

**FAO SPECIFICATIONS AND EVALUATIONS
FOR AGRICULTURAL PESTICIDES**

HEXAZINONE

3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-
2,4-(1*H*,3*H*)-dione



FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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DISCLAIMER¹

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/pm/jmps/en/>.

PART ONE

SPECIFICATIONS

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HEXAZINONE

INFORMATION

Common name:

hexazinone (E-ISO, (m)F-ISO, BSI, ANSI, WSSA)

Synonyms:

none

Chemical names:

IUPAC, 3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione.
CA, 3-cyclohexyl-6-(dimethylamino)-1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione.

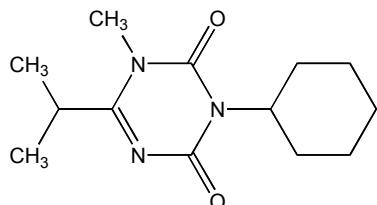
CAS No:

[51235-04-2]

CIPAC No:

374

Structural formula:



Molecular formula:

C₁₂H₂₀N₄O₂

Relative molecular mass:

252.31

Identity tests:

HPLC retention time, IR spectrum.

HEXAZINONE

TECHNICAL MATERIAL

FAO Specification 374/TC (February 2006*)

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 (374/2003, 374/2011). 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 (374/2003, 374/2011) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of hexazinone, together with related manufacturing impurities, in the form of white to light grey fine crystalline solid, and shall be free from visible extraneous matter and added modifying agents or stabilizers.

2 Active ingredient

2.1 Identity tests (CIPAC 374/TC/M-, CIPAC Handbook J, 2000, p.72, 2000)

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 Hexazinone content (CIPAC 374/TC/M-, CIPAC Handbook J, p.72, 2000)

The hexazinone content shall be declared (not less than 950 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 Carbamic acid, ethyl ester (ethyl carbamate) (Note 1)

Maximum: 0.05 g/kg (50 ppm).

Note 1 The analytical methods for determination of ethyl carbamate a 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/pm/jmps/ps/en/>

PART TWO

EVALUATION REPORTS

HEXAZINONE

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Hexazinone

FAO EVALUATION REPORT 374 / 2011

Recommendations

The meeting recommended that:

(I) the existing FAO specification for hexazinone TC should be extended to encompass the product of Nutrichem Co., Ltd. China

Appraisal

The data for hexazinone were evaluated in support of the extension of the existing FAO specification 374/TC (2002), published in 2006. The reference specification and the supporting data were provided by E.I. DuPont de Nemours and Company, USA.

The meeting was provided with confidential information on the manufacturing process, together with 5-batch analytical data and manufacturing specification for purity and all impurities ≥ 1 g/kg. Mass balances were in the range of 99.4 – 99.8 %. The confidential data presented are identical to those submitted for registration in China.

The Nutrichem TC data is in compliance with the existing specification. One of the impurities did not appear in the reference profile of impurities. Because the specified content of this impurity is less than 3 g/kg, equivalence could be assessed in a Tier-1 approach, which is essentially based on chemical evidence like comparison of manufacturing specifications and some *in vitro* mutagenicity data (cf. Section 3.2, FAO/WHO Manual, November 2010 - second revision of the First Edition). No *in vivo* acute toxicity data are available for the Nutrichem TC.

Nutrichem proposed an analytical method for the determination of hexazinone in TC that is similar but not identical to the published CIPAC method 374/TC/M/- (CIPAC Handbook J, p. 72). The Meeting requested, based on the requirements of the FAO/WHO Manual (collaboratively validated analytical method for the active ingredient, Section 3.1 C), a bridging study for the Nutrichem method and a confirmation that the CIPAC method is applicable to the TC. Nutrichem submitted the bridging study and re-examined the batches using the CIPAC-method. The results of both methods (CIPAC method and Nutrichem in-house) are in good agreement for all batches.

