WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

NOVALURON

(±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea

WORLD HEALTH ORGANIZATION

GENEVA

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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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[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 has followed 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 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. 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/whopes).

PART ONE

SPECIFICATIONS

NOVALURON

NOVALURON

INFORMATION

ISO common name: novaluron (provisionally approved E-ISO) (applied to the racemate)

Synonyms: novaluron (BSI)

Chemical name:

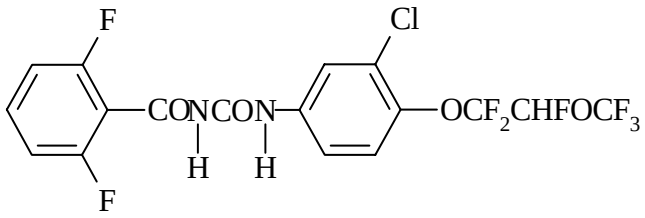
IUPAC: (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea

CA: (±)-N-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy] phenyl] amino]carbonyl]-2,6-difluorobenzamide

CAS No: 116714-46-6

CIPAC No: 672

Structural formula:



Molecular formula: $C_{17}H_9ClF_8N_2O_4$

Relative molecular mass:

492.7

Identity tests: Ultra-violet, infra-red, nuclear magnetic resonance and mass spectra.

NOVALURON TECHNICAL MATERIAL (TC)

WHO Specification 672/TC (December 2004*)

*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 (*672/2003*). It should be applicable to relevant products of this manufacturer 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 (*672/2003*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist of novaluron together with related manufacturing impurities and shall be a pale pink to white powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 672/TC/M/- 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 **Novaluron content** (CIPAC 672/TC/M/- Note 1)

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

Note 1 Methods for the identification and determination of novaluron content were adopted by CIPAC in 2004 but are not yet published. Prior to publication, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org or from the Secretary, Dr László Bura, Central Service for Plant Protection and Soil Conservation, Budaörsi út 141-145, 1118 Budapest, Hungary.

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

NOVALURON EMULSIFIABLE CONCENTRATE (EC)

WHO Specification 672/EC (December 2004*)

*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 (*672/2003*). It should be applicable to relevant products of this manufacturer 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 (*672/2003*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist of technical novaluron, complying with the requirements of WHO specification 672/TC (December 2004), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 **Identity tests** (CIPAC 672/EC/M/- 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 **Novaluron content** (CIPAC 672/EC/M/- Note 1)

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

Declared content, in g/kg or g/l at 20 ± 2°C	Tolerance
above 25 up to 100 Note: The upper limit is included in this range.	± 10% of the declared content

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

3 Physical properties

3.1 **Emulsion stability and re-emulsification** (MT 36.3) (Note 3)

The formulation, when diluted at 30 ± 2°C with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"Cream", maximum: 0.5 ml "Free oil", maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 0.5 ml "Free oil", maximum: 0 ml
Note: in applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt	

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

Maximum: 20 ml after 1 min.

4 Storage stability

4.1 **Stability at 0°C** (MT 39.3)

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

4.2 **Stability at elevated temperature** (MT 46.3)

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 5) and the formulation shall continue to comply with the clause for:

- emulsion stability and re-emulsification (3.1).

Note 1 Methods for the identification and determination of novaluron content were adopted by CIPAC in 2004 but are not yet published. Prior to publication, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org or from the Secretary, Dr László Bura, Central Service for Plant Protection and Soil Conservation, Budaörsi út 141-145, 1118 Budapest, Hungary.

Note 2 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 This test will normally only be carried out after the heat stability test 4.2.

Note 4 The test should be carried out at the highest application concentration.

Note 5 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

NOVALURON

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

NOVALURON

EVALUATION REPORT 672/2003

Explanation

The data for novaluron were evaluated in support of new FAO and WHO specifications for TC and EC.

Novaluron is under patent in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Egypt, France, Germany, Great Britain, Holland, Hungary, Israel, Italy, Japan, Mexico, South Africa, Spain, Sweden and the USA until 2006-2007.

Novaluron has not been evaluated by the FAO/WHO JMPR, nor by an IPCS Expert Group. However, for the purposes of this evaluation, an assessment of the summarized data on toxicology and ecotoxicology was made by the IPCS Secretariat. Novaluron is currently under review by the European Commission, the US EPA, the Japanese JMAFF, the Canadian PMRA and is under evaluation by WHOPES[1]. Data on novaluron have also been submitted, and the product approved, in many countries in South America, non-EU European countries, Switzerland, USA (for use on ornamentals), Israel, South Africa, India, Korea, Thailand, Turkey.

The draft specifications and supporting data were provided by Makhteshim Chemical Works Ltd, Israel, in 2002.

Uses

Novaluron is an insecticide which inhibits chitin synthesis, affecting the moulting stages of insect development. It acts by ingestion and contact and causes abnormal endocuticular deposition and abortive moulting. It is used in agriculture/horticulture on a wide range of crops including cotton, soya, maize, pome fruit, citrus, potato and vegetables against a wide range of pests. Novaluron is under evaluation by WHOPES as a mosquito larvicide.

