidy-inducing agent.	CK-435-006, 1994/7000835
Primary rat hepatocytes	Unscheduled DNA Synthesis *in vitro* test	94.5	Study conducted according to U.S. EPA Guideline No.: 84-4. Doses: 0, 0.05, 0.075, 0.1, 0.125, 0.15 and 0.3 μg/ml.	Because of excessive toxicity at 0.30 μg/ml, the highest dose evaluated was 0.15 μg/ml. No significant increase in the incorporation of tritiated thymidine into nuclear DNA of the cultured cells was found at any dose level. No induction of DNA damage in cultured rat hepatocytes.	1993/7001146, CK-435-003
Chinese Hamster Ovary cell culture	Mammalian Cell CHO/HGPRT Mutagenicity *in vitro* test	94.5	Study conducted according to U.S. EPA Guideline No.: 84-1 and 84-2. Doses: 0, 5, 10, 50, 100, 250 and 500 μg/ml with metabolic activation; 0, 2.5, 5, 10, 50, 100, and 250 μg/ml without metabolic activation.	Because of excessive toxicity at 500 μg/ml, the highest dose evaluated was 250 μg/ml. No induced mutations at the HGPRT locus in CHO cells. Not mutagenic.	CK-435-004, 1994/7000834

[6] Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study number
Mouse (m, f)	*in vivo* Micronucleus Assay in Mouse Bone Marrow Cell	94.5	Single exposure. Study conducted according to U.S. EPA Guideline No.: 84-2. Doses: 0, 7.5, 15, 30 mg/kg b.w. (males); 0, 5, 10, 20 mg/kg b.w. (females).	No effect on the number of micronucleated polychromatic erythrocytes in the bone marrow at any dose level at any sacrifice interval for males or females. Does not cause chromosomal damage *in vivo*. Not genotoxic.	CK-435-002, 1992/7001141

Results from a battery of *in vitro* and *in vivo* genotoxicity studies showed no indication of a mutagenic or genotoxic potential of chlorfenapyr technical material.

Table 6. Ecotoxicology profile of technical chlorfenapyr

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Lepomis macrochirus (bluegill fish)	Acute toxicity	94.5	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-1. Doses: 0, 5.03, 9.53, 14.7, 26.5, and 43.6 μg/L.	LC_{50} = 11.6 μg/L NOEC = 5.03 μg/L	CK-511-001; 1992/7001143
Oncorhynchus mykiss (rainbow trout)	Acute toxicity	94.5	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-1. Doses: 0, 2.61, 4.68, 8.01, 18.4, and 32.4 μg/L.	LC_{50} = 7.4 μg/L NOEC = 2.61 μg/L	CK-511-002; 1992/7001128
Ictalurus punctatus (channel catfish)	Acute toxicity	94.9	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-1. Doses: 0, 7.23, 11.7, 24.9, 39.5, and 56.2 μg/L.	LC_{50} = 12.3 μg/L NOEC = 7.23 μg/L	CK-511-005; 1996/7000986
Cyprinodon variegatus (sheepshead minnow)	Acute toxicity	94.5	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-1. Doses: 0, 16.2, 30.7, 48.4, 84.9, and 155 μg/L.	LC_{50} = 60.2 μg/L NOEC = 30.7 μg/L	CK-511-004; 1993/7001166
Daphnia Magna (water flea)	Acute toxicity: immobility	94.5	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-2. Doses: 0, 1.40, 2.52, 3.86, 6.31, and 10.7 μg/L.	EC_{50} = 6.1 μg/L NOEC = 2.52 μg/L	CK-521-001; 1992/7001127