For the determination of the relevant impurity ethyl-carbamate Nutrichem proposed a determination by HPLC-MS, while the method available on the FAO homepage is by GC/FID. The Meeting requested a peer validation on the HPLC-MS method or the use of the published GC-FID method. Nutrichem submitted a peer validation based on three independent laboratories. This was considered to fulfill the requirements of the Manual and accepted by the Meeting. Both methods may be downloaded from the FAO AGP website using the link provided in Note 1 of the TC specification.

Based on the studies and documents submitted, the Meeting concluded that the hexazinone TC produced by Nutrichem is considered equivalent to that of the reference profile in Tier-1 of the equivalence process.

No copies of the studies on physical-chemical properties of hexazinone were submitted for evaluation.

**SUPPORTING INFORMATION
FOR
EVALUATION REPORT 374 / 2011**

Table 1. Physico-chemical properties of pure hexazinone

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	3.6×10^{-5} Pa at 25°C (extrapolated)	98.54	OECD 104, by extrapolation, EPA Guideline 830.7950	207-2-11-0651
Melting point.	114.0~115.5 °C	98.54	EPA Guideline 830.7200	NC-2009-037
Temperature of decomposition	not available	-	-	-
Solubility in water	29.8 g/l at 20 ± 0.5 °C	98.54	EPA Guideline 830. 7840	NC-2009-037
Octanol/water partition coefficient	$\log P_{ow} = 1.95$ at 26.5 °C	98.54	EPA Guideline 830. 7570	NC-2009-037
Hydrolysis characteristics	Half-life : 1 year at room temperature at pH 4, 7 and 9	98.54	OECD 111 and EPA Guideline 835. 2120	NC-2010-050
Photolysis characteristics	not available	-	-	-
Dissociation characteristics	$pK_a = 1.8$	98.54	EPA Guideline 830.7370	NC-2009-037
Solubility in organic solvents	617.5 g/l in methanol at 20 ± 0.5 °C 0.53 g/l in n-hexane at 20 ± 0.5 °C 134.7 g/l in n-octanol at 20 ± 0.5 °C	98.54	EPA Guideline 830. 7840	NC-2009-037

Table 2. Chemical composition and properties of hexazinone technical materials (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 99.4 – 99.8 %. No unknowns were identified in the 5 batch analyses.			
Declared minimum [a.i.] 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:	Ethyl carbamate, 0.05 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	114 - 115 °C	98.54	EPA Guideline 830.7200	NC-2009-037
Solubility in organic solvents	617.5 g/L in methanol 0.53 g/ L in n-hexane 134.7 g/L in n-octanol, all at 20 °C.	98.54	EPA Guideline 830.7840	NC-2009-037

FORMULATIONS

Nutrichem Co. Ltd. Produces the TC and it is to formulators.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is the CIPAC method published in Handbook J. In addition, a reverse phase HPLC, using DAD detection at 265 nm and external standardisation was validated and used. The method for determination of the non-relevant impurities is based on GC-FID with internal standardization.

The analytical method for determination of the relevant impurity ethyl carbamate is based on HPLC-MS, with a chromatography on a ZORBAX XDB C₈ reverse phase column. Detection of ethyl carbamate was by in single ion monitoring (SIM) mode on m/z 90 and 112 respectively, and quantification with an external standard.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD/EPA, as indicated in Table 1.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The content of hexazinone is expressed as hexazinone.

Annex I

Hazard Summary Provided by the Proposer

Toxicological summaries

Notes.

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

Note: According to the tiered equivalence approach and proposed Tier-1 equivalence, no data on acute toxicity of technical hexazinone *in vivo* was submitted.

