WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

PYRIPROXYFEN

4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether

World Health Organization

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Disclaimer[1]

WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

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

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

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

INTRODUCTION

WHO establishes and publishes specifications* 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 1st edition of Manual for Development and Use of FAO and WHO Specifications for Pesticides (2002). 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 1st edition of the "FAO/WHO Manual on Pesticide Specifications."

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 "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.

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. 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.

* Footnote: The publications are available on the Internet under (http://www.who.int/quality/en/).

PART ONE

SPECIFICATIONS

PYRIPROXYFEN

PYRIPROXYFEN

INFORMATION

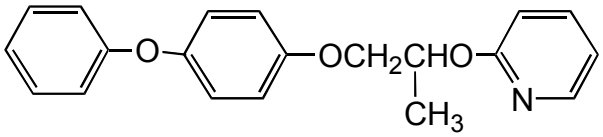
ISO common name
pyriproxyfen (BSI, draft E-ISO)

Synonyms
none

Chemical names
IUPAC 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether

CA 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

Structural formula



Empirical formula
$C_{20}H_{19}NO_3$

Relative molecular mass
321.37 g/mol

CAS Registry number
95737-68-1

CIPAC number
715

Identity tests

HPLC retention time, IR spectrum.

PYRIPROXYFEN TECHNICAL MATERIAL

WHO specification 715/TC (July 2006*)

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 (715/2005). It should be applicable to TC produced by this manufacturer but it is not an endorsement of it, nor a guarantee that it complies with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report 715/2005, as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of pyriproxyfen together with related manufacturing impurities and shall be a white to pale yellow solid or a colourless to yellow clear liquid, substantially odourless, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (715/TC/M/2, CIPAC Handbook, 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 **Pyriproxyfen content** (715/TC/M/3, CIPAC Handbook, Note 1)

The pyriproxyfen content shall be declared (not less than 970 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 Methods for the identification and determination of pyriproxyfen content were adopted by CIPAC in 2006 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/quality/en/.

PYRIPROXYFEN GRANULES

WHO specification 715/GR (July 2006*)

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 (715/2005). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. 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 manufacturers who use TC from other sources. The evaluation report 715/2005, as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of granules containing technical pyriproxyfen, complying with the requirements of WHO specification 715/TC (July 2006) together with pumice and any necessary formulants. It shall be dry, free flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (715/GR/M/2, CIPAC Handbook, 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 **Pyriproxyfen content** (715/GR/M/3, CIPAC Handbook, Note 1)

The pyriproxyfen content shall be declared (5 g/kg) and, when determined, the average measured content shall not differ from that declared by more than ± 15%.

3 Physical properties

3.1 **Nominal size range** (MT 58.2, CIPAC Handbook F, p.173, 1995)

The nominal size range of the formulation shall be declared (300 to 1000 µm). Not less than 850 g/kg of the formulation shall be within the nominal declared size range.

3.2 **Dustiness** (MT 171, CIPAC Handbook F, p.425, 1995, Note 2)

Essentially non-dusty.

3.3 **Attrition resistance** (MT 178, CIPAC Handbook H, p.304, 1998)

Minimum: 98% attrition resistance.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/quality/en/.

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.128, 2000)

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 mean content found before storage (Note 3) and the formulation shall continue to comply with the clauses for:

- nominal size range (3.1);
- dustiness (3.2).
- attrition resistance (3.3).

Note 1 Methods for the identification and determination of pyriproxyfen content were adopted by CIPAC in 2006 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

Note 2 Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method, MT 171, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.

Note 3 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

PYRIPROXYFEN

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FAO/WHO EVALUATION REPORT 715/2005

Recommendations

The Meeting recommended that:

(i) the specifications for pyriproxyfen TC and GR proposed by Sumitomo, as amended, should be adopted by WHO;

(ii) the specifications for pyriproxyfen TC and EC proposed by Sumitomo, as amended, should be adopted by FAO.

Appraisal

The Meeting considered data and information submitted by Sumitomo Chemical Co. Ltd, in support of proposed new FAO and WHO specifications for TC, GR and EC.

Pyriproxyfen is not under patent. It is under review in the EU.

Pyriproxyfen is a juvenile hormone mimicking insecticide, used for control of flies, beetles, midges and mosquitoes in public health applications. It is also used in agriculture in some countries, e.g. the USA.

Pyriproxyfen is a solid (melting range 48-50ºC) of low volatility and only slightly soluble in water. It has no discernible acidic or basic characteristics and is stable to hydrolysis at pH 4-9 at 25C, but is prone to slow photolysis.