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Mysidopsis bahia (mysid shrimp)	Acute toxicity	96.8	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-3 (c). Doses: 0, 0.32, 0.73, 0.89, 1.52, 2.52, and 5.08 μg/L.	LC_{50} = 2.0 μg/L NOEC = 0.32 μg/L	CK-521-004; 1994/7000842
Crassostrea virginica (Eastern oyster)	Acute toxicity: shell growth inhibition	94.5	96-h flow-through exposure. Study conducted according to U.S. EPA Guideline 72-3 (b). Doses: 1.81, 4.23, 5.46, 8.17, and 13.2 μg/L.	EC_{50} = 9.3 μg/L NOEC = 5.46 μg/L	CK-522-001; 1993/7001153
Selenastrum capricornutum (freshwater green alga)	Algal growth inhibition test	94.9	72-h static exposure. Study conducted according to OECD Method 201. Doses: 0.020, 0.035, 0.074, 0.133, 0.326 and 1.27 mg/L.	E_bC_{50} = 132 μg/L NOE_RC = 20 μg/L	CK-521-006; 1995/7000716
Lepomis macrochirus (bluegill fish)	Bioconcentration	97.1-97.3	33-day flow-through exposure. 54-day study conducted according to U.S. EPA Guideline 165-4. Dose: 1.0 μg/L (nominal). 2 radiolabels : Phenyl (U)-^{14}C] label or [2-Pyrrole-^{14}C] label.	Bioconcentration factors (BCF): 2084 to 2136 (total radioactivity); 83 to 114 (chlorfenapyr active substance). Uptake rate constant: 356 to 412 μg/Kg fish/μg/L water/day. Depuration rate constant: 0.171 day^{-1}. DT_{50} for clearance of the total radioactive residue during the depuration phase: 3 to 4 days.	CK-519-001; 1994/7000786
Oncorhynchus mykiss (rainbow trout)	Prolonged toxicity	94.5	28-day flow-through exposure. Study conducted according to OECD Method 204. Doses: 0, 0.86, 1.74, 3.86, 8.91, and 20 μg/L.	NOEC = 0.86 μg/L LOEC = 1.74 μg/L LC_{50} = 4.58 μg/L	CK-512-003; 1993/7001102
Oncorhynchus mykiss (rainbow trout)	Fish Early Life Stage toxicity	94.5	94-day flow-through exposure. Study conducted according to U.S. EPA Guideline 72-4(a). Doses: 0, 0.459, 0.907, 1.78, 3.68, and 7.64 μg/L.	NOEC = 3.68 μg/L LOEC = 7.64 μg/L based on post-hatch survival	CK-512-002; 1993/7001103

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Daphnia magna (water flea)	Chronic Toxicity Full Life-Cycle	94.5	21-day flow-through exposure. Study conducted according to U.S. EPA Guideline 72-4(b) and OECD 202, Part B. Doses: 0, 0.278, 0.448, 0.987, 1.88, 3.57 and 7.70 μg/L.	NOEC = 3.57 μg/L LOEC = 7.70 μg/L	CK-523-001; 1994/7000840
Mysidopsis bahia (mysid shrimp)	Chronic Toxicity Full Life-Cycle	94.5	28-day flow-through exposure. Study conducted according to U.S. EPA Guideline 72-4. Doses: 0, 0.172, 0.385, 0.966, 1.89 and 3.86 μg/L.	NOEC = 0.17 μg/L LOEC = 0.39 μg/L	CK-523-002; 1994/7000791
Hyalella azteca	Acute toxicity to freshwater sediment-dwelling organisms	94.9	Single application to sediment. 10-day study conducted according to U.S. EPA Guideline 73-1. Doses: 0, 6.25, 12.5, 25.0, 50.0, and 100 mg ai/kg of dry sediment (nominal).	NOEC = 10.9 mg/kg in the sediment LC_{50} = 21.2 mg/kg in the sediment	CK-521-007; 1997/7000878
Leptocheirus plumulosus	Acute toxicity to saltwater sediment-dwelling organisms	94.5	Single application to sediment. Static 10-day study conducted according to U.S. EPA Guideline 73-1. Doses: 0, 0.05, 0.10, 0.20, 0.40, and 0.80 mg ai/kg of dry sediment (nominal).	NOEC = 0.09 mg/kg in the sediment LC_{50} = 0.19 mg/kg in the sediment	CK-521-008; 1998/7000835
Chironomus riparius (midge)	Toxicity to freshwater sediment-dwelling organisms	94.9	Single application to water. Static 28-day study conducted according to EEC Annex II Series 8.2.7. Doses: 0, 18.8, 37.5, 75, 150, and 300 μg ai/L (nominal).	NOEC = 18.8 μg/L LC_{50} = 49.5 μg/L	CK-549-007; 1997/7000799
Soil microbes	Inhibition of respiration and nitrification of soil microflora	94.5	Single application in 2 soils. 28/91-day study conducted according to BBA Part VI 1.1. Doses: 400 and 4000 µg a.i. per kg dry soil (nominal).	No significant effect on carbon fixation, NOEC ≥ 4.0 mg/kg. More than 25% inhibition of nitrogen fixation after 56 days in 1 soil.	CK-625-001; 1995/7000712
Eisenia foetida (earthworm)	Acute toxicity	94.5	Single application to soil. 14-day study conducted according to OECD 207. Doses: 0, 5.0, 10, 20, 40, and 80 mg/kg dry soil (nominal).	LC_{50} = 23 mg a.i./kg soil	CK-531-003; 1994/7000855
Eisenia foetida (earthworm)	Chronic toxicity, growth & reproduction	94.5	Single application to soil. 156-day study conducted according to Draft International Standard ISO/DIS 11268-2, Soil quality.	No significant effects on mortality, reproduction, morphology, or change in body weight at 0.84 and 4.2 mg ai per kg dry soil.	CK-534-001; 1995/7000765