Identity

ISO common name: novaluron (provisionally approved E-ISO) (applied to the racemate)

Synonyms: novaluron (BSI)

Chemical name:

IUPAC: (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea

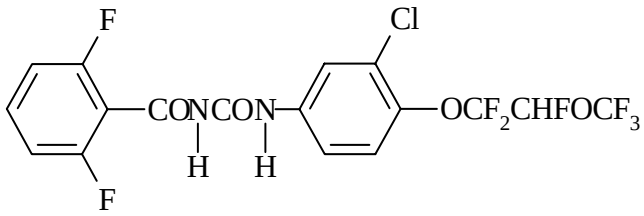
CA: (±)-N-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy] phenyl] amino]carbonyl]-2,6-difluorobenzamide

CAS No: 116714-46-6

[1] The WHOPES evaluation report and recommendations are expected to be completed in 2004.

CIPAC No: 672

Structural formula:



Molecular formula: $C_{17}H_9ClF_8N_2O_4$

Relative molecular mass:

492.7

Identity tests: Ultra-violet, infra-red, nuclear magnetic resonance and mass spectra. UV-absorption spectra have the following characteristics, according to the acidity/alkalinity of the conditions:

Sample solution conditions	Absorption maximum (nm)	Molar absorption coefficient (ε)
Acidic (0.1M HCl in methanol water, 3:2 v/v)	253	9.8×10^3
Neutral (methanol/water, 3:2)	253	15.4×10^3
Basic (0.1M NaOH in methanol/water, 3:2 v/v)	263	20.5×10^3

Note: the change in molar absorption is due to degradation, not ionisation; novaluron is prone to hydrolysis under basic conditions.

Physico-chemical properties

Table 1. Physico-chemical properties of pure novaluron.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	1.6×10^{-5} Pa at 25°C	99.5	OECD 104 equivalent to EEC A4
Melting point and temperature of decomposition:	Melting point: 176.5 to 178.0°C Decomposition temperature: not determined	99.5	OECD 102 equivalent to EEC A1
Solubility in water:	3 μg/l at 20 °C at neutral pH	99.5	OECD 105 equivalent to EEC A6
Octanol / water partition coefficient:	log P_{OW} = 4.3 at 20-25 °C, pH 7.1	99.5	OECD 117 equivalent to EEC A8
Hydrolysis characteristics:	Stable at pH 5 and pH 7 at 25°C. At pH 9: half-life at 25°C: 101 days (rate constant: 0.006846 $days^{-1}$) half-life at 50°C: 1.2 days (rate constant: 0.58614 $days^{-1}$) half-life at 70°C: 0.09 days (2.2 hours) (rate constant: 7.4355 $days^{-1}$) Half-life at 20°C at pH 9 estimated (Arrhenius equation) as 217 days (rate constant: 0.00320 $days^{-1}$).	>97	Makhteshim method

Parameter	Value(s) and conditions	Purity %	Method reference
Photolysis characteristics:	DT_{50} = 139 days of natural summer sunlight at latitude 40°N, assuming 12 hours of daylight, pH 5	>97	Makhteshim method
Dissociation characteristics:	Does not dissociate.	-	-

Novaluron is an insecticide of the benzoyl urea family, which incorporates two benzene ring structures and is a racemate of two enantiomers. It has a low vapour pressure. Novaluron is of low water solubility (3 μg/l), which is independent of pH, and has a log P_{ow} of 4.3 (values >3 are generally indicative of fat solubility). Aqueous hydrolysis and photolysis rates are slow and these processes are not likely to be significant in degradation in the environment. Novaluron is non-flammable and not explosive, according to EEC Methods A10 and A14, respectively, and has no oxidizing properties.

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.	Confidential information supplied and held on file by WHO. Mass balances in an early 3-batch analysis study were 99.52 to 100.11 % and percentages of unknowns were <0.1 %. Mass balances in a subsequent 5 batch study of full production batches were 99.5 to 99.7%.
Declared minimum [a.i.] content:	985 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them:	None
Relevant impurities < 1 g/kg and maximum limits for them:	None relevant
Stabilizers or other additives and maximum limits for them:	None
Melting or boiling temperature range	Melting point: 176 to 179°C

Hazard summary

Notes.

(i) The proposer provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from novaluron 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 novaluron technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result
Rat (male and female)	Acute oral	Single dose by oral gavage followed by 14-day observation period. US EPA subdivision F, § 82-1 ≅ OECD No. 401	Novaluron TC: LD_{50} = >5000 mg/kg bw Rimon 10 EC: LD_{50} = >5000 mg/kg bw (expressed as nominal novaluron)
Mouse (male and female)	Acute oral	Single dose by oral gavage followed by 14-day observation period. JMAFF 59 NohSan No. 4200 ≅ US EPA subdivision F, § 81-1	LD_{50} = >5000 mg/kg bw