The Meeting was provided with commercially confidential information on the manufacturing process and 5- batch analysis data on all impurities ≥1 g/kg. Mass balances were very high (99.5–99.8%), with no unknowns detected. The data were confirmed as essentially similar to those submitted for registration in Italy.

The Meeting agreed with the manufacturer that none of the impurities should be designated as relevant.

The analytical method for determination of pyriproxyfen in TC, GR and EC is based on reversed-phase HPLC with UV detection at 254 nm and internal standardization with p-benzyldiphenyl. The method was validated by collaborative study and adopted by CIPAC in 2006.

Analytical methods for the determination of impurities were GC-FID using ethyl benzene internal standard, for residual solvent, and reversed-phase HPLC with external standardization, for the other impurities.

Physical properties of the formulations are determined by CIPAC methods, as indicated in the specifications.

The proposed specifications were in accordance with the requirements of the manual (FAO/WHO 2002).

TC. The description clause indicates that pyriproxyfen TC may be in the form of a solid or liquid, despite having a melting point in the range 48-50°C. The

manufacturer explained that crystallization occurs very slowly, even in a refrigerator, and therefore the TC may remain in liquid form for a relatively long period after shipment.

GR. The manufacturer proposed the use of hand sieving to determine compliance with the clause for size range but the Meeting agreed that the standard method, MT 58, should be referenced in the specification.

EC. The specification is for agricultural products only, presently containing approximately 100 g/l pyriproxyfen. The manufacturer proposed that flash point (minimum 60ºC) should be included in the specification, in order to prevent the introduction of more hazardous products onto the market. The Meeting observed that FAO/WHO specifications do not include a clause for flash point, because the minimum acceptable is location and application dependent. It was agreed that a footnote should be inserted into the specification, to draw attention to the need for products to adhere national requirements for flash point.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 715/2005

Physico-chemical properties of pyriproxyfen

Table 1. Physico-chemical properties of pure pyriproxyfen

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	<1.33 x 10^{-5} Pa at 22.8°C	100	EPA 63-9/OECD 104	NNP-0030
Melting point	48.0-50.0°C	100	OECD 102	NNP-0054
Boiling point	318°C	99.7	OECD 103	NNP-0086
Temperature of decomposition	Not available	-	-	-
Solubility in water, at 25ºC and pH6	0.367 ± 0.004 mg/l	99.4	EPA CG-1500	NNP-0026
Octanol/water partition coefficient, at 25ºC and pH 5.6	log P K_{OW} = 5.37	99.4	OECD 107	NNP-0025
Hydrolysis characteristics, at 25ºC	Stable at pH 5, 7 and 9	Radiochemical purity: 99.3 & 99.4%	OECD 111	NNM-0015
Photolysis characteristics	Photo-degradation in water under artificial sunlight, approximately equivalent to double the light intensity of natural midday sunlight at 43º N in July: Half-life = 3.72-6.36 days at 25°C and pH 7	Radiochemical purity: 99.9 & 99.2%	EPA161-2	NNM-0037
Dissociation characteristics	Dissociation constant could not determined due to low water solubility	-	-	NNP-0022

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.5-99.8%, with no unknowns.
Declared minimum pyriproxyfen 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
Melting temperature of the TC	48-50°C

Hazard summary

Pyriproxyfen was evaluated by the FAO/WHO JMPR in 1999 and 2001. The 1999 JMPR established an ADI of 0-0.1 mg/kg bw, on the basis of a 1-year study in dogs and a safety factor of 100 and concluded that it was not necessary to establish an acute reference dose because of low acute toxicity of pyriproxyfen. The 2001 JMPR assessed the safety of pyriproxyfen as a mosquito larvicide in potable water and concluded that intake at the target concentration for control would not present unacceptable risks.

The WHO hazard classification of pyriproxyfen is: U, unlikely to present acute hazard in normal use (WHO 2002).

Formulations

The main formulation types available are GR and EC. These formulations are registered and sold in Turkey, UAE, Saudi Arabia, Belgium, Cyprus, Denmark, France, Greece, Hungary, Netherlands, Poland and Spain. Pyriproxyfen is not co-formulated with other pesticides.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is based on reversed phase HPLC, using UV detection at 254 nm and internal standardization with *p*-benzyldiphenyl (NNA-0011). The method was validated by collaborative study and adopted by CIPAC in 2006.