Table 2. Mutagenicity profile of technical hexazinone based on in vitro vivo tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number <small>Error! Bookmark not defined.</small>
<i>S. typhimurium</i> (strains TA1535, TA1537, TA98 & TA100) <i>E.Coli</i> (strain WP2(pkM101))	<i>in vitro</i> bacterial gene mutation assay	98.16 %	OECD Guideline 471 48 h Between 5.09 and 0.06 mg/plate With and without metabolic activation by S9	non mutagenic / non pro-mutagenic	B-01115

Note: According to the tiered equivalence approach and proposed Tier-1 equivalence, no data on ecotoxicity of technical hexazinone in was submitted.

Annex 2

References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO/WHO	2010	Manual on development and use of FAO and WHO specifications for pesticides. November 2010 - second revision of the First Edition. FAO Plant Production and Protection Paper: http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/manual/it/
	FAO	2006	FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES Hexazinone
NC-2009-037		2009	Chemical and Physical Characterization of Hexazinone 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-2010-050		2010	Determination of hydrolysis rate of Hexazinone TGAI. GLP. Nutrichem Laboratory Co., Ltd. Unpublished
B-01115		2010	BACTERIAL REVERSE MUTATION TEST – Hexazinone. GLP.. Unpublished
NC-2009-038	Hongxia Li	2009	Preliminary Analysis and Enforcement Analytical Method of Hexazinone TGAI. NC-2009-038. Report NC-2009-038. GLP. Nutrichem Laboratory Co., Ltd., China. Unpublished.
207-2-11-0651		2010	Vapour Pressure of Hexazinone. Study 207-2-11-0651. Report 207-2-11-0651. GLP. Jai Research Foundation, India. Unpublished.
NC-2011-075	Hongxia Li	2011	Preliminary Analysis of Active Ingredient in hexazinone TGAI – 5-batch Analysis of Active Ingredient in Hexazinone TGAI with CIPAC Method. GLP. Nutrichem Laboratory Co., Ltd., China. Unpublished.
NC2009 038C	Yue Wang		Peer Validation of Analytical Methodology for the Assay of Ethyl Carbamate in Hexazinone TGAI, Nutrichem Laboratory Co., Ltd.

HEXAZINONE

FAO/WHO EVALUATION REPORT 374/2003

Explanation

The data for hexazinone were evaluated for review of existing FAO specifications for the technical material (374/TC/S/F), granules (374/GR/S/F), water dispersible granules (374/WG/S/F), water soluble powders (374/SP/S/F) and soluble concentrates (374/SL/S/F), which were developed in 1998 under the old procedure (AGP: CP/364).

Hexazinone had not been evaluated by the FAO/WHO JMPR or by WHO/PCS. A complete review by the United States EPA (Registration Eligibility Decision) was completed in 1994. A subsequent review (Tolerance Reassessment Eligibility Decision) was completed in 2002 by the US EPA.

The draft FAO specification and supporting data were provided by E. I. du Pont de Nemours and Company in September 2002.

Uses

Hexazinone is a herbicide that inhibits photosynthesis. It is used in sugarcane, alfalfa and in non-crop weed control.

Identity

ISO common name:

hexazinone

Chemical name(s)

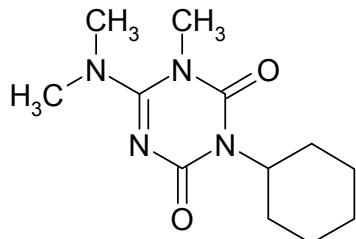
IUPAC: 3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione

CA: 3-cyclohexyl-6-(dimethylamino)-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione

Synonyms or code names:

DPX-A3674

Structural formula:



Molecular formula:

C₁₂H₂₀N₄O₂

Relative molecular mass:

252.3 g/mol

CAS Registry number:

51235-04-2

CIPAC number:

374

Identity tests:

HPLC retention time and IR spectrum.

