

**WHO SPECIFICATIONS AND EVALUATIONS  
FOR PUBLIC HEALTH PESTICIDES**

**NICLOSAMIDE**

2',5-dichloro-4'-nitrosalicylanilide

**2002**



**WORLD HEALTH ORGANIZATION  
GENEVA**

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## Disclaimer<sup>1</sup>

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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<sup>1</sup> 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 1<sup>st</sup> 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.

\* Footnote: The publications are available on the Internet under (<http://www.who.int/ctd/whopes>).

## **PART ONE**

### **SPECIFICATIONS**

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#### **NICLOSAMIDE**

NICLOSAMIDE INFORMATION  
NICLOSAMIDE TECHNICAL MATERIAL  
NICLOSAMIDE TECHNICAL CONCENTRATE  
NICLOSAMIDE EMULSIFIABLE CONCENTRATE  
NICLOSAMIDE WETTABLE POWDER

# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## NICLOSAMIDE

### INFORMATION

#### *Common names*

Niclosamide (for niclosamide: E-ISO, [m] F-ISO)

Niclosamide olamine (for niclosamide olamine: E-ISO, [m] F-ISO)

#### *Synonyms*

Niclosamide (BAN, Germany for veterinary use)

Niclosamide olamine (BAN)

Clonitralid (Germany for niclosamide olamine in public health use)

#### *Chemical names*

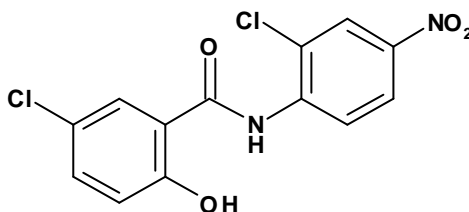
##### *IUPAC*

2',5-dichloro-4'-nitrosalicylanilide

##### *CA*

5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

#### *Structural formula*



#### *Molecular formulae*

$C_{13}H_8Cl_2N_2O_4$  (niclosamide)

$C_{15}H_{15}Cl_2N_3O_5$  (niclosamide-olamine)

#### *Relative molecular masses*

327.1 (niclosamide)

388.2 (niclosamide-olamine)

#### *CAS Registry numbers*

50-65-7 (niclosamide)

1420-04-8 (niclosamide-olamine)

#### *CIPAC code numbers*

599 (niclosamide)

599.110 (niclosamide-olamine)

# NICLOSAMIDE TECHNICAL MATERIAL

## WHO Specification WHO/599/TC (2002)

*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 (599/2002). 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 (599/2002) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of niclosamide together with related manufacturing impurities, in the form of a yellowish to grey-greenish powder, free from visible extraneous matter and added modifying agents.

### 2 Active ingredient

#### 2.1 Identity tests (CIPAC 599/TC/M/2, CIPAC Handbook J, 85-87, 2000)

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

#### 2.2 Niclosamide content (CIPAC 599/TC/M/3, CIPAC Handbook J, 85-87, 2000)

The niclosamide content shall be declared (not less than 960 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

### 3 Relevant Impurities

#### 3.1 Water (CIPAC MT 30.5)

Maximum: 10 g/kg.

## NICLOSAMIDE OLAMINE TECHNICAL MATERIAL (Note 1)

### WHO Specification WHO/599.110/TC (2002)

*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 (599/2002). 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 (599/2002) as PART TWO forms an integral part of this publication.*

#### 1 Description

The material shall consist of niclosamide, complying with the requirements of WHO specification 599/TC (2002), in the form of the ethanolamine (olamine) salt, together with related manufacturing impurities, in the form of a yellowish to brownish powder, free from visible extraneous matter and added modifying agents.

#### 2 Active ingredient

##### 2.1 Identity tests (CIPAC 599.110/TC/M/2, CIPAC Handbook J, 85-88, 2000)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, it shall comply with at least one additional test (Note 2).

##### 2.2 Niclosamide content (CIPAC 599.110/TC/M/3, CIPAC Handbook J, 85-88, 2000)

The niclosamide content shall be declared (not less than 810g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

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Note 1 The appropriate designation of certain technical grade active ingredients, traded in the form of salts or other derivatives, is under consideration. The designation has implications for the code used (TC, TK or other) and for the clauses for description and expression of the active ingredient content. This specification may be subject to revision if a change of designation is recommended by a future FAO/WHO Joint Meeting on Pesticide Specifications.