Impurities in pyriproxyfen were determined by reversed-phase HPLC, using UV detection at 254 nm and external standardization, and GC-FID and internal standardization with ethylbenzene for the residual solvent.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and EPA, 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 GR and EC formulations, comply with the requirements of the FAO/WHO manual (1st edition).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as pyriproxyfen.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Sumitomo provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from pyriproxyfen having impurity profiles similar to those referred to in Table 2, above.

Table A. Toxicology profile of pyriproxyfen technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (m,f)	oral	97.2	EPA Guideline 81-1	LD_{50} >5000 mg/kg bw (m,f)	NNT-0005
Rat (m,f)	dermal	97.2	EPA Guideline 81-2	LD_{50} >2000 mg/kg bw (m,f)	NNT-0006
Rat (m,f)	inhalation	97.0	EPA Guideline 81-3	LC_{50} >1300 mg/m^3 (m,f)	NNT-0022
Rabbit (m,f)	skin irritation	97.2	EPA Guideline 81-5	Non-irritating	NNT-0004
Rabbit (m,f)	eye irritation	97.2	EPA Guideline 81-4	Minimally irritating	NNT-0004
Guinea pig	skin sensitization	97.2	Maximization method, EPA Guideline 81-6	Not a sensitizer	NNT-0003

Table B. Toxicology profile of pyriproxyfen technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (m,f)	feeding, toxicity	95.3	90 d, EPA82-1	NOAEL = 23 mg/kg/d (m) NOAEL = 28 mg/kg/d (f)	NNT-0045
Rat (m,f)	inhalation, toxicity	97.0	28 d, in-house method close to OECD 412	NOAEL = 482 mg/m³/d (m,f)	NNT-0031
Dog (m,f)	Feeding (capsule) toxicity	95.3	52 weeks, EPA 83-1	NOAEL = 10 mg/kg/d (m) NOAEL = 30 mg/kg/d (f)	NNT-0081 NNT-0102
Rat (m,f)	feeding, carcinogenicity	95.3	104 weeks, EPA 83-5	NOAEL = 27.31 mg/kg/d (m) NOAEL = 35.1 mg/kg/d (f) Carcinogenicity: negative	NNT-0085
Mouse (m,f)	feeding, carcinogenicity	95.	78 weeks, EPA 83-2	NOAEL = 16.37 mg/kg/d (m) NOAEL = 107.3 mg/kg/d (f) Carcinogenicity: negative	NNT-0084
Rat (m,f)	feeding, 2 generation reproduction	95.3	EPA83-4	NOAEL (parental systemic toxicity) = 1000 ppm NOAEL (parental reproductive effect) = 5000 ppm, NOEL (pup developmental toxicity) = 1000 ppm	NNT-0087
Rat (f)	feeding, teratogenicity and embryotoxicity	97.2	EPA 83-3	NOAEL (maternal) = 100 mg/kg bw/d, NOAEL (developmental) = 100 mg/kg bw/d NOAEL (reproduction) = 1000 mg/kg bw/d Not teratogenic	NNT-0029
Rabbit (f)	feeding, teratogenicity and embryotoxicity	97.2	EPA 83-3	NOAEL (maternal) = 100 mg/kg bw/d, NOAEL (developmental) = 300 mg/kg bw/d Not teratogenic	NNT-0033

Table C. Mutagenicity profile of pyriproxyfen technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity %	Conditions and doses	Result	Reference
Salmonella typhimurium, *Escherichia coli*	Ames test, *in vitro*, gene mutation	97.2	With and without S9 mix: 10, 50, 100, 500, 1000 or 5000 µg/plate	Negative	NNT-0034
Chinese hamster ovary cell (CHO-K1)	Chromosomal aberration *in vitro*	97.2	Without S9 mix: 10, 30 or 100 µg/ml With S9 mix: 30, 100 or 300 µg/ml	Negative	NNT-0054
Chinese hamster lung cell (V79)	Gene mutation in mammalian cell *in vitro*	95.3	Without S9 mix: 10, 30 or 100 µg/ml With S9 mix: 3, 10, 30, or 100 µg/ml	Negative	NNT-0067
Mouse (m,f) bone marrow cell	Micronucleus assay *in vivo*	95.3	5000 mg/kg bw (p.o.)	Negative	NNT-0082