Physico-chemical properties

Table 1. Physico-chemical properties of pure hexazinone.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	<1.33 x 10 ⁻⁵ Pa at 25°C	99.7%	OECD 104 (gas saturation method using thermal evolution analyzer)
Melting point, boiling point and/or temperature of decomposition	Melting point: 113-115°C Boiling point: not available Decomposition temperature: not available	98.0%	OECD 102
Solubility in water	29.8 g/l at 25°C at pH 7	>99.9%	OECD 105, CIPAC MT 157, OTS CG-1500
Solubility in organic solvents	acetone, 792 g/l at 20°C chloroform, 3880 g/l at 20°C dimethylformamide, 836 g/l at 20°C methanol, 2650 g/l at 20°C toluene, 386 g/l at 20°C hexane, 3 g/l at 20°C	not stated	not stated
Partition coefficient n-octanol/water	log P _{ow} = 1.2 at 25°C and pH 7	97.2%	OECD 107, OTS CG-1400 HPLC collection LSC analysis method
Hydrolysis characteristics	No detectable hydrolysis after 30 days at 25°C and pH 5, 7 or 9	>97% radiochemical purity	EPA Pesticide Assesment Guidelines 161-1 (1982)
Photolysis characteristics	Photolytically stable at pH 7 and 25°C	>96% radiochemical purity	EPA/600-3-82-022 (1982)
Dissociation characteristics	pKa ~ 2.2	>95%	OECD 112 OTS CG-1200

Table 2. Chemical composition and properties of hexazinone 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 983–997 g/kg.
Declared minimum hexazinone content	950 g/kg (see Note)
Relevant impurities ≥ 1 g/kg and maximum limits for them	None.
Relevant impurities < 1 g/kg and maximum limits for them:	Carbamic acid, ethyl ester < 50 mg/kg.
Stabilisers or other additives and maximum limits for them:	None.
Melting or boiling temperature range	113–115°C

Note: the minimum purity declared by the proposer was 957.5 g/kg but the Meeting agreed that a value of 950 g/kg should be adopted, because the analytical method is not sufficiently precise to support the more accurate value.

Toxicological summaries

Notes.

- (i) The proposer confirmed that most of the toxicological and ecotoxicological data included in the summary below were derived from hexazinone 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 hexazinone technical material, based on acute toxicity, dermal, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted, a.i. form and purity	Result
Rat	Oral	USEPA Pesticide Assessment Guidelines Subdivision F, 81-1 TC (>98 %)	LD ₅₀ = 1200 mg/kg bw (USEPA MRID 41235004) ¹
Rat	Inhalation	EEC Annex V Method B2 & OECD 403 SP (90%)	LC ₅₀ > 5 mg/l (USEPA MRID No. 41756701) ¹
Rabbit	Dermal	OECD 402. EEC Annex V (B3) USEPA 81-2	LD ₅₀ > 5000 mg/kg bw (not review by the EPA)
Rabbit	Skin irritation	Occluded exposure for 24h. Observation for 24h. (1973) TC + surfactants (purity not stated)	Slightly irritating (USEPA MRID No. 00104974) ¹
Rabbit	Eye irritation	USEPA (1982) Pesticide Registration Guidelines. TC (>95%)	Severe irritant (USEPA MRID No. 00106003) ¹
Guinea pig	Skin sensitization	Buehler method TC (>99%)	Not a sensitizer (USEPA MRID No. 41235005) ¹

¹ US EPA MRIDs: United States Environmental Protection Agency Master Record Identification. Studies showing MRIDs indicate official acceptance of study result in both the EPA Reregistration Eligibility Decision (1994) and Tolerance Reassessment Eligibility Decision (2002).