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
			Doses: 0.84 mg and 4.2 mg ai per kg dry soil (nominal).		
Various Crop Plants and Weeds	Acute toxicity to non-target plants	N/A	Herbicide Screening Procedure. Pre- and/or post-emergence exposure at doses ranging from 63 to 2000 g/ha.	Low herbicidal activity post-emergence and no herbicidal activity when applied pre-emergence to over 30 species of plants.	CK-549-016; 1930/7000989
Anas platyrhynchos (mallard duck)	Acute toxicity LD_{50}	94.5	Single exposure. 21-day study conducted according to U.S. EPA Guideline No: 71-1. Doses: 0, 1, 2, 4, 8, 16, 32, 64, and 128 mg/kg b.w. (nominal).	LD_{50} = 10.3 mg/kg b.w. NOEL = 1 mg/kg b.w.	CK-505-001; 1993/7001095
Colinus virginianus (Northern bobwhite)	Acute toxicity LD_{50}	94.5	Single exposure. 21-day study conducted according to U.S. EPA Guideline No: 71-1. Doses: 0, 1, 2, 4, 8, 16, 32, 64, and 128 mg/kg b.w. (nominal).	LD_{50} = 34 mg/kg b.w. NOEL = 8 mg/kg b.w.	CK-505-002; 1993/7001094
Anas platyrhynchos (mallard duck)	Acute toxicity LC_{50}	94.5	5-day exposure. 8-day study conducted according to U.S. EPA Guideline No: 71-2. Doses: 0, 4, 6, 9, 13.5, and 20.3 mg/kg diet. (nominal).	LC_{50} = 8.6 mg/kg diet NOEC < 4 mg/kg diet	CK-505-003; 1993/7001093
Colinus *virginianus* (Northern bobwhite)	Acute toxicity LC_{50}	94.5	5-day exposure. 8-day study conducted according to U.S. EPA Guideline No: 71-2. Doses: 0, 10, 20, 40, 80, 160, and 320 mg/kg diet. (nominal).	LC_{50} = 132 mg/kg diet NOEC = 10 mg/kg diet	CK-505-004; 1993/7001158
Anas platyrhynchos (mallard duck)	Effects on bird reproduction	94.5	20-week exposure. Study conducted according to U.S. EPA Guideline No: 71-4 and OECD Method 206. Doses: 0, 0.5, 1.5, and 2.5 mg/kg diet (nominal).	NOEC for reproductive effects = 0.5 mg/kg diet	CK-505-008; 1994/7000889
Colinus virginianus (Northern bobwhite)	Effects on bird reproduction	94.5	20-week exposure. Study conducted according to U.S. EPA Guideline No: 71-4 and OECD Method 206. Doses: 0, 0.5, 1.5, and 4.5 mg/kg diet (nominal).	NOEC for reproductive effects = 1.5 mg/kg diet	CK-505-007; 1994/7000890
Apis mellifera (honey bee)	Acute contact and oral toxicity	94.5	Single exposure.	LD_{50} contact = 0.45 µg/bee LD_{50} oral = 1.7 µg/bee	CK-541-004; 1995/7001534

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
			96-h study conducted according to U.S. EPA Guideline No: 141-1 and EPPO 170. Doses: 0.031, 0.063, 0.1, 0.25 , 0.50 and 1.0 µg a.s./bee (nominal) for the contact test and 0.13, 0.25, 0.50, 1.0, 2.0, and 4.0 µg a.s./bee (nominal) for the oral test.		

Annex 2: References

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