Species	Test	Duration and conditions	Result
Rat (male and female)	Percutaneous	Single application, in place for 24 h followed by 14-day observation period. OECD No. 402 ≅ US EPA subdivision F, § 81-2 ≅ JMAFF 59 NohSan No. 4200	Novaluron TC: LD_{50} = >2000 mg/kg bw Rimon 10 EC: LD_{50} = >2000 mg/kg bw (expressed as nominal novaluron)
Rat (male and female)	Acute inhalation	Single 4-hour exposure followed by 14-day observation period. OECD No. 403 ≅ US EPA subdivision F, § 81-3	LC_{50} = >5.15 mg/l
Rabbit (male and female)	Acute skin irritation	Single 4-hour exposure followed by 3-day observation period. OECD No. 404 ≅ US EPA Subdivision F, § 81-5 ≅ JMAFF 59 NohSan No. 4200	Novaluron TC: Non-irritant. Rimon 10 EC: Slight irritant, due to one of the formulants.
Rabbit (male)	Acute eye irritation	Single dose followed by 7 day observation period. OECD No. 405 ≅ US EPA Subdivision F, § 81-4 ≅ JMAFF 59 NohSan No. 4200	Novaluron TC: Non-irritant. Rimon 10 EC: Irritant, due to one of the formulants Rimon 10 EC at a dilution equivalent to 1 g/kg novaluron (the maximum concentration recommended for agricultural use): Non-irritant.
Guinea pig (male)	Skin sensitization, Buehler	Topical exposure at day 0, 7 and 14 for 6 h, challenged at day 28 for 24 h OECD No. 406 ≅ US EPA Subdivision F, § 81-6 Note: TC not tested because it was negative in the more stringent maximization test reported below.	Rimon 10 EC: Sensitizing, due to one of the formulants. Rimon 10 EC at a dilution equivalent to 0.1% novaluron (the worst case likely for spray application): Non-sensitizing (i.e. for bystanders and operators)
Guinea pig (male)	Skin sensitization, maximization	USA EPA Subdivision F, § 86-5 ≅ JMAFF 59 NohSan No. 4200, plus method as described by Magnusson and Kligman	Novaluron TC: Non-sensitizing. Rimon 10 EC: Sensitizing, due to one of the formulants. Rimon 10 EC at a dilution equivalent to 0.1% novaluron (the worst case likely for spray application): Non-sensitizing (i.e. for bystanders and operators)

Novaluron technical is of very low acute toxicity. After oral administration, only rats showed certain clinical signs, like pilo-erection and hunched posture, and they

recovered within 5 hours of dosing. Slight signs of conjunctival irritation were noted one hour after application to the eye of rabbits but these did not persist. In a Magnusson and Kligman maximization test, none of the animals displayed signs of allergic skin reaction.

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

Species	Test	Duration and conditions	Result
Short-term toxicology			
Mouse (male and female)	Oral	28 day Dietary administration of TC EEC B7 Directive 88/302/EEC ≅ OECD guideline No. 407	NOAEL = 70 ppm (11.65 mg/kg bw/day) was only marginally involved and was considered on the whole well tolerated.
Mouse (male and female)	Oral	28 day Dietary administration of TC OECD guideline No. 407	NOAEL = 50 ppm (7.3 mg/kg bw/day)
Mouse (male and female)	Oral	90 day + 8 week reversibility Dietary administration of TC OECD 408 (1981) ≅ US EPA § 82-1 (1984) ≅ JMAFF 59 Noh-San No. 4200 (1985) ≅ EEC No. L383A, (1992) and L333, (1988)	NOAEL = 100 ppm (12.8 mg/kg)in mice, 10,000 ppm novaluron TC was generally well tolerated but erythrocyte changes (as described below) were observed at doses from 100 ppm. The NOEL was 30 ppm and the NOAEL was 100 ppm.
Rat (male and female)	Oral	28 day Dietary administration of TC EEC B7 – Directive 92/69/EEC ≅ OECD guideline No. 407	NOAEL = 20 ppm (2.1 mg/kg bw/day)
Rat (male and female)	Oral	90 day Dietary administration of TC JMAFF 59 Noh-San No. 4200 (1985) ≅ US EPA § 82-1 (1984)	NOAEL = 320 ppm (22.2 mg/kg bw/day) rats tolerated well a maximum daily dose of 10,000 ppm TC, but erythrocyte changes (described below) were observed at even the lowest dose tested, 10 ppm in diet. At higher doses, secondary splenic and hepatic changes were also observed.
Rat (male and female)	Oral	90 day Dietary administration of TC OECD 408 (1981) ≅ US EPA Subdivision F, § 82-1 (1984)	NOAEL = 100 ppm (6.93 mg/kg bw/day) rats tolerated well a maximum daily dose of 400 ppm TC, but erythrocyte changes (described below) were observed at even the lowest dose tested, 50 ppm in diet; at higher doses, secondary splenic and hepatic changes were also observed.

Species	Test	Duration and conditions	Result
Rat (male and female)	Oral	90 day + 4 week reversibility Dietary administration of TC OECD 408 (1981) ≅ US EPA § 82-1 (1984) ≅ JMAFF 59 Noh-San No. 4200 (1985) ≅ EEC No. L383A, (1992) and L333, (1988)	NOAEL = 50 ppm (4.2 mg/kg bw/day) rats tolerated well a daily dose of 20,000 ppm TC, but erythrocyte changes (described below) were observed at even the lowest dose tested, 50 ppm in diet; at higher doses, secondary splenic and hepatic changes were also observed. The US EPA concluded that the NOAEL is 100 ppm (8.3 mg/kg bw/d) [http://www.epa.gov/opprd001/factsheet/novaluron.pdf].
Dog (male and female)	Oral	90 day + 4 week reversibility Dietary administration of TC OECD guideline No. 408 (1981) ≅ US EPA FIFRA, § 82-1 (1984) ≅ JMAFF 59 Noh-San No. 4200 (1985) ≅ EEC (Official Journal of the European Communities, No. L383A (1992) and L333 (1988)	NOAEL = 100 mg/kg bw/day dogs tolerated well the highest dose tested (1000 mg/kg bw/d) but showed minor erythrocyte changes at a dose level of 100 mg/kg/d.
Dog (male and female)	Oral	90 day Dietary administration of TC Additional low dose NOEL study JMAFF 59 Nohsan No. 4200 (1985) ≅ US EPA Subdivision F, § 82-1 (1984) ≅ OECD Section 4-12 (1981) ≅ 87/302/EEC (1987)	NOAEL = 10 mg/kg bw/day (also a NOEL)
Dog (male and female)	Oral	12 months Dietary administration of TC JMAFF 59 NohSan No. 4200 (1985) ≅ OECD No. 408 (1981) ≅ EEC 87/302/EEC (1987) ≅ EPA FIFRA, subdivision F, § 82-1 (1984)	NOAEL = 10 mg/kg bw/day
Rat (male and female)	Dermal	28 days Dermal application of TC JMAFF 59 Noh-San No. 4200 (1985) ≅ USA EPA, subdivision F, § 82-2 (1984) ≅ OECD 407 (1981) ≅ Directive 87/302/EEC (1987)	NOAEL = 1000 mg/kg bw/day, (NOEL= 75 mg/kg bw/day)