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

Species	Test	Duration and conditions or guideline adopted, a.i. form and purity	Result
Male and female rat (ChR-CD)	Oral 90-day feeding study	90 days (1973) TC (purity not stated)	NOEL = 1000 ppm (50 mg/kg) LOEL = 5000 ppm (250 mg/kg) (USEPA MRID No. 00104977) ¹
Dog (Beagle)	Oral 90-day feeding study	90 days (1973) TC (97.5%)	NOEL = 1000 ppm (25 mg/kg) LOEL = 5000 ppm (125 mg/kg) (USEPA MRID No. 00114484) ¹
Rabbit	21-day dermal toxicity	OECD 410 TC (>98.1%)	NOEL > 1000 mg/kg/day (USEPA MRID No. 4230900) ¹
Male and female rat (Crl:CD [®] BR)	Oral 2-year chronic tox. and carcinogenicity	Oral 2-year feeding (1975) WP (90% a.i.)	NOEL = 200 ppm (10 mg/kg) LOEL = 1000 ppm (50 mg/kg) (USEPA MRID No. 00108638) ¹
Male and female mouse (CD-1)	Oral 24-month carcinogenicity feeding study	Oral 2-year feeding (1981) TC (>95%)	NOEL = 200 ppm (28 and 34 mg/kg/day respectively for males and females). Considered by USEPA "not classifiable as to human carcinogenicity" (USEPA MRIDs 0079203, 41359301, 4250930) ¹
Male and female rat (Sprague-Dawley)	Two-generation reproduction study	US EPA Subdivision F 83-4 (1982) TC (>98%)	NOEL = 200 ppm (10 mg/kg/day) LOEL = 2000 ppm (100 mg/kg /day) (USEPA MRID No. 4206650) ¹
Female rat (Sprague-Dawley)	Developmental toxicity study	US EPA (1982) TC (94.2%)	NOEL = 100 mg/kg/day LOEL = 400 mg/kg/day (USEPA MRID No. 40397501) ¹

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

Species	Test	Conditions, a.i. purity	Result
<i>Salmonella typhimurium</i> (strains TA1535, TA1537, TA1538, TA98 & TA100)	<i>In vitro</i> bacterial gene mutation assay	Absence and presence of S9 metabolic activation TC (95%)	Negative for mutagenic activity (USEPA MRID No. 00098982) ¹
Chinese hamster ovary (CHO)cells	<i>In vitro</i> mammalian cytogenetics assay	Absence and presence of an S9 metabolic activation USEPA 870.5375 (1996), EEC 92/69 method B.10 (1992) TC (95%)	Positive for structural chromosome aberrations without activation. Negative for aberrations with activation (USEPA MRID No. 00130709) ¹
Chinese hamster ovary (CHO) cells	<i>In vitro</i> mammalian cell gene mutation assay	Absence and presence of S9 activation USEPA 84-2 (1982), EEC 87/302 part B (1987) hexazinone (95%)	Negative for CHO/HGPRT gene mutations (USEPA MRID No. 00076956) ¹

¹ USEPA MRIDs: United States Environmental Protection Agency Master Record Identification. Studies showing MRIDs indicate official acceptance of study result in both the EPA Reregistration Eligibility Decision (1994) and Tolerance Reassessment Eligibility Decision (2002).

Species	Test	Conditions, a.i. purity	Result
Rat primary hepatocytes (Sprague-Dawley)	<i>In vitro</i> unscheduled DNA synthesis (UDS)	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 83-1 TC (95%)	Negative for UDS (USEPA MRID No. 00130708) ¹
Male and female rat (Sprague-Dawley)	<i>In vivo</i> bone marrow cytogenetic assay	Oral gavage dosing TC (95%)	Negative for the induction of structural chromosome aberrations in bone marrow cells (USEPA MRID No. 00131355) ¹

Table 6. Ecotoxicology profile of hexazinone technical material.