Note 2 Niclosamide olamine may be distinguished from niclosamide (free acid) by means of IR spectroscopy.

# NICLOSAMIDE EMULSIFIABLE CONCENTRATE

## WHO Specification WHO/599/EC (2002)

*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 (599/2002). 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 (599/2002) as PART TWO forms an integral part of this publication.*

### 1 Description

The material shall consist of technical niclosamide, complying with the requirements of WHO specification 599/TC (2002), 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 599/EC/M/2, CIPAC Handbook J, 90, 2000)

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

#### 2.2 Niclosamide content (CIPAC 599/EC/M/3, CIPAC Handbook J, 90, 2000)

The niclosamide content shall be declared (g/kg or g/l at  $20 \pm 2$  °C, Note 1) and, when determined, the average measured content shall not differ from that declared by more than the tolerance, given below.

Declared content, g/kg or g/l at $20 \pm 2$ °C	Tolerance
above 100 up to 250	$\pm 6\%$ of the declared content
Note: the upper limit is included in the range	

### 3 Physical properties

#### 3.1 Emulsion stability and re-emulsification (CIPAC MT 36.1.1) (Note 2)

The formulation, when diluted at  $30 \pm 2$  °C (Note 3) with CIPAC standard waters A and D, shall comply with the following::

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

#### 3.2 Persistent foam (CIPAC MT 47.2) (Note 4)

Maximum: 25 ml after 1 min.

### 4 Storage stability

#### 4.1 Stability at 0 °C (CIPAC MT 39.3)

After storage at  $0 \pm 2$  °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 (CIPAC MT 46.3)

After storage at  $54 \pm 2$  °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).

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**Note 1** 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 2** This test will normally only be carried out after the heat stability test, 4.2.

**Note 3** Unless another temperature is specified.

**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.

# NICLOSAMIDE OLAMINE WETTABLE POWDER

WHO Specification WHO/599.110/WP (2002)

*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 (599/2002). 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 (599/2002) as PART TWO forms an integral part of this publication.*

## 1 Description

The material shall consist of an homogeneous mixture of technical niclosamide olamine, complying with the requirements of WHO specification 599.110/TC (2002), together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder, free from visible extraneous matter and hard lumps.

## 2 Active ingredient

### 2.1 Identity tests (CIPAC 599/WP/M/2, CIPAC Handbook J, 88-89, 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 Niclosamide content (CIPAC 599/WP/M/3, CIPAC Handbook J, 88-89, 2000)

The niclosamide content shall be declared (g/kg) and, when determined, the content measured shall not differ from that declared by more than the appropriate tolerance, given in the table below.

Declared content, g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
above 250 up to 500	$\pm 5\%$ of the declared content
above 500	$\pm 25$ g/kg
Note: the upper limit is included in the lower range	

## 3 Physical properties

### 3.1 Wet sieve test (MT 59.3)

Maximum: 2% retained on a 75  $\mu\text{m}$  test sieve.

### 3.2 Suspensibility (MT 184) (Notes 1 & 2)

A minimum of 60% of the niclosamide content found under 5.11.2.2 shall be in suspension after 30 min in CIPAC standard water D at  $30 \pm 2^\circ\text{C}$  (Notes 3 & 4).

### 3.3 Wettability (MT 53.3)

The formulation shall be completely wetted in 1 min without swirling.

### 3.4 Persistent foam (MT 47.2) (Note 5)

Maximum: 85 ml after 1 min.

## 4 Storage stability

### 4.1 Stability at elevated temperature (MT 46)

After storage at  $54 \pm 2^{\circ}\text{C}$  for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for: wet sieve test (3.1), suspensibility (3.2) and wettability (3.3).

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Note 1 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in methods MT 15.1 or MT 177.

Note 2 This test will normally only be carried out after the heat stability test 4.1.

Note 3 Unless another temperature is specified.

Note 4 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 5 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.