Species	Test	Duration and conditions	Result
Long-term toxicity and carcinogenicity			
Rat (male and female)	Oral	104 weeks Dietary administration of TC JMAFF 59 NohSan No. 4200 (1985) ≅ USA EPA FIFRA, Subdivision F, § 83-5 (1984) ≅ OECD 453 (1981) ≅ Directive 87/302/EEC (1987)	700 or 20000 ppm: Bw increased (1st 4 weeks only): changes in the erythrocyte status, secondary haematological changes; increases in absolute and relative organ weights for spleen (females 700 ppm, males 20000 ppm) Toxicity phase: increased liver periacinar hepatocytic hypertrophy (males 2000 ppm): increased incidence and severity in spleen of haemosiderosis (males & females 20000 ppm) Oncogenicity phase: increased incidence and severity in spleen of haemosiderosis; increase in cortical tubular pigment in kidneys (males & females 700/20000 ppm): increased incidence of pigment laden Kuppfer cells in liver (females 20000 ppm)
Mouse (male and female)	Oral	78 weeks carcinogenicity Dietary administration of TC JMAFF 59 NohSan No. 4200 (1985) ≅ USA EPA FIFRA, Subdivision F, § 83-2 (1984) ≅ OECD 451 (1981) ≅ Directive 87/302/EEC (1987)	450 or 7000 ppm: Bw increased (1st 4 weeks only) also Week 26 for F, 450 ppm and at Week 52 for F, 7000 ppm; changes in the erythrocyte status, secondary haematological changes; increases in absolute and relative organ weights for spleen and liver (females): increases in swollen spleens (males/females): increase in incidence and severity in spleen of haemosiderosis and extramedullary haemopoiesis (males/females) splenic congestion (males): increase in cortical tubular pigment in kidneys (females): increased incidence of pigment laden Kuppfer cells in liver (males/females 7000 ppm)
Rat (female)	Oral terato-genicity	20 days oral administration of TC OECD 414 (1981) equivalent to USEPA 83-3 (1984) and JMAFF 59 Noh-San No. 4200 (1985)	NOAEL = 1000 mg/kg/day (maternal, increased bw) NOAEL = 1000 mg/kg/day (litter, increased food intake). No adverse effect on maternal bodyweight, food consumption, litter survival, growth and development *in utero*.
Rabbit (female)	Oral terato-genicity	29 days oral administration of TC OECD 414 (1981) equivalent to USEPA 83-4 (1984), JMAFF 59 Noh-San No. 4200 (1985) and EEC No. L383A (1992) and L333 (1988)	NOAEL = 1000 mg/kg/day (maternal, no adverse treatment-related effects; animals dosed at 1000 mg/kg/day decreased bw on cessation of treatment). NOAEL = 300 mg/kg/day (litter)

Species	Test	Duration and conditions	Result
Rat (male and female)	Oral 2-genera-tion	Oral administration of TC OECD 416 (1983) equivalent to USEPA 83-4 (1984), JMAFF 59 Noh-San No. 4200 (1985) and EEC Directive 87/302/EEC (1987)	NOAEL = 12000 ppm, equivalent to 1009.8 mg/kg/day and higher (reproductive performance). Increased bw, increased spleen wt, haemosiderosis of spleen at 12000 ppm. Treatment had no adverse effect in terms of reproductive capability, fertility or pregnancy.

M: Male; F: Female; Bw: Bodyweight.

No evidence of cumulative toxicity or of serious pathological change was identified in any species in repeated administration tests. There was no evidence of oncogenic potential in the rat or mouse. At high doses, the erythrocyte was identified as the primary target of novaluron toxicity, with secondary effects apparent in the spleen and less commonly in the liver. The spectrum of effects was essentially similar in rats, mice and dogs and the underlying mechanism was probably the same. Most pathological effects can be linked to the adverse effect on erythrocytes. An increased bodyweight gain was noted at higher doses in rats, mice and dogs but no pathological change was identified to correlate with this. Although no explanation for this effect was identified, increases in growth are not considered to be adverse, nor to represent toxicity.

The mechanism of the effects on erythrocytes has not been elucidated but the effects can be rationalized. It is probable that novaluron causes oxidative damage to the mature erythrocyte. There was no evidence of decreased production of red blood cells and, in fact, production of red blood cells increased to compensate for the loss of cells in circulation. Haematopoeisis was increased in both normal sites (sternum, femur) and in functional reserve sites (spleen, liver). The *de novo*-produced cells were normal but there was evidence of greater than usual numbers of immature cells in the circulation (reticulocyte numbers and cell size [MCV] were both increased and Howell-Jolly bodies were observed). The absence of effects on the bone marrow myeloid:erythroid ratio indicates that the functional reserve capacity to compensate for faster turnover of erythrocytes had not been exceeded and thus all three species were easily able to cope with the degree of damage done to circulating erythrocytes. The reduction in erythrocyte count was much less than would be needed to reduce the oxygen-carrying capacity of the blood to a level of clinical concern. There was no evidence of a reduced capacity to produce haemoglobin, in the quantities necessary to produce fully functional erythrocytes.