Table D. Ecotoxicology profile of pyriproxyfen technical material

Species	Test	Purity %	Duration and conditions	Results	Reference
Daphnia magna	Acute	95.3	EPA 72-2 flow through, 48 h	LC_{50} = 0.4 mg/l	NNW-0036
Rainbow trout	Acute	95.3	EPA 72-1 flow through, 96 h	LC_{50} >0.325 mg/l	NNW-0035
Bluegill sunfish	Acute	95.3	EPA 72-1 flow through, 96 h	LC_{50} >0.270 mg/l	NNW-0034
Selenastrum capricornutum (alga)	Effect on growth	97.2	OECD 201, 72 h	EC_{50} = 0.064 mg/l NOEC = 0.02 mg/l	NNW-0068
Earthworm	Acute	99.0	OECD 207	LC_{50} >1000 mg/kg dry soil	NNW-0012
Apis mellifera (honey bee)	Acute oral and contact	99.7	OECD 213/214, 48 h	Contact and oral LD_{50} >0.1 mg ai/bee	NNW-0149
Bobwhite quail	Acute oral	95.3	EPA71-1	LD_{50} >2000 mg/kg	NNW-0028
Mallard duck	Acute oral	95.3	EPA71-1	LD_{50} >2000 mg/kg	NNW-0027

ANNEX 2. REFERENCES

Sumitomo document number or other reference	Year and title of report or publication details
FAO/WHO 2002	Manual on the development and use of FAO and WHO specifications for pesticides, 1st edition. FAO plant production and protection paper, 173. FAO, Rome, 2002.
NNA-0011	1988. Analytical methods to verify certified limits of Sumilarv technical grade.
NNM-0015	1989. Hydrolysis of S-31183 in buffered aqueous solutions.
NNM-0037	1995. Artificial sunlight photodegradation of pyriproxyfen in aqueous media at pH 7.
NNP-0022	1989. Dissociation constant of Sumilarv.
NNP-0025	1989. Partition coefficient (n-octanol/water) of pyriproxyfen.
NNP-0026	1989. Water solubility of pyriproxyfen.
NNP-0030	1989. Vapour pressure determination of Sumilarv.
NNP-0054	1993. Melting point determination of pyriproxyfen.
NNP-0086	2001. Determination of boiling point of pyriproxyfen.
NNT-0003	1986. Skin sensitization test with S-31183 in guinea pigs.
NNT-0004	1987. Primary eye and skin irritation tests with S-31183 in rabbits.
NNT-0005	1987. Acute oral toxicity of S-31183 in rats.
NNT-0006	1987. Acute dermal toxicity of S-31183 in rats.
NNT-0022	1987. Acute inhalation toxicity of S-31183 in rats.
NNT-0029	1988. Study by administration of S-31183 during the period of fetal organogenesis in rats.
NNT-0031	1988. Subacute inhalation toxicity study of S-31183 in rats.
NNT-0033	1988. Study of S-31183 by oral administration during the period of fetal organogenesis in rabbits.
NNT-0034	1988. Reverse mutation test of S-31183 in bacterial systems.
NNT-0045	1989. Subchronic toxicity study with S-31183 in rats.
NNT-0067	1990. *In vitro* gene mutation test of S-31183 in V79 Chinese hamster cells.
NNT-0054	1989. *In vitro* chromosomal aberration test of pyriproxyfen in Chinese hamster ovary cells (CHO-K1).
NNT-0081	1991. Amended final report: S-31183: Toxicity study by oral (capsule) administration to beagle dogs for 52 weeks.
NNT-0082	1991. Mouse micronucleus test on S-31183.
NNT-0084	1991. Oncogenicity study in mice with S-31183.
NNT-0085	1991. Combined chronic toxicity and oncogenicity study in rats with S-31183.
NNT-0087	1991. A dietary 2-generation (1 litter) reproduction study of S-31183 in the rat.
NNT-0102	1993. S-31183: Toxicity study by oral (capsule) administration to beagle dogs for 52 weeks (additional investigation).
NNW-0012	1988. Acute toxicity (LC_{50}) study of S-31183 to earthworms.
NNW-0027	1989. The avian single-dose oral LD_{50} study of S-31183 to the mallard duck.
NNW-0028	1989. The avian single-dose oral LD_{50} study of S-31183 to the bobwhite quail.
NNW-0034	1989. Acute flow-through toxicity of Sumilarv to bluegill (Lepomis macrochirus).
NNW-0035	1989. Acute flow-through toxicity of Sumilarv to rainbow trout (Salmo gairdneri).
NNW-0036	1989. Acute flow-through toxicity of Sumilarv to Daphnia magna.
NNW-0068	1991. Acute toxicity of pyriproxyfen to Selenastrum capricornutum Prinz.
NNW-0149	2001. Pyriproxyfen – Acute contact and oral toxicity tests with honey bees (*Apis mellifera*).
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification, 2000-2002. World Health Organization, Geneva, 2002.