FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

PICLORAM

4-amino-3,5,6-trichloropyridine-2-carboxylic acid

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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DISCLAIMER[1]

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

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of plant protection products 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.

Since 1999 the development of FAO specifications has followed the **New Procedure**, first described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" (FAO Plant Production and Protection Paper No. 149) and, subsequently, in the 1st edition of the "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (FAO Plant Production and Protection Paper No. 173, 2002). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2000 onwards, the publication of FAO 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 1st edition of the "FAO/WHO Manual on Pesticide Specifications."

Part Two: The Evaluation Report(s) on the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO Specifications developed 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. FAO 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 those which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

NOTE: publications are available on the internet at http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/

PART ONE

SPECIFICATIONS

PICLORAM

INFORMATION

ISO common name

Picloram (E-ISO, BSI, ANSI, WSSA, JMAF); piclorame ((m) F-ISO)

Synonyms

2-pyridinecarboxamide, 4-amino-3,5,6-trichloro

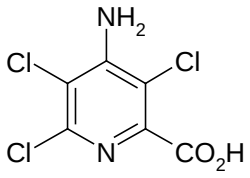
Picloram acid

Chemical names

IUPAC 4-amino-3,5,6-trichloropyridine-2-carboxylic acid

CA 4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid

Structural formula



Molecular formula

$C_6H_3Cl_3N_2O_2$

Relative molecular mass

241.5 (picloram acid); 279.6 (picloram potassium salt); 432.8 (picloram tri-*iso*-propanolamine salt)

CAS Registry number

1918-02-1

CIPAC number

174

Identity tests

HPLC retention time and LC-MS for technical picloram acid.

Potassium counter-ion is identified by ion chromatography in the SL.

Tri-*iso*-propanolamine (TIPA) counter-ion by LC-MS in the SL.

PICLORAM TECHNICAL MATERIAL

FAO Specification 174/TC (October 2012*)

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 174/2012, 174/2011 and 174/2005. It should be applicable to relevant products of these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation reports 174/2012, 174/2011 and 174/2005, as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of picloram (acid) together with related manufacturing impurities. It shall be an white to dark brown powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 174/TC/M/2, Handbook L, p. 104, 2006)

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 **Picloram (acid) content** (CIPAC 174/TC/M/3, Handbook L, p. 104, 2006)

The picloram (acid) content shall be declared (not less than 920 g/kg based on the dry active ingredient, Note 1) and when determined, the average measured content obtained shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 **Hexachlorobenzene** (Note 2)

Maximum: 0.05 g/kg

Note 1 Picloram TC may be a wet cake. For production of picloram water based formulations there is no need to dry as a first step and this wet cake can be used directly. The water content of the wet cake shall not exceed 275 g/kg, is typically 170 g/kg, and can be measured using method CIPAC MT30.5, Manual J, p.120, 2000.

Note 2 The methods for determination of hexachlorobenzene in technical and formulated picloram are available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/

PICLORAM

SOLUBLE CONCENTRATE

FAO Specification 174/SL (October 2012*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report 174/2004*. It should be applicable to relevant products of these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report* 174/2004, *as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of technical picloram, complying with the requirements of FAO specification 174/TC (October 2012), in the form of the potassium or tri-*iso*-propanolamine salt dissolved in water, together with any other necessary formulants. It shall be a clear or opalescent liquid, free from visible suspended matter and sediment, to be applied as a true solution of the active ingredient in water.

2 Active Ingredient

2.1 Identity tests (CIPAC 174/SL/M/2, CIPAC Handbook L, p. 104, Note 1)

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

2.2 Picloram (acid) content (CIPAC 174/TC/M/2, Notes 1 & 2)

The picloram (acid) content shall be declared (g/kg or g/l at 20 ± 2ºC) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance:

Declared content, g/kg or g/l at 20 ± 2°C	Permitted tolerance
Above 25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content

Note: in each range the upper limit is included.

3 Relevant impurities

3.1 Hexachlorobenzene (Note 3)

Maximum: 0.005% of the picloram acid content found under 2.2.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/

4 Physical Properties

4.1 **pH range** (MT 75.3)

pH range of undiluted product: 7.5 to 11.2.

4.2 **Solution stability** (MT 41)

The formulation, after the stability test at 54°C (clause 5.1) and following dilution with CIPAC standard water D and standing at 30 ± 2°C for 18 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. Any visible sediment or particles produced shall pass through a 45 µm test sieve.

4.3 **Persistent foam** (MT 47.2) (Note 4)

Maximum: 60 ml after 1 minute.

5 Storage Stability

5.1 **Stability at elevated temperature** (MT 46.3) (Note 5)

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 clause for:

pH range (4.1).

Note 1 The methods for identification of potassium and tri-*iso*-propanolamine in picloram in SL are available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

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

Note 3 The methods for determination of hexachlorobenzene in technical and formulated picloram are available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 4 The mass of the sample to be used in the test should correspond to the highest rate of use recommended by the supplier.

Note 5 Samples of the product taken before and after the storage stability test should be analyzed together after the test to reduce the analytical error.