Oxidative damage to erythrocytes was evident from the presence of methaemoglobin, which is formed by oxidation of haemoglobin. The process is reversible and of little toxicological significance when small proportions are present. The presence of low levels of sulphaemoglobin was also noted and, although it has no oxygen-carrying capacity, its presence was considered to be little toxicological relevance at the concentrations observed. Heinz bodies are formed when damaged haemoglobin precipitates onto the cell membrane. They also result from oxidative damage to red cells and their presence leads to the early destruction of the cells by the spleen. The resultant increased cell turnover led to the pathological changes (increased spleen weight, red pulp congestion, increased haemosiderosis) observed in the spleen. Transport of haemoglobin catabolism products (haemosiderin and bilirubin), *via* the reticulo-endothelial system to the liver, was probably responsible for the pigmented Kuppfer cells and macrophages noted in that organ.

The adverse effects on erythrocytes would be expected to regress, as damaged cells are cleared from the circulation, following cessation of treatment. This was apparent, but incomplete, over a 4-week period after treatment of rats and dogs and was complete in 8 weeks in mice.

In a 2-generation study, F0 and F1 rats were treated between 10 weeks before mating and throughout the mating period, gestation and lactation and F2 rats were treated until all had attained sexual maturity. This treatment regime produced no treatment-related effects on reproductive capability, fertility or pregnancy. The NOEL for reproductive performance was 12000 ppm.

Developmental toxicity studies produced no effect in rat litters, with a NOEL of 1000 mg/kg/day, the highest dose tested. Maternal effects were confined to increased bodyweight gain at all dosages which was not an adverse effect, producing a maternal NOAEL of 1000 mg/kg/day. In the rabbit study, maternal bodyweight gain was low, following cessation of treatment, but not during treatment. The maternal NOEL for rabbits was 300 mg/kg/day and the NOAEL for litters was also 300 mg/kg/day .

The carcinogenicity studies proved negative, although the erythrocyte changes and anaemia observed indicated that the animals had been exposed to a sufficient dose. The doses of 20,000 ppm in rats (equivalent to 875 mg/kg bw/day for male and 1104 mg/kg bw/day female) and 7,000 ppm in mice (equivalent to 800 mg/kg bw/day for the male and 913 mg/kg bw/day for the female) may be considered to be the maximum tolerated dose (MTD).

Overall, the toxicological profile of novaluron is quite simple. There is one key target, the mature erythrocyte, which is subject to oxidative damage. Acute toxicity is low, there are no clear specific effects on reproductive function and no evidence of mutagenic or oncogenic potential.

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

Species	Test	Conditions	Result
Gene mutation assays			
Salmonella typhimurium (TA 1535, TA 1537, TA 1538, TA 98 and TA 100	Reverse mutation test for bacteria *In vitro*	Tests 1 & 2: ± S9 mix: 3333, 1000, 333, 100, 33, 10 µg novaluron as TC/plate Ames, B. N., McCann, J. and Yamasaki, E., Directive 92/69/EEC Method B14	Negative
Salmonella typhimurium (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 *uvrA*	Reverse mutation test for bacteria *In vitro*	Tests 1 & 2: ± S9 mix 312.5, 625, 1250, 2500, 5000 µg novaluron as TC/plate OECD No. 471 and 472 (1983) ≅ 92/69/EEC B.13 and B.14 (1992) ≅ US EPA § 152-17 (1984) ≅ JMAFF 59 NohSan No. 4200 (1985)	Negative

Species	Test	Conditions	Result
Two strains of *Bacillus subtilis,* H17 *rec*$^+$ a repair proficient strain and M45 *rec*$^-$ a repair deficient strain	Bacterial DNA repair (*rec*) assay *In vitro*	<u>One spot test</u>: 5000, 1500, 500, 150, 50 µg novaluron as TC/disk <u>3 differential killing assays</u>: 5000-1500-500-150-50 µg novaluron as TC/ml All ± S9 mix JMAFF 59 NohSan, Notification No. 4200 (1985)	Negative
Mouse lymphoma L5178Y cells	Mammalian cell gene mutation test (to thioguanine resistance) *In vitro*	<u>Test 1 & 2</u>: ±S9 mix 50, 100, 125, 150, 175, 200 µg novaluron TC/ml USA EPA FIFRA § 84-2 (1984) ≅ OECD 476/208(V2) (1984)	Negative
Chromosome aberration assays			
Cultured human lymphocytes	Mammalian cytogenetic test *In vitro*	<u>Test 1</u>: ±S9 mix 5000, 1000, 200, 50 µg novaluron TC/ml <u>Test 2</u>: ±S9 mix 1000, 200, 40 µg novaluron TC/ml With S9 mix, exposure time: 3 hour, cell harvest 21 hours later. Without S9 mix, exposure time: 24 hours OECD 473 (1983)	Negative
Cultured human epithelioid HeLaS3 cells	Mammalian cytogenetic test *In vitro*	<u>Tests 1 & 2</u>: ± S9 mix 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256 µg novaluron TC/ml OECD 482 (1986)	Negative
Male and female Swiss mice - bone marrow cells	Micronucleus test *In vivo*	0, 1250, 2500, 5000 mg novaluron TC/kg OECD 474 (1982) ≅ EEC method No. B12 (1984) [the positive control, mitomycin produced a large, highly significant increase in the frequency of micronuclei, so the negative result is reliable]	Negative

Table 6. Ecotoxicology profile of novaluron technical material.

Species	Test	Duration and conditions	Result
Birds			
Bobwhite quail	Acute oral toxicity	Single dose of novaluron TC administered by intubation. US EPA Subdivision E, § 71-1.	LD_{50} >2000 mg/kg NOEL = 2000 mg/kg
Bobwhite quail	Short-term dietary toxicity	Dietary inclusion of novaluron TC for 5 days. US EPA Subdivision E, §71-2.	LC_{50} >5200 ppm NOEL = 5200 ppm
Bobwhite quail	Sub-chronic toxicity and reproduction	Dietary inclusion of novaluron TC for 22 weeks. US EPA § 71-4.	NOEL = 300 ppm

Species	Test	Duration and conditions	Result
Mallard duck	Acute oral toxicity	Single dose of novaluron TC administered by intubation. US EPA Subdivision E, § 71-1.	LD_{50} >2000 mg/kg NOEL = 2000 mg/kg
Mallard duck	Short-term dietary toxicity	Dietary inclusion of novaluron TC for 5 days. US EPA Subdivision E, §71-2.	LC_{50} >5200 ppm NOEL = 5200 ppm
Mallard duck	Sub-chronic toxicity and reproduction	Dietary inclusion of novaluron TC for 22 weeks. US EPA § 71-4.	NOEL = 30 ppm
Aquatic species			
Rainbow trout	Acute toxicity	Dynamic flow-through of novaluron TC, 120 h. OECD No. 203 ≅ US EPA Subdivision E, § 72-1.	96 hour NOEC/ LC_{50} = ≥1.0 mg/l LOEC = >1.0 mg/l (nominal)
Bluegill sunfish	Acute toxicity	Dynamic flow-through of novaluron TC, 96 h. OECD No. 203 ≅ US EPA Subdivision E, § 72-1.	96 hour NOEC/ LC_{50} = ≥1.0 mg/l LOEC = >1.0 mg/l (nominal)
Carp	Acute toxicity	Semi-static, novaluron TC, 96 h. OECD No. 203 ≅ EEC method C1 ≅ JMAFF draft guidelines.	96-hour LC_{50} = >0.744 mg/l The NOEC was not clearly defined
Rainbow trout	Chronic toxicity - juvenile fish	Dynamic flow-through of novaluron TC, 28 days. OECD No. 204.	28-day NOEC = >6.16 μg/l (mean measured level in unfiltered medium); >2.59 μg/l (mean measured level in centrifuged samples)
Fathead minnow	Early life stage	Dynamic flow-through of novaluron TC, 28 days. EPA OPPTS 850. 1400 ≅ OECD No. 210.	28-day LC_{50} = >3.2 μg/l NOEC = 3.2 μg/l
Fathead minnow	Fish life cycle test (reproduction assessment)	Dynamic flow-through of novaluron TC, Up to 47 days. Adapted from USA EPA 540/9-86-137.	NOEC = 3.0 μg/l (nominal) LOEC = >3.0 μg/l (nominal)

Species	Test	Duration and conditions	Result
Bluegill sunfish	Bioconcentration	Dynamic flow-through of novaluron TC, 35 days. US EPA FIFRA, Subdivision E, § 72.6, Subdivision N, § 165-4 ≅ OECD No. 305E ≅ 91/414/EEC as amended by Commission Directive 96/12/EC.	BCF (measured) values in fish = 14216x (35 days @ 0.05 μg/l) 14645x (35 days @ 0.5 μg/l) BCF (kinetic) values = 17518x (35 days @ 0.05 μg/l) 16408x (35 days @ 0.5 μg/l) Measured 90% steady-state: 21 days Calculated 90% steady-state: 32.6-49.0 days Calculated elimination t½ (days) whole fish: 3.9 (0.05 μg/l); 7.3 (0.5 μg/l) Depuration (42 days) <10% of Day 35 exposure levels remained in whole fish.
Daphnia	Acute immobilisation test - aquatic invertebrates	Static, novaluron TC, 48 h. OECD Guideline 202.	48 hour EC_{50} = 58 μg/l (nominal) NOEC = 18 μg/l (nominal)
Daphnia	Acute toxicity - aquatic invertebrates	Static, novaluron TC, 48 h. OECD Guideline 202 ≅ EEC method C2 ≅ US EPA Subdivision E, § 72-2.	48 hour EC_{50} = 0.279 μg/l 95% confidence interval of 0.205 to 0.426 μg/l NOEC = 0.205 μg/l (nominal)
Daphnia magna	Recovery time of freshwater ecosystems	48 h survival under static conditions in media collected from outdoor microcosms at intervals after treatment. Rimon 10 EC applied at 0.1, 0.5 and 1 μg a.i./l at 7, 14 and 28 days after treatment. No regulatory guideline.	At the highest treatment and shortest interval, 1 μg/l and 7 days, the residual novaluron level was no longer acutely toxic to Daphnia. Positive controls gave expected results.
Mayfly	Acute toxicity - aquatic invertebrates	Daily renewal re-circulating system, novaluron TC, 9 days. Based on methods: OPPTS 850. 1010 and 850. 1020 ≅ ASTM standard test methods E 1706-95b ≅ Standard Methods for the Examination of Waste and Wastewater (20^{th} edition, 1998).	9-day LC_{50} = 0.032 μg/l (nominal) 9-day EC_{50} = 0.34 μg/l (nominal) NOEC = 0.00512 μg/l (nominal)
Damselfly	Acute toxicity - aquatic invertebrates	Semi-static, novaluron TC, 21 days. Based on methods: OPPTS 850. 1010 and 850. 1020 ≅ ASTM standard test methods E 1706-95b ≅ Standard Methods for the Examination of Waste and Wastewater (20^{th} edition, 1998).	21-day LC_{50} = 0.184 μg/l (nominal) 21-day EC_{50} = >0.25 μg/l (nominal) NOEC = 0.114 μg/l (nominal)

Species	Test	Duration and conditions	Result
Lumbriculus variegatus	Acute toxicity - aquatic invertebrates	Semi-static, novaluron TC, 96 h 10 days. Based on methods: ASTM standard test methods E 1706-95b ≅ Standard Methods for the Examination of Waste and Wastewater (20th edition, 1998).	96-hour LC_{50} = >5 μg/l (nominal) 10-day LC_{50} = >5 μg/l (nominal) NOEC = ≥5 μg/l (nominal)
Asellus	Acute toxicity - aquatic invertebrates	Dynamic flow-through, novaluron TC, 14 days. Based on methods: OPPTS 850. 1010 and 850. 1020 ≅ ASTM standard test methods E 1706-95b ≅ Standard Methods for the Examination of Waste and Wastewater (20th edition, 1998).	14-day LC_{50} = 1.6 μg/l (nominal) 14-day EC_{50} = 4.5 μg/l (nominal) NOEC = 0.47 μg/l (nominal)
Crangonyx	Acute toxicity - aquatic invertebrates	Semi-static, novaluron TC, 21-day. Based on methods: OPPTS 850. 1010 and 850. 1020 ≅ ASTM standard test methods E 1706-95b ≅ Standard Methods for the Examination of Waste and Wastewater (20th edition, 1998).	21-day LC_{50} = >0.47 μg/l (nominal) NOEC = 0.213 μg/l (nominal)
Brachionus calyciflorus	Acute and chronic toxicity - aquatic invertebrates	Static, novaluron TC, 24 h and 48 h. Based on methods: ASTM standard test methods 11.05, E 1440-91 (1996) ≅ Standard Methods for the Examination of Waste and Wastewater (20th edition, 1998).	24-hour LC_{50} = >5 μg/l (nominal) 48-hour LC_{50} = >5 μg/l (nominal) NOEC's = ≥5 μg/l (nominal)
Daphnia	Reproductive toxicity - aquatic invertebrates	Semi-static, novaluron TC, 21 days. OECD No. 202 ≅ US EPA Subdivision E, § 72-4.	21-day LC_{50} = 57.9 ng/l NOEC = 29.9 ng/l
Green algae *(Selenastrum)*	Effects on algal growth	Static, novaluron TC, 96 h. OECD No. 201 ≅ EEC method C3 ≅ US EPA Subdivision J, § 122-3h.	96-hour EC_{50} = >9.68 mg/l NOEC = ≥9.68 mg/l E_rC_{50} and E_bC_{50} = >9.68 mg/l
Chironomus riparius	Sediment dwelling species	Static, novaluron TC, 28 days. "Long term toxicity test with *Chironomus riparius*: Development and validation of a new test system (BBA 1995)", Streloke, M. and Kopp, H.	EC_{50} = 0.09 μg/l NOEC = 0.04 μg/l

Species	Test	Duration and conditions	Result
Lemna	Aquatic plant growth inhibition	14 days, novaluron TC. US EPA Subdivision J, § 122-2 and § 122-3 ≅ OECD Draft Guideline 'Duckweed, Static Growth Inhibition Test' (21 December 1981).	14-day EC_{50} = >777 μg/l formulated product equivalent to 75.4 μg/l ai NOEC = >777 μg/l formulated product equivalent to 75.4 μg/l ai E_rC_{50} and E_bC_{50} = >777 μg/l formulated product equivalent to 75.4 μg/l ai
Other species			
Honey bee	Acute toxicity	Single oral or topically applied dose, novaluron TC, 48 h. EPPO No. 170 ≅ UK Control of Pesticides Regulations, Working document 7/3 ≅ US EPA Subdivision L, § 141-1.	48-hour LD_{50}: Oral LD_{50}:> 100 μg/bee Contact LD_{50}:> 100 μg/bee
Earthworm	Acute toxicity	Treated artificial soil, novaluron TC, 14 days. OECD No. 207 ≅ EEC directive 87/302/EEC, Part C.	LC_{50} 1000 ppm (14 day) NOEL 1000 ppm
Earthworm *(Eisenia foetida)*	Bioconcentration	Treated artificial soil, radio-labelled Rimon 10EC, 28 days. Radiochemical purity of material added 98.7-99.6%. Added to blank formulation, with and without dilution with unlabelled novaluron	Concentration of radioactive residues was directly proportional to novaluron application rate. Bioconcentration factors 0.42 and 0.41 for high- and low-level application, respectively.
Soil non-target micro-organisms	Effects on soil non-target micro-organisms	Single application to test soil, novaluron TC, 28 days. SETAC 1995 - "Procedures for assessing the environmental Fate and Ecotoxicity of Pesticides", Part 2, section 4. Soil Micro-organisms.	Low risk to soil micro-flora

Novaluron was of very low toxicity to the birds and mammals tested. Novaluron was of low toxicity to earthworms and had no adverse effects on soil microflora, although the DT_{90} in soil is >100 days The major metabolite of novaluron in soil, 275-352 I, is more toxic to earthworms, although the risk is low (acute toxicity/exposure ratio >10,000). Technical novaluron was of low toxicity to honey bees. The very low vapour pressure of novaluron indicates that there is little potential for volatilization from soil or plant surfaces.

In general, novaluron LC_{50}, EC_{50} and NOEC values for fish and algae were higher than the highest concentration achievable, due to its very low water solubility, but novaluron does accumulate in fish.

Aquatic invertebrates, particularly *Daphnia* and mayfly, are sensitive to novaluron but it was demonstrated that re-invasion and re-colonization could occur within 2 weeks and, as a consequence, no long-term impact on arthropod populations in surface waters is expected.

Novaluron has not been fully evaluated by the WHO/PCS or by the FAO/WHO JMPR and has not yet been allocated a WHO/PCS hazard classification.

The proposed classification and labelling of novaluron, according to EU Council Directive 67/548/EEC, is as follows:

Hazard symbol:	N
Indication of danger:	dangerous for the environment.
Risk phrases:	R50/R53, very toxic to aquatic organisms and may cause long-term adverse effects to the aquatic environment.
Safety phrases:	S36/37/39, wear suitable protective clothing, gloves and eye/face protection; S56, dispose of this material and its container to hazardous or special waste collection point; S61, avoid release to the environment.

Applying the criteria of the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS)[1], PCS secretariat would classify novaluron in Class I for both acute and chronic aquatic toxicity.

Formulations

The formulations available are mainly emulsifiable concentrates (EC), which are used as agricultural/horticultural insecticides, as well as in public health (mosquito and fly control).

These formulations are registered and sold in many countries in South America, Australia, Europe other than the EU countries (where it is under evaluation), several countries in Asia, Israel and South Africa.

Methods of analysis and testing

The analytical method for novaluron in the TC and formulations was submitted to collaborative study, under the auspices of CIPAC, in 2003[2]. The active ingredient is determined by reversed-phase HPLC with UV detection at 260 nm.

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

Physical properties

The physical properties, the methods for testing them and the limits proposed for the EC formulations, comply with the requirements of the FAO/WHO Manual (1st edition, 2002).

Containers and packaging

There are no special requirements for containers and packaging.

Expression of the active ingredient

The active ingredient is expressed as novaluron.

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1 Globally Harmonized System of Classification and Labelling of Chemicals. United Nations, New York and Geneva, 2003, 443 pages.

2 2004 footnote. The analytical method was adopted by CIPAC in June, 2004.

Appraisal

Novaluron is a benzoylurea insecticide, acting by inhibition of chitin synthesis. It is a racemic mixture, the compound having a single chiral centre. It has low volatility, very low water solubility, does not form salts or dissociate and is mainly used in the form of EC formulations.. It is stable to hydrolysis at pH 5 and 7 but is slowly hydrolyzed at pH 9, 25ºC. It undergoes only slow photolysis (pH 5). Its log P_{ow} is 4.3 but, although marked bioaccumulation in fish occurred in laboratory tests, in field tests the degree of bioaccumulation was less and bioaccumulated novaluron was eliminated fairly rapidly.

The Meeting was provided with commercially confidential information on the manufacturing process and data on all impurities which may approach, or exceed, 1 g/kg. Initially, data on impurities were based on the analysis of 3 pilot production batches but a further 5 batches from full-scale production were later analyzed, in which the manufacturer corrected the identification of certain minor impurities (previously tentatively identified), which were present at <1 g/kg. The 5-batch study was submitted to support registration in the UK, USA, Japan, Australia, Switzerland, Canada and Korea. The data evaluated were confirmed as being identical to those submitted in support of the registration in Switzerland. Mass balances were high and no relevant impurities were identified by the Meeting.

Novaluron is of generally low acute, sub-acute and chronic toxicity. High doses can lead to erythrocyte damage and consequential effects on the spleen, together with some evidence of weight gain, although erythrocyte formation is not significantly affected and recovery appears to occur within weeks. Positive assessments were obtained in skin and eye irritation, and skin sensitization tests of the EC formulation but did not occur with the TC, indicating that novaluron itself is not an irritant, nor a sensitizer. Negative assessments were obtained in tests for carcinogenicity and mutagenicity. Novaluron does not show signs of reproductive or developmental toxicity, although there was some evidence of increased maternal weight gain.

Novaluron is of low toxicity to birds, fish, earthworms and aquatic plants but is highly toxic to aquatic invertebrates. The Meeting agreed that novaluron should be considered extremely toxic to crustaceans but was informed that the Swiss authorities had concluded that the lack of persistence in aqueous systems meant that there was no significant chronic exposure and therefore the long-term risks to crustaceans were considered acceptable.

The analytical method for determination of novaluron in the TC and EC is based on HPLC detection and was submitted for validation by CIPAC collaborative study in 2003[1].

Recommendations

The meeting recommended that the draft specifications for novaluron TC and EC proposed by Makhteshim should be adopted by FAO and WHO, subject to:

(i) satisfactory validation and adoption by CIPAC of the analytical method for determination of novaluron[1];

[1] 2004 footnote. The analytical method was adopted by CIPAC in June, 2004.

(ii) and, in the case of specifications for public health pesticides, completion of successful testing and evaluation of the products by WHOPES and publication of the corresponding report and recommendations.