Species	Test	Duration and conditions, a.i. purity	Result
<i>Daphnia magna</i> (Water flea)	Acute 48-hour static toxicity	EPA Method (1976) TC (95%)	EC ₅₀ = 151.6 ppm (USEPA MRID No. 00116269) ¹
<i>Daphnia magna</i> (Water flea)	Life cycle and reproductive test	U.S. EPA Pesticide Assessment Guideline; Subdivision E, 72-4 TC (>98%)	LOEC = 81 mg/l NOEC = 29 mg/l MATC = 48.5 mg/l (USEPA MRID Nos. 00078041, 41406002) ¹
<i>Selenastrum capricornutum</i> (Green alga)	120-hour effect on growth and growth rate	U. S. EPA Guidelines 122-2, 123-2. EPA Method 560/6-82-002, EC-22 TC (>98%)	EC ₅₀ = 7 ppb (USEPA MRID No. 41287001) ¹
<i>Anabaena flos-aquae</i> (Blue-green alga)	120-hour effect on growth and growth rate	U.S. EPA Non-Target Aquatic Plant Studies, Pesticides Assessment Guidelines, Subdivision J, 122-2, 123-2 (1982) TC (>98%)	EC ₅₀ = 0.21 ppm (USEPA MRID No. 43302701) ¹
<i>Lemna gibba</i> G3	14-day influence on growth and reproduction	EPA Method 600/9-78-018 TC (>98%)	EC ₅₀ = 37.4 ppb (USEPA MRID No. 43225101) ¹
<i>Skeletонema costatum</i>	120-hour effect on growth and growth rate	EPA Method 600/9-78-010 (1978) TC (>98%)	EC ₅₀ = 12 ppb (USEPA MRID No. 43225102) ¹
<i>Navicula pelliculosa</i>	120-hour effect on growth and growth rate	U.S. EPA Non-Target Aquatic Plant Studies, Pesticides Assessment Guidelines, Subdivision J, 122-2, 123-2 (1982) TC (>98%)	EC ₅₀ = 12 ppb (USEPA MRID No. 43302701) ¹
<i>Crassostrea virginica</i> (Eastern oyster)	48-hour developmental toxicity	EPA Method 660/3-75-009 TC (95%)	EC ₅₀ > 320 ppm (USEPA MRID No. 00047164) ¹

¹ USEPA MRIDs: United States Environmental Protection Agency Master Record Identification. Studies showing MRIDs indicate official acceptance of study result in both the EPA Reregistration Eligibility Decision (1994) and Tolerance Reassessment Eligibility Decision (2002).

Species	Test	Duration and conditions, a.i. purity	Result
<i>Palaemonetes pugio</i> (Grass shrimp)	96-hour toxicity	EPA Method 660/3-75-009 TC (95%)	LC ₅₀ = 78 ppm (USEPA MRID No. 00047164) ¹
<i>Uca pugilator</i> (Fiddler crab)	96-hour toxicity	EPA Method 660/3-75-009 TC (95%)	LC ₅₀ >1000 ppm (USEPA MRID No. 00047164) ¹
<i>Apis mellifera</i> (Honey bee)	48-hour acute contact toxicity	U.S. EPA Non-Target Insect Data; Pesticides Assessment Guidelines 141-1 TC (98%)	LD ₅₀ and NOEL >100 µg/bee (USEPA MRID No. 41216502) ¹
<i>Colinus virginianus</i> (Bobwhite quail)	Acute oral toxicity	Wildlife International Method (1978) TC (96.8%)	LD ₅₀ >2251 mg ai/kg bw (USEPA MRID No. 00073988) ¹
<i>Colinus virginianus</i> (Bobwhite quail chicks)	8-day acute dietary study	EPA Protocol (1973) TC (97.5%)	LC ₅₀ >5000 ppm (USEPA MRID No. 00107878) ¹
<i>Anas platyrhynchos</i> (Mallard ducklings)	8-day acute dietary study	EPA Protocol (1973) TC (97.5%)	LC ₅₀ >5000 ppm (USEPA MRID No. 00104981) ¹
<i>Oncorhynchus mykiss</i> (Rainbow trout)	Acute 96-hour static toxicity	APHA Standard Method (1970) TC (97.5%)	LC ₅₀ >320 ppm (USEPA MRID No. 00104980) ¹
<i>Lepomis macrochirus</i> (Bluegill sunfish)	Acute 96-hour static toxicity	APHA Standard Method (1970) TC (97.5%)	LC ₅₀ >370 ppm (USEPA MRID 00104980) ¹
<i>Pimephales promelas</i> (Fathead minnow)	Acute 96-hour static toxicity	APHA Standard Method (1970) TC (97.5%)	LC ₅₀ = 274 ppm (USEPA MRID No. 00104980) ¹
<i>Pimephales promelas</i> (Fathead minnow)	Fish early life stage toxicity	EPA Method 540/0-86-136 (1986) (98%)	MATC = 24.6 ppm NOEL = 17 mg/l LOEL = 35.5 mg/l (USEPA MRID No. 41406001) ¹