Note 6 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 REPORT(S)

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#### NICLOSAMIDE

2002 Evaluation report based on submission of data from Bayer AG. (TC, TK, EC, SC for agricultural use, WP)

WHO SPECIFICATIONS AND EVALUATIONS FOR  
PUBLIC HEALTH PESTICIDES

**NICLOSAMIDE**

EVALUATION REPORT 599/2002

**Explanation**

The data for niclosamide were evaluated in support of new FAO specifications and for review of existing WHO specifications. SC formulations had not been evaluated by WHOPEP and therefore the proposed SC specification was considered only in the context of agricultural uses, on behalf of FAO.

Niclosamide is not under patent.

Niclosamide was evaluated by WHO and FAO in 1988 and the information was published in "Data Sheet on Pesticides, No. 63, Niclosamide" (WHO/VBC/DS/88.63). This publication contains data on niclosamide, its ethanalamine salt, its piperazine salt and its hydrate. Further information on the compound and its formulations is available in the WHO documents WHO/SMF/6, WHO/SMF/4.R1, WHO/SMF/4.R2, WHO/SMF/2R2 and WHO/SMF/1.R3. Niclosamide was evaluated by the US EPA in 1999 and the results were published in Reregistration Eligibility Decision (RED) fact sheet number EPA-738-R-99-007. The data for the US EPA RED fact sheets were provided by the US-Fish and Wildlife Service, part of the US Department of the Interior, to whom Bayer AG provided all data on Niclosamide and its formulations in 1990.

The draft specification and the supporting data for the evaluation were provided by Bayer AG in 2001.

**Uses**

Niclosamide is a lampricide and molluscicide. It kills a wide variety of snails, cestodes and *Cercariae* by affecting the respiration and the carbohydrate metabolism. It probably disturbs oxidation processes by inhibiting oxygen uptake. The main target pest in agricultural use is the golden apple snail (*Pomacea canaliculata*) in paddy fields (rice-cultivation). It is also used in public health for control of snails which are the intermediate hosts of *Schistosoma spp.*, the infectious agents of schistosomiasis. The compound is quickly metabolized in water and does not exhibit a long-term effect (Andrews et al, 1983).

It is also applied to commercially managed fish ponds, in order to clean them from undesirable fish prior to re-filling the pond. Niclosamide is highly toxic to fish but, due to its short half-life in water, the batch of new fish may be added only a few days after application of the pesticide.

## Identity

### Common names

Niclosamide (for niclosamide: E-ISO, [m] F-ISO)

Niclosamide olamine (for niclosamide olamine: E-ISO, [m] F-ISO)

### Synonyms

Niclosamide (BAN, Germany for veterinary use)

Niclosamide olamine (BAN)

Clonitralid (Germany for niclosamide olamine in public health use)

### Chemical names

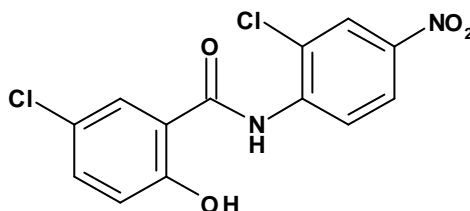
#### IUPAC

2',5-dichloro-4'-nitrosalicylanilide

#### CA

5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

### Structural formula



### Molecular formulae

$C_{13}H_8Cl_2N_2O_4$  (niclosamide)

$C_{15}H_{15}Cl_2N_3O_5$  (niclosamide-olamine)

### Relative molecular masses

327.1 (niclosamide)

388.2 (niclosamide-olamine)

### CAS Registry numbers

50-65-7 (niclosamide)

1420-04-8 (niclosamide-olamine)

### CIPAC code numbers

599 (niclosamide)

599.110 (niclosamide-olamine)