PART TWO

EVALUATION REPORTS

PICLORAM

PICLORAM

FAO/WHO EVALUATION REPORT 174/2012

Recommendation

The Meeting recommended that

(i) the new specification for picloram TC, proposed by Dow AgroSciences, as amended, should be adopted by FAO

(ii) the existing FAO specification for picloram TK should be withdrawn

Appraisal

The Meeting reviewed the existing FAO specification for picloram TK (July 2005) in 2011 in the context of a pending equivalence case. The specification for picloram TK actually fulfilled the criteria for a TC. Dow AgroSciences agreed to propose a specification for a TC, where with regard to the existing TK specifications few clauses needed to be modified:

- Description: The TC still has the aspect of an amber to dark brown powder and was extended to encompass the description of the Nutrichem material, which is white to light tan. To cover both materials, the description «white to dark brown powder» was chosen.
- The minimum content of the active is now 920 g/kg on a dry weight basis, and a footnote is added that picloram TC is a wet cake, with a maximum water content of 275 g/kg. As the TC is formulated into SL formulations, the water content has to be limited to a reasonable amount to cover the concentration ranges of the SL (see picloram SL specification). For obvious reasons, the range of tolerance for the TK is no longer necessary for the TC.
- The CIPAC analytical method is now published in Handbook L, and the correct reference has been inserted.
- The analytical method for the determination of hexachlorobenzene, the relevant impurity identified in picloram technical material, is applicable to the TC as wet cake as well. The link in the footnote refers to the same independent-laboratory validated method.
- However, as in the TC the limit of the relevant impurity is expressed as g/kg (FAO/WHO Specification manual), the limit is changed from 0.005 % of the picloram content found under 2.2 to: maximum 0.05 g/kg, neglecting the fact that the TC has a content of 920 g/kg minimum.

In the same instance, the SL specification was editorially revised and the following minor changes were introduced:

- The reference to the October 2012 TC specification was introduced
- The identity test and method for determination of active ingredient content is published in CIPAC Handbook L and the references have been corrected
- The footnote with the link to the FAO website was corrected with the last version (October 2012).

PICLORAM

FAO/WHO EVALUATION REPORT 174/2011

Recommendation

The Meeting recommended that

(i) the existing specification for picloram technical can be extended to the TC from Nutrichem Co. Ltd. China subject to the satisfactory resolution of some points
(ii) the existing FAO specification for picloram TK should be revised and converted into a TC specification after due consultation of the proposer

Appraisal

The Meeting considered data submitted in 2010 by Nutrichem Co. Ltd. in support of an equivalence determination with the reference profile that supported the existing picloram specification 174/TK (July 2005). The data submitted were in accordance with the requirements of the November 2010 - second revision of the First Edition of the Manual on development and use of FAO and WHO specifications for pesticides and supported the existing specification.

Picloram is not under patent. It has not been evaluated by the FAO/WHO JMPR but was considered by WHO/IPCS for hazard classification. It has been evaluated and reviewed by the European Commission as part of the EU review of existing active substances for inclusion in the former Annex I of the Council Directive 91/414/EEC. It has been included in Annex I (01-01-2009), with a minimum purity of 920 g/kg dry weight basis (782 g/kg wet weight by calculation).

The Meeting was provided with commercially confidential information on the manufacturing process for picloram, the manufacturing specifications for the TC and five-batch analytical data on the purity and impurities ≥1 g/kg. Mass balances ranged from 99.03 to 100.37 % in the 5-batch data and amount of unknowns were < 1g/kg. The declared minimum active ingredient content (955 g/kg) was higher than that of the existing FAO specifications (920 g/kg on a dry weight basis). Confidential data were similar to those submitted for registration in China.

Manufacturing maximum limits for impurities identified in the technical material did not exceed the limits in the reference profile, except for water. The water content was not considered reason for non-equivalence. Only one new impurity was identified, which has the related structural formula as picloram with the difference that one chloride ion (-Cl) being replaced by a hydroxyl group (-OH). Since this impurity does not show any structural

alert and the mutagenicity results are negative, the Meeting considered this impurity as non-relevant.

A mutagenicity test (Ames test) on Nutrichem's picloram technical has been conducted as tier-1 data. The study results showed that the test material did not induce mutation under the conditions of the study.

Two main issues were identified by the Meeting:

- The company had used an in-house method for determination of the content of picloram in picloram technical instead of the CIPAC Method published in Handbook L. The company agreed to carry out a bridging study to compare the results of the in-house method with those of the collaboratively validated method. The results submitted later on demonstrated that the results in the 5-batch study elaborated with the in-house method are valid.
- The company used an own method to determine the content of the relevant impurity hexachlorobenzene in picloram technical. The method is based on negative-ion chemical ionization gas chromatography using external standardization, but initially was not peer validated. The company agreed to carry out an independent laboratory validation of this method, and the results of the study showed that the method is acceptable. The method has a comparable limit of quantitation (LOQ) of 0.001 g/kg hexachlorobenzene in picloram technical as the method proposed by Dow AgroSciences based on EI and single ion monitoring which has a LOQ of ~0.0005 mg/kg. This value refers to the SL formulation containing 220 g/kg picloram acid and hence corresponds to about 0.002 g/kg for picloram TC.

Both methods are provided for download using the link in Note 2 in the TC specification and the link in Note 3 of the SL specification, respectively. As with both methods the sample is dissolved in chloroform and equilibrated with sodium chloride solution, the methods are considered to be applicable to the TC as well as to the SL formulations.

The data submitted allowed the Meeting to conclude on equivalence of Nutrichem Co. technical picloram with the reference profile. The Meeting concluded that the Nutrichem's picloram TC was equivalent to the picloram reference TC based on Tier-1 evaluation as detailed in the FAO and WHO specification manual (2010 edition). The Tier-1 is mainly based on chemical evidence (impurity profile, manufacturing specification etc.) and includes only a mutagenicity study to detect the presence of exceptional hazardous-mutagenic-impurities, which could go undetected by chemical analysis. For that reason, the hazard data package is reduced to an *in vitro* mutagenicity study with *S. Typhimurium* and *E. coli*. As with the reference material, the Ames-test results were negative.

The physical and chemical properties of pure picloram were virtually the same as those for the reference material for melting point, solubility in water, octanol/water partition coefficient and dissociation characteristics.

Data on vapour pressure as well as photolysis characteristics are not available. Minor differences in the other physicochemical properties are due to the differences in purity of the tested material or the experimental conditions (such as pH).

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 174 / 2011

PICLORAM

INFORMATION

ISO common name

Picloram (E-ISO, BSI, ANSI, WSSA, JMAF); piclorame ((m) F-ISO)

Synonyms

2-pyridinecarboxamide, 4-amino-3,5,6-trichloro

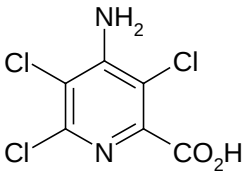
Picloram acid

Chemical names

IUPAC 4-amino-3,5,6-trichloropyridine-2-carboxylic acid

CA 4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid

Structural formula



Molecular formula

$C_6H_3Cl_3N_2O_2$

Relative molecular mass

241.5 (picloram acid); 279.6 (picloram potassium salt); 432.8 (picloram tri-*iso*-propanolamine salt)

CAS Registry number

1918-02-1

CIPAC number

174

Identity tests

HPLC retention time and LC-MS for technical picloram acid.

Potassium counter-ion is identified by ion chromatography in the SL.

Tri-*iso*-propanolamine (TIPA) counter-ion by LC-MS in the SL.

Table 1. Physico-chemical properties of pure picloram

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	not available	-	-	-
Melting point.	185.1-188.2 °C (decomposition around the melting range)	98.54	OECD 102 and EPA Guideline 830.7200	NC-2010-028
Temperature of decomposition	(decomposition around the melting range)	98.54	OECD 102 and EPA Guideline 830.7200	NC-2010-028
Solubility in water	0.52 g/l at 20 °C	98.54	OECD 105 and EPA Guideline 830. 7840	NC-2010-028
Octanol/water partition coefficient	log P_{OW} = 0.63 at 25°C, pH 3 log P_{OW} = 1.83 at 25°C, pH 1 log P_{OW} = -2.01 at 25°C, pH 7 log P_{OW} = -2.21 at 25°C, pH 9	98.54	OECD 107 shake flask method and EPA Guideline 830.7550	NC-2010-028
Hydrolysis characteristics	Half-life ＞1 year at room temperature at pH 5, 7, 9	98.54	OECD 111 and EPA Guideline 835. 2120	NC-2010-051
Photolysis characteristics	not available			
Dissociation characteristics	pKa = 2.118	98.54	OECD 112, titration method and EPA Guideline 830.7370	NC-2010-028
Solubility in organic solvents	26.46 g/l Methanol at 20 ± 0.5 °C ＜0.71 g/l n-hexane at 20 ± 0.5 °C 4.47 g/l n-octanol at 20 ± 0.5 °C	98.54	OECD 105 and EPA Guideline 830. 7840	NC-2010-028

Table 2: Chemical composition and properties of picloram 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. Mass balances were 99.3 – 100.37 % and percentages of unknowns were 0 – 0.7 %.
Declared minimum [a.i.] content	955 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	Hexachlorobenzene Max 0.001 g/kg
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	185.1 – 188.2°C. (decomposition around the melting range)	98.54	OECD 102 and EPA Guideline 830.7200	NC-2010-028
Solubility in organic solvents	26.46 g/l Methanol at 20 ± 0.5°C ＜0.71 g/l n-hexane at 20 ± 0.5 °C 4.47 g/l n-octanol at 20 ± 0.5 °C	98.54	OECD 105 and EPA Guideline 830. 7840	NC-2010-028

Picloram has not been evaluated by FAO/WHO JMPR.

The IPCS hazard classification of picloram is: None (unlikely to present acute hazard in normal use).

EFSA's conclusion following the peer review process for picloram propose a classification with: R43: May cause sensitisation by contact.

METHODS OF ANALYSIS AND TESTING

The CIPAC method for the determination of picloram content in picloram technical and SL formulations is based on reversed-phase HPLC on an ODS column with UV detection at 240 nm and benzamide as internal standard. The method is published in Handbook L and also includes identity tests for picloram based on comparison of UV spectra, HPLC retention time and HPLC-MS with full scan in negative ion electrospray ionization mode.

The in-house method proposed by Nutrichem for determination of picloram content was successfully compared with the CIPAC method 174/TC/(M)/3 in a bridging study. The in-house method is based on reversed phase HPLC with a ZORBAX Eclipse XDB-C8 column, using DAD detection at 240 nm and external standardisation.

The methods for determination of impurities are based on reversed-phase HPLC with DAD detection and external standardization.

The method for the determination of the relevant impurity, hexachlorobenzene (HCB), in the TC is a GC-MS method where the ion source is operated in the negative-ion chemical ionization mode with methane as reactant gas (NCI). Under these conditions, hexachlorobenzene shows only the molecular ion cluster 282, 284, 286 and 288, and single ion monitoring is used on m/z 282, 284 and 286. External standardization is used and a limit of quantification of ~ 1 mg hexachlorobenzene per kg of picloram technical was achieved, which corresponds to the proposed limit of HCB in picloram produced by Nutrichem. The method was successfully submitted to an independent laboratory validation exercise. The method can be downloaded from the FAO website using the link in the footnotes in the TC- and SL-specifications.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD or EPA, as indicated in the specifications.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as picloram (acid equivalent).

Annex I Hazard Summary

Notes.

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

ACUTE TOXICITY

No data was available on acute toxicity of the picloram technical material produced by Nutrichem.

SUBACUTE AND CHRONIC TOXICITY

No data was available on subacute to chronic toxicity of the picloram technical material produced by Nutrichem.

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Table 3. Mutagenicity profile of the technical material based on in vitro and in vivo tests

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
S. typhimurium (strains TA1535, TA1537, TA98 & TA100) *E.Coli (strain WP2(pkM101))*	*in vitro* bacterial gene mutation assay	98.76	OECD Guideline 471 48h Between 5.06 and 0.06 mg/plate with and without S9 metabolic activation	non mutagenic / non pro-mutagenic	B-01114

ECOTOXICITY

No information was available on ecotoxicity of the picloram technical material.

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

Annex 2
References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO	2005	FAO specifications and evaluations for agricultural pesticides: Picloram
	FAO/WHO	2006	Manual on development and use of FAO and WHO specifications for pesticides. February 2006 Revision of First Edition. FAO Plant Production and Protection Paper. Revised.
NC-2010-028	Hongxia Li	2010	Chemical and Physical Characterization of Picloram TGAI: Color, Physical State, Odor, Stability, Oxidation/Reduction, pH, UV-Vis, Melting Point, Density, Dissociation Constant, Partition Coefficient and Water Solubility.GLP. Nutrichem Laboratory Co. Ltd. Unpublished
NC-2010-051	Hongxia Li	2010	Determination of hydrolysis rate of Picloram TGAI. GLP. Nutrichem Laboratory Co. Ltd. Unpublished
B-01114		2010	BACTERIAL REVERSE MUTATION TEST – Picloram. GLP. Unpublished
ABC-2010-01	Yeming Zhang	2010	Five-batch Analysis of Picloram Technical. Study ABC-2010-01. Report ABC-2010-01.version 01. GLP. Achiever Biochem Co., Ltd., China. Unpublished

PICLORAM

EVALUATION REPORT 174/2004

Explanation

The data for picloram were evaluated in support of proposed new FAO specifications for TC, TK and SL.

Picloram is not under patent.

Picloram had not been evaluated by the FAO/WHO JMPR but was considered by WHO/IPCS for hazard classification. It was registered for the first time in the United States in 1964. USEPA issued the Registration Standard on March 29, 1985 and the revised Registration Standard on Sep 30, 1988. US EPA conducted a full picloram re-registration in Aug 1995 (USEPA 1995). Picloram is currently under review by the European Commission (Stage 3/List B).

The draft specifications and the supporting data were provided by Dow AgroSciences in 2003.

Uses

Picloram is a herbicide, discovered in the early 1960's by The Dow Chemical Company and introduced to the marketplace in 1963. It is a systemic herbicide that deregulates plant growth and is registered for uses to control woody plants and broadleaf weeds. It is used in the management of unwanted vegetation in rangeland, grass pastures, forestry as well as non-cropland and rights-of-way sites, such as around industrial and military installations, roads, railways, airports, under powerlines and along pipelines. In some countries there are additional uses in rice, sugarcane, cereals and oilseed rape.

Identity of the active ingredient

ISO common name

Picloram (E-ISO, BSI, ANSI, WSSA, JMAF); piclorame ((m) F-ISO)

Synonyms

2-pyridinecarboxylic acid: 4-amino-3,5,6-trichloro-

2-pyridinecarboxamide, 4-amino-3,5,6-trichloro

Picloram acid

Chemical names

IUPAC 4-amino-3,5,6-trichloropyridine-2-carboxylic acid

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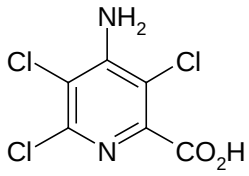
Structural formula



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Potassium counter-ion by ion chromatography in the SL.

Tri-*iso*-propanolamine (TIPA) counter-ion by LC-MS in the SL.

Physico-chemical properties of pure picloram

Table 1. Physico-chemical properties of pure picloram (acid and certain salts)

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	8×10^{-8} Pa at 25°C	99.4	EEC A4, Knudson-Effusion/weight loss method
Melting point, boiling point and/or temperature of decomposition	Melting point: 174-183°C (acid) >260°C (potassium salt) 61-66°C (tri-*iso*-propanolamine salt) Boiling point: not determined as picloram decomposes around the melting point. Decomposition temperature: >174°C (acid)	 99.4 88.85 a.e.* 54.0 a.e.*	 OECD 102 and 103 EEC A1, DSC Schriber *et al*. 1989 Schriber *et al*. 1989

Parameter	Value(s) and conditions	Purity %	Method reference
Solubility in water	picloram (acid) 0.56 g/l at 20°C at pH 3 picloram is a strong acid and solubility at pH 5, 7, 9 refers mainly or wholly to the salt	99.4	EEC A6, Shake flask method
	picloram potassium salt 530 g/l (458 g/l a.e.*) at 20°C, pH not stated	88.85 a.e.*	Schriber *et al*. 1989, RP-HPLC of supernatant of saturated solution
	picloram tri-*iso*-propanolamine salt >675 g/l (>377 g/l a.e.*) at 20°C, pH not stated	54.0 a.e.*	Schriber *et al*. 1989RP-HPLC of supernatant of saturated solution
Octanol/water partition coefficient	log P_{ow} = -1.05 ± 0.05 at 20°C at pH 5 (P=0.089) log P_{ow} = -1.92 ± 0.06 at 20°C at pH 7 (P=0.012) log P_{ow} = -2.09± 0.02 at 20°C at pH 10 (P=0.0081)	98.5	OECD 107 shake flask method
Hydrolysis characteristics	Picloram is stable under acidic, neutral and basic conditions.	99.4	USEPA (1995) Reregistration Eligibility Decision Picloram, EPA 738-R95-019.
Photolysis characteristics	Aqueous photolysis: half-life = 2.6 days in mid-summer, latitude 40 deg N, 25°C. Picloram is stable to photo-degradation on soil surfaces	99.7% radiopurity	USEPA (1995) Reregistration Eligibility Decision Picloram, EPA 738-R95-019.
Dissociation characteristics	pKa = 2.3 at 22°C	99.4	DAS Method ML-AL 89-040540

* a.e. = acid equivalents, i.e. expressed as picloram (acid).

Chemical composition and properties of picloram technical concentrate (TK)

Note: picloram technical material (TC) may be produced by drying the TK, though this is not done commercially.

Table 2. Chemical composition and properties of picloram technical concentrate (TK)

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 99.6–100.5% and percentages of unknowns were <0.1%.
Declared minimum picloram content	920 g/kg on a dry basis.
Relevant impurities ≥1 g/kg and maximum limits for them	None.
Relevant impurities <1 g/kg and maximum limits for them:	Hexachlorobenzene (HCB), 0.05 g/kg (0.005% or 50 ppm) of picloram (acid)
Stabilizers or other additives and maximum limits for them:	None.
Melting temperature range of the TC	Melting point range is 174-185°C and decomposition occurs above the melting point.

Toxicological summaries

Notes.

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

(iii) Unless otherwise stated, results are presented as picloram (acid) although picloram salts were administered in some cases, as indicated.

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

Species	Test	Duration and conditions or guideline adopted	Result
Male and female F344 rats	Oral	USEPA 81-1	LD_{50} ≥5000 mg/kg bw (males) LD_{50} = 4012 mg/kg bw (females)
Male and female NZW rabbits	Dermal	USEPA 81-2	LD_{50} ≥2000 mg/kg bw
Male and female F344 rats	inhalation	USEPA 81-3	LC_{50} ≥0.035 mg/l
Male and female NZW rabbits	Eye irritation	USEPA 81-4	Moderate irritation; all signs resolved within 7 days post-treatment
Male and female NZW rabbits	Skin irritation	USEPA 81-5	Non-irritant
Male Hartley Guinea pigs	Skin sensitization	USEPA 81-6	Negative; non-sensitizer

Table 3b. Toxicology profile of Tordon™ 22K*, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result
Male and female F344 rats	Oral	USEPA 81-1	LD_{50} = > 5000 mg/kg bw
Male and female NZW rabbits	Dermal	USEPA 81-2; OECD 402	LD_{50} = > 5000 mg/kg bw
Male and female NZW rabbits	Inhalation	USEPA 81-3; OECD 403; EEC B2	LC_{50} = > 8.11 mg/L
Male and female NZW rabbits	Eye irritation	USEPA 81-4	Slight to moderate irritation; all effects resolved by 14 days post-treatment
Male and female NZW rabbits	Skin irritation	USEPA 81-5	Slight irritation which did not persist; irritancy was less than trigger level for classification
Male Hartley Albino guinea pigs	Skin sensitization	USEPA 81-6; OECD 406	Very slight (2/10) to slight (8/10) erythaema following challenge using the Buehler method; under the conditions employed, test material caused positive sensitization

* Tordon™ 22K is an SL of picloram potassium salt, containing 22% picloram (™ trade name of Dow AgroSciences).

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

Species	Test	Duration and conditions or guideline adopted	Result
Male and female NZW rabbits	Short-term toxicity	21-day dermal using 0, 75.3, 251, or 753 mg/kg bw/d (as potassium salt; picloram acid equivalents of 65, 217, or 650 mg/kg bw/d)	NOAEL ≥753 mg/kg bw/d
Male and female Beagle dogs	Short-term toxicity	One month dietary using 0, 125, 250, or 375 mg/kg bw/d	NOAEL not established LOAEL= 125 mg/kg bw/d
Male and female Beagle dogs	Sub-chronic toxicity	Six month dietary using 0, 7, 35, or 175 mg/kg bw/d	NOAEL = 35 mg/kg bw/d LOAEL = 175 mg/kg bw/d Liver = target organ
Male and female Fischer 344 rats	Sub-chronic toxicity	13-week dietary using 0, 15, 50, 150, 300, or 500 mg/kg bw/d	NOAEL = 50 mg/kg bw/d LOAEL = 150 mg/kg bw/d Liver = target organ
Male and female B6C3F1 mice	Sub-chronic toxicity	13-week dietary using 0, 1000, 1400, and 2000 mg/kg bw/d	NOAEL = ≤ 1000 mg/kg bw/d LOAEL = 1000 mg/kg bw/d Liver = target organ
Male and female Beagle dogs	Long term toxicity	12-month dietary using 0, 7, 35, or 175 mg/kg bw/d	NOAEL = 35 mg/kg bw/d LOAEL = 175 mg/kg bw/d Liver = target organ
Male and female Fischer 344 rats	Long term toxicity	2-year dietary oncogenicity study using 0, 250 or 500 mg/kg bw/d	NOAEL = Not established LOAEL = 250 mg/kg bw/d Not carcinogenic Liver and kidney = target organs
Male and female Fischer 344 rats	Long term toxicity	2-year dietary oncogenicity study using 0, 20, 60, or 200 mg/kg bw/d	NOAEL = 20 mg/kg bw/d LOAEL = 60 mg/kg bw/d Not carcinogenic Liver = target organ
Male and female B6C3F1 mice	Long term toxicity	2-year dietary using 0, 100, 500, or 1000 mg/kg bw/d	NOAEL = 1000 mg/kg bw/d No target organs Not carcinogenic
Male and female Sprague-Dawley rats	Reproductive toxicity	FIFRA 83-4; OECD 416; EEC 87/302; Dose levels of 0, 20, 200, or 1000 mg/kg bw/d	Parental NOAEL = 200 mg/kg bw/d Parental LOAEL = 1000 mg/kg bw/d Litter NOAEL = 1000 mg/kg bw/d No reproductive effects; renal toxicity in parental F0 and F1 males and females
Female NZW rabbits	Teratology	0, 40, 200, or 400 mg/kg/day (using the potassium salt)	Maternal NOAEL = 40 mg/kg bw/d Maternal LOAEL = 200 mg/kg bw/d Developmental NOAEL = 400 mg/kg bw/d No teratogenic effects
Female CD rats	Teratology	0, 100, 500, or 1000 mg/kg bw/d (using the potassium salt.)	Maternal and developmental NOAEL = 1000 mg/kg bw/d No teratogenic effects

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

Species	Test	Conditions	Result
In vitro tests			
S. typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation; USEPA 84-2	5, 16.67, 50, 166.7, 500, 1667, and 5000 ug/plate; with and without metabolic activation.	Negative
Chinese hamster ovary cells	CHO/HGPRT Forward mutation assay; USEPA 84-2	250, 500, 750, 1000, 1250 ug/mL in presence of S9; 125, 250, 500, 625, 750 ug/mL in absence of S9	Negative
Rat hepatocyte	Unscheduled DNA synthesis; Guideline 84-2	10, 33.3, 100, 333.3, 1000 ug/mL	Negative
In vivo tests			
Mouse (CD1-ICR BR)	Micronucleus (marrow cells)	171, 514, 1543 mg/kg bw	Negative
Rat (Sprague-Dawley)	Chromosome aberrations using bone marrow cells	20, 200, 2000 mg/kg bw	Negative

Table 6. Ecotoxicology profile of technical picloram

All values are reported in terms of acid equivalents, i.e. corrected for purity of the material tested or verified against an analytical standard (the specification of the material tested is given in parenthesis).

Species	Test	Duration and conditions	Result
Avian toxicity			
Anas platyrhynchos (mallard duck)	Acute oral toxicity	FIFRA 71-1	LD_{50} >2510 mg a.e./kg (acid, 93.8%) LD_{50} >2250 mg a.e./kg (K^+ salt, 38.6% a.e.)
Colinus virginianus (bobwhite quail)	Short-term dietary toxicity	FIFRA 71-2	5-day LC_{50} >5620 ppm a.e. (K^+ salt, 38.6% a.e.)
Colinus virginianus (bobwhite quail)	Reproductive toxicity	FIFRA 71-4 OECD 206	NOEC 1500 ppm a.e. (acid, 85.2%)
Aquatic toxicity			
Oncorhynchus mykiss (rainbow trout)	Acute toxicity	FIFRA 72-1 OECD 203	96h LC_{50} 13.7 mg a.e./l* (acid, 80.3%)
Lepomis macrochirus (bluegill sunfish)	Acute toxicity	FIFRA 72-1 OECD 203	96h LC_{50} 39.9 mg a.e./l* (acid, 80.3%)
Oncorhynchus mykiss (rainbow trout)	Chronic toxicity	60-day embryo-larval test	NOEC 0.586 mg a.e./l* (acid, 93.8%)
Lepomis macrochirus (bluegill sunfish)	Bioaccumulation	28-day flow-through study (draft EPA guidelines)	BCF <1 (^{14}C acid, 10 mCi/mM)
Daphnia magna	Acute toxicity	FIFRA 72-2 OECD 202, Part 1	48h EC_{50} 68.5 mg a.e./l* (acid, 80.3%)
Gammarus pseudolimnaeus (gammarid shrimp)	Acute toxicity	OECD 202, Part 1	96h LC_{50} 56.6 mg a.e./l (acid, 89.5%)

Species	Test	Duration and conditions	Result
Planorbella trivolvis (ramshorn snail)	Acute toxicity	OECD 202, Part 1	96h LC_{50} 137 mg a.e./l (acid, 89.5%)
Daphnia magna	Chronic toxicity	FIFRA 72-4 OECD 202, Part 2	21-day NOEC 6.79 mg a.e./l (acid, 89.5%)
Chironomus riparius (midge)	Chronic toxicity	OECD 219	28-day NOEC 100 mg a.e./l (acid, 89.5%)
Pseudokirchneriella subcapitata (previously *Selenastrum capricornutum*)	Algal growth inhibition	FIFRA 123-2 OECD 201	96h EC_{50} 98.4 mg a.e./l* (acid 80.3%) 120h EC_{50} 73.9 mg a.e./l* (K^+ salt, 30.41% a.e.)
Anabaena flos-aquae	Algal growth inhibition	FIFRA 123-2	120h EC_{50} 38.2 mg a.e./l (acid 85.2%)
Lemna gibba (duckweed)	Growth inhibition	FIFRA 123-2 OECD 221	14-day EC_{50} 158 mg a.e./l* (acid 80.3%)
Arthropod toxicity			
Apis mellifera (honeybee)	Oral exposure Contact exposure	OECD 213 OECD 214	48h LD_{50} >100 μg a.e./bee (acid, 85.2%) 48h LD_{50} >100 μg a.e./bee (acid, 85.2%) 48h LD_{50} >86 μg a.e./bee* (K^+ salt, 30.41% a.e.)
Soil-dwelling organisms			
Eisenia foetida (earthworm)	Acute toxicity	OECD 207	14-day LC_{50} >5587 mg a.e./kg dry soil* (acid, 89.5%)
Eisenia foetida (earthworm)	Sub-lethal toxicity	ISO 11268-2	56-day NOEC 125 g a.e./ha, equivalent to 0.167 mg a.e./kg dry soil (acid, 78.0%)
Micro-organisms			
Soil micro-organisms	Inhibition of microbial respiration and nitrogen turnover	OECD 216 OECD 217	No adverse effect at 125 g a.e./ha, equivalent to 0.167 mg a.e./kg dry soil (acid, 78.0%)
Sewage micro-organisms	Inhibition of respiration	OECD 209	EC50 >117 mg a.e./l* (acid, 85.2%)

* reported value corrected for purity for the purposes of this table.

Picloram has not been evaluated by FAO/WHO JMPR. The WHO hazard classification is “U: unlikely to present acute hazard in normal use” (WHO 2002).

Formulations and co-formulated active ingredients

The main formulation types available are soluble liquid (SL) concentrates containing picloram potassium salt.

Picloram may be co-formulated with 2,4-D, MCPA, triclopyr, fluroxypyr and other herbicides.

These SL salt formulations are registered and sold in North, Central and South America and in many countries throughout Europe and Asia.

Methods of analysis and testing

An analytical method for the active ingredient (not including identity tests, other than retention time), based on HPLC and which may be used for picloram salt formulations or mixtures with 2,4-D, was published in CIPAC Handbook 1B in 1983. The method was based on anion exchange chromatography, using salicylic acid as internal standard and UV detection at 280 nm. The manufacturer stated that this early CIPAC method is no longer acceptable, partly because the specified HPLC column is obsolete and partly because current formulations cannot be analyzed satisfactorily by this procedure.

A new method based on HPLC, but including identity tests, is currently undergoing collaborative study under the auspices of CIPAC, for completion in 2005. In this method the picloram is determined by reversed-phase chromatography using UV detection at 240 nm and internal standardization with benzamide.

An LC-MS method was provided for identification of the tri-*iso*-propanolamine counter-ion in SL formulations, based on positive-ion electrospray ionization and detection of the protonated molecule (*m/z* 193) or the protonated di-*iso*-propanolamine fragment (*m/z* 98), depending upon the cone voltage (22V or 52V respectively). Basically the same LC-MS method, but using negative ion detection of the characteristic isotopic pattern of the deprotonated molecule, may be used to confirm the identity of the picloram.

The potassium counter-ion in the SL is identified by ion chromatography.

The methods for determination of impurities were based on reversed-phase HPLC with UV detection and external standardization.

The analytical method for determination of the relevant impurity, hexachlorobenzene (HCB), in the TK is based on reversed-phase HPLC with UV detection. Alternatively, capillary GC-MS used for the determination of HCB in SL formulations is also applicable to the TK. The method had been satisfactorily peer validated.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD/EC, while those for the formulations were CIPAC, as indicated in the specifications.

Physical properties

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as picloram (acid equivalent).

Appraisal

The Meeting considered draft specifications for picloram TC, TK and SL, and supporting data, for the development of new FAO specifications. The data submitted by Dow AgroSciences were in accordance with the requirements of the FAO/WHO Manual.

Picloram had not been evaluated FAO/WHO JMPR nor IPCS but WHO had allocated a hazard classification (unlikely to present acute hazard in normal use).

Picloram is no longer under patent.

Picloram is a systemic herbicide that deregulates plant growth. It is used to control unwanted broadleaf weeds and deeply rooted herbaceous weeds, woody plants in range and pasture land and forests as well as on new crop land. In some countries it is used in rice, sugarcane, cereals and oilseed rape production.

In its form as a free acid, picloram is slightly water-soluble, while its potassium and tri-*iso*-propanolamine salts are soluble. It is stable in water at acidic, neutral and basic pH. It is subject to fairly rapid photolysis in water, with a half-life of 2.6 days in mid-summer at 40 degrees N latitude, but photolysis does not occur on soil surfaces. The λ_{max} of picloram acid in unbuffered methanolic solution is 223 nm and therefore direct photolysis seems unlikely. Picloram is of very low volatility.

The manufacturer presented the Meeting with commercially confidential information on the manufacturing process for picloram and concomitant impurities. Five-batch analysis data and manufacturing limits related to the TC, which is not produced commercially but is produced when required by drying the TK wet cake produced commercially. Mass balances were high (99.6-100.5%) and percentages of unknowns were <0.1%. Minimum active ingredient content for the TC was declared to be not less than 920g/kg. The data on manufacturing process and purity/impurity provided to the Meeting were confirmed as similar to those submitted for registration in the USA (revised statement of formula based on recent analysis submitted to the US EPA in April 2004).

The Meeting agreed with the manufacturer that the impurity, HCB, is relevant, as it is a persistent organic pollutant according to the Stockholm Convention. A peer validated method was provided for the determination of HCB, based on capillary GC-MS, over a range of 0.5 to 3.0 ppm. Recovery of HCB in the range 0.5-3.0 ppm in picloram (acid equivalent) was 80-100%, with acceptable Horwitz RSDs. The proposed specification limit for HCB in technical picloram of 50 ppm (i.e. 0.05 g/kg or 0.005%), expressed on the basis of picloram acid, was supported by the data provided and accepted by the Meeting.

A full CIPAC method currently exists for the determination of picloram, alone or in mixtures with 2,4-D, although no additional identity test is provided and the technique is based on SAX HPLC, using a column that is no longer available. The method is also unsuitable for the analysis of current formulations. A new method based on reversed-phase HPLC is currently being validated through CIPAC.

LC-MS may be used as the ultimate identity test for picloram, while routine identity in formulations can be determined by the HPLC retention time in the method currently being collaboratively studied under auspices of CIPAC. An ion chromatography method is available for identification of potassium as the counter-ion when the potassium salt of picloram is used in the SL. An LC-MS method is available for identification of the tri-*iso*propanolamine (TIPA) counter-ion in SL formulations.

The physico-chemical properties of picloram were determined using OECD/EC methods, with CIPAC procedures used for assessment of formulations, as indicated in the specifications.

The US EPA has assigned a restricted use category to picloram, due to its hazard to non-target plants, but concluded that it is of moderate- to low toxicity in laboratory animals. Picloram and its derivatives are considered by US EPA to be only slightly toxic by oral and dermal routes of exposure and it is therefore placed in Toxicity Categories III and IV (the lowest of four categories). US EPA has placed picloram acid in the inhalation toxicity Category I, the highest of four categories, although its potassium and tri-*iso*-propanolamine salts are placed in inhalation toxicity Category II. The manufacturer explained that the apparent difference reflects the highest aerosol concentrations that could be produced from the acid and salt formulation in the experiments. No deaths or toxicological effects were observed at the highest concentrations and therefore no LOEL could be established. Tordon™ 22K (the potassium salt SL) is assessed as a skin sensitizer, whereas picloram is not. The manufacturer explained that the sensitization response was not strong and that, because none the SL components is a sensitizer, it had been concluded that the sensitization result had derived from a slight excess of KOH (i.e. high pH) in the SL. The manufacturer also stated that a study of Tordon™ 22K in 29 human volunteers had shown no positive indications of skin irritation or sensitization. After evaluating exposure risk to handlers from dermal and inhalation routes, US EPA considered the risks to handlers to be minimal. Picloram is non-carcinogenic and not associated with significant reproductive or developmental toxicity.

Picloram is moderately toxic to fresh-water fish and slightly toxic to invertebrates like *Daphnia* but practically non-toxic to birds, mammals and honey bees. It is one of the more mobile herbicides in soils and is unlikely to degrade in groundwater, with a high potential for contamination of surface water. Field monitoring studies have only found a limited number of positive detections of picloram in ground water.

While the TC is the basis for the physicochemical properties and much of the toxicological data, it is not currently the basic starting material for producing formulations and the Meeting agreed it was not appropriate to develop an FAO specification for it. Thus the specification for technical grade picloram (acid) is for the technical concentrate (TK).

The Meeting agreed certain minor amendments to the draft specifications but, otherwise, the specifications were in accordance with normal requirements of the FAO/WHO Manual.

Recommendations

The Meeting recommended that the specifications for picloram, TK and SL, as amended, should be adopted by FAO, subject to adoption by CIPAC of the new analytical method for determination of the active ingredient content.

References

FAO/WHO 2002	Manual on development and use of FAO and WHO specifications for pesticides, 1st edition, 2002, Rome
Schriber *et al*. 1989	Schriber C.A. and Baker R.B., 21 Dec 1989. Water solubility characteristics of various picloram salts, Dow Chemical Company report GH-C 2278, unpublished.
USEPA 1995	United States EPA Registration Eligibility Decision (RED), Picloram, August 1995.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002, WHO, Geneva, 2002.