Hexazinone is of low acute toxicity by oral, dermal or inhalation routes. It is slightly irritating to skin and a severe eye irritant but is not a skin sensitizer. Hexazinone has not been classified as a human carcinogen and is not mutagenic. Hexazinone has not been evaluated by the FAO/WHO JMPR.

Hexazinone has not been evaluated formally by WHO/PCS but has been classified according to WHO hazard rating as Class III, slightly hazardous (WHO 2002).

¹ USEPA MRIDs: United States Environmental Protection Agency Master Record Identification. Studies showing MRIDs indicate official acceptance of study result in both the EPA Reregistration Eligibility Decision (1994) and Tolerance Reassessment Eligibility Decision (2002).

Formulations

The main formulation types available are water dispersible granules (WG), water soluble powders (SP), granules (GR) and soluble concentrates (SL). These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

Hexazinone is determined by reversed-phase HPLC, using water (pH 3)/acetonitrile (1+1, v/v) as eluent and UV detection at 254 nm. The method and an additional identity test were published in CIPAC Handbook J, p. 72, 2000. The manufacturer confirmed that the CIPAC WG method is suitable for analysis of the GR formulation, without modification.

Impurities were determined by GC-FID. The relevant impurity, ethyl carbamate, was quantified using two techniques: headspace with GC-FID and GC-MS. DuPont method A3674.300 (R), for the determination of ethyl carbamate in hexazinone TC and formulations had not been peer-validated*.

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

Physical properties

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

Containers and packaging

There are no special requirements for containers or packaging but both the technical material and the formulated products are severe eye irritants and the formulated products should be labelled in accordance with local/national guidelines.

Expression of the active ingredient

The active ingredient is expressed as hexazinone.

Appraisal

The data considered by the Meeting were submitted in support of a review of existing FAO specification for TC, GR, WP, SP and SL.

* Du Pont 2005: Hexazinone (DPX-A3674) Determination of Ethyl Carbamate (IN-08387) in Hexazinone Technical Headspace Gas Chromatographic (GC) Trace Level Method (Method No. A3674.160.01.ST)

Hexazinone is a broad-spectrum herbicide, which can be applied pre- or post-emergence, to control a range of important grass and broad-leaf weeds in sugar cane, forestry, alfalfa, pastures, vegetation management and various other crops, such as blueberries and pineapples.

Hexazinone is a solid of low volatility, moderately soluble in water and very soluble in organic solvents, except those of very low polarity. It is stable to hydrolysis (pH 4-9) and photolysis and weakly basic.

Information was submitted on the manufacturing process, together with batch analysis and manufacturing specifications data. In batch analyses, accountability was good (983–997 g/kg). Confirmation was received from the U.S. EPA that the information submitted on the manufacturing process and batch analytical data were the same as those submitted for registration in the USA.

The proposer stated that carbamic acid ethyl ester (ethyl carbamate) should be a relevant impurity, on the basis it may be formed as a trace impurity during the manufacturing process. The International Agency for Research on Cancer (IARC) classifies carbamic acid, ethyl ester, as a carcinogen (class 2A, probably carcinogenic to humans) and the U.S. EPA also considers this impurity to be of toxicological concern. The opinion of WHO/PCS supported these positions and the Meeting therefore agreed that ethyl carbamate should be included as a relevant impurity in the specifications, with a limit of 50 mg/kg. The Meeting agreed that no other impurity should be considered relevant.