**Physico-chemical properties of pure niclosamide or its olamine salt**  
(Table 1)

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	8 x 10 <sup>-11</sup> Pa at 20°C (extrapolated) 3 x 10 <sup>-10</sup> Pa at 25°C (extrapolated)	99.9	OECD 104, by extrapolation
Vapour pressure (niclosamide-olamine)	3.9 x 10 <sup>-8</sup> Pa at 20 °C (extrapolated) 9.7 x 10 <sup>-8</sup> Pa at 25°C (extrapolated) (represents the dissociation pressure of niclosamide-olamine)	99.8	OECD 104, by extrapolation
Melting point, boiling point and/or temperature of decomposition	Melting point: 230 °C Boiling point: not known Decomposition temperature: 208 °C (niclosamide-olamine)	not stated  ~100%	not stated
Solubility in water (niclosamide & niclosamide-olamine)	5 x 10 <sup>-6</sup> g/l at 20°C at pH 4 2 x 10 <sup>-4</sup> g/l at 20°C at pH 7 4 x 10 <sup>-2</sup> g/l at 20°C at pH 9	99.9	EEC A6 OECD 105
Partition coefficient (niclosamide & niclosamide-olamine)	log P <sub>OW</sub> = 5.95 at 20°C at pH ≤ 4.0 log P <sub>OW</sub> = 5.86 at 20°C at pH 5.0 log P <sub>OW</sub> = 5.63 at 20°C at pH 5.7 log P <sub>OW</sub> = 5.45 at 20°C at pH 6.0 log P <sub>OW</sub> = 4.48 at 20°C at pH 7.0 log P <sub>OW</sub> = 3.30 at 20°C at pH 8.0 log P <sub>OW</sub> = 2.48 at 20°C at pH 9.3	99.9	EEC A8 OECD 107
Hydrolysis characteristics	<sup>14</sup> C-niclosamide did not degrade either in buffered solutions adjusted to pH 5.0, 6.9, or 8.7; or in pond water (pH 7.0-7.8) incubated in the dark for up to 56 days.	not stated	EPA RED, 1999
Photolysis characteristics	95% of <sup>14</sup> C-niclosamide in aqueous solution was degraded after 14 d exposure to long-wavelength u.v. light.	not stated	not stated
Dissociation characteristics	pK <sub>a</sub> = 5.6	99.9	calculated using solubility data (OECD 105)

**Chemical composition and properties of niclosamide technical materials (free acid or olamine salt TC) (Table 2)**

Manufacturing process, maximum limits for impurities <sup>3</sup> 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 98.6 – 100.2 % and percentages of unknowns were 0.2 – 0.3 %.
Declared minimum niclosamide content of niclosamide (free acid TC)	960 g/kg
Declared minimum niclosamide content of niclosamide-olamine (olamine salt TC)	810 niclosamide/kg, equivalent to 960 g niclosamide olamine/kg
Relevant impurities <sup>3</sup> 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 or boiling temperature range of niclosamide	227 to 232°C
Melting or boiling temperature range of niclosamide-olamine	201 to 214°C (with decomposition)

## Toxicological summaries

Notes.

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

Species	Test	Duration and conditions or guideline adopted	Result [(isomer/form)]
rats, male and female	oral	rabbits, male and female	LD <sub>50</sub> dermal ≥ 10.000 mg/kg bw (Hecht & Gloxhuber, 1962)
rats, female	oral		LD <sub>50</sub> > 5000 mg/kg bw (Flucke, 1978)
rats, male and female	dermal	not stated	LD <sub>50</sub> = >4000 mg/kg bw only determined for EC 250, not TC, Kröthlinger, 1997
rabbits, male and female	dermal	not stated	LD <sub>50</sub> >2000 mg/kg bw only determined for WP 70, not TC, Nelson & Bauman, 1969
rats, male and female	inhalation	dust, 1 h exposure	LC <sub>50</sub> = >20.000 mg/m <sup>3</sup> , Crawford et al, 1970
rabbits	skin irritation	not stated	irritating, especially at high doses or with repeated application, Kimmerle, 1971, Lorke & Lischka, 1965, Crawford & Roney, 1971
rabbits	eye irritation	not stated	strongly irritating to eyes, locally corrosive to cornea, Crawford & Roney, 1971, Nelson, 1969, Kimmerle, 1971
guinea pigs	skin sensitization	Buehler patch test	not sensitizing, result obtained from EC 250, not for TC, Stropp, 1997
guinea pigs	skin sensitization	not stated	moderate dermal sensitizer, Frost, 1988

EPA Toxicity Category III (EPA RED, 1999)

Skin-sensitization studies and dermal penetration studies with the pure a.i. (niclosamide or niclosamide-olamine) have not been conducted.

*Table 4. Toxicology profile of the technical material based on repeated administration (subacute to chronic)*

Species	Test	Duration and conditions or guideline adopted	Result
rats, males and females	subacute oral	4 weeks	NOAEL = 2000 mg/kg bw/day, Nakashani et al, 1967
dogs	subacute oral	