The Meeting considered the specification requirements for minimum purity of the TC because, on the basis of the historical production records, the proposer had requested a limit of 957.5 g/kg. This figure also represented the minimum purity declared in support of the EPA evaluation and to national regulatory agencies in other countries. However, the quoted reproducibility (R) of the CIPAC method is 22 g/kg at 998 g/kg and thus the analytical method probably has insufficient precision to support such an accurately specified limit. The Meeting therefore agreed that the specified minimum should be 950 g/kg.

The proposer was asked to justify the manufacturing specification limits for certain impurities and stated that they were set on the basis of experience of the manufacturing process. The Meeting accepted the explanation.

Analytical methods for determination of hexazinone in the TC and formulations are full CIPAC methods, with the exception of the GR. The manufacturer stated that the CIPAC method for WG is applicable to GR without modification.

A method was provided for determination of the ethyl carbamate impurity in the technical material and formulated products but this had not been subjected to independent laboratory validation.

Draft specifications were submitted for TC, SP, WG, GR and SL. Clauses for water content and pH range were originally included but the Meeting and proposer agreed that these were unnecessary, because the water content was effectively controlled by other clauses, and because neither the active ingredient nor formulations would be adversely affected by the pH.

The Meeting questioned the designation of the WG (water dispersible granule) specification, on the basis that the relatively high water solubility of hexazinone could make it an SG (water soluble granule). The proposer stated that, at the highest formulation concentrations recommended in the spray tank, the active ingredient is partly in solution

and partly in suspension. The Meeting therefore agreed that the specification should be for a WG.

The Meeting questioned the proposed limit of 3% for the degree of dissolution test for the SP but the proposer confirmed that the small amount of residual material had not been found to pose difficulties over many years of practical use in the field. The existing specification did not comply with current requirements for SP (FAO/WHO 2002) but, using approximately similar tests, the specification limit was 2%. The Meeting accepted the proposed limit.

Subject to provision of suitable concentration ranges for active ingredient content of the formulations, the Meeting agreed that all other specification clauses fulfilled the requirements of the Manual.

Hexazinone has not been evaluated by the FAO/WHO JMPR or IPCS but it is of low acute toxicity by oral, dermal or inhalation routes and is classified by WHO as slightly hazardous. It has not been classified as a human carcinogen and is not mutagenic. Hexazinone is not a skin sensitizer but it is slightly irritating to skin and both hexazinone and its formulated products are classified as severe eye irritants. The Meeting agreed that appropriate labelling should be used on packaging, although this requirement is not part of the specifications development process.

Recommendations

The Meeting recommended that:

- the existing FAO specifications for hexazinone TC, GR, WG, SP and SL should be withdrawn when the revised specifications are published;
- the proposed specifications for hexazinone TC, GR, WG, SP and SL, as amended, should be adopted by FAO, subject to satisfactory peer validation of the method for determination of ethyl carbamate impurity*;
- although not a requirement of the FAO specifications, hexazinone products should be labelled as severe eye irritants.

References

Du Pont 2005 Hexazinone (DPX-A3674) Determination of Ethyl Carbamate (IN-08387) in Hexazinone Technical Headspace Gas Chromatographic (GC) Trace Level Method (Method No. A3674.160.01.ST)

FAO/WHO 2002 Manual on development and use of FAO and WHO specifications for pesticides, 1st edition. FAO plant production and protection paper 173. FAO, Rome, 2002.

WHO 2002 The WHO recommended classification of pesticides by hazard and guidelines to classification, 2000-2002. WHO, Geneva, 2002.

*Note added in editing, 2012: Acceptable independent laboratory validation was provided subsequently (Du Pont 2005) for the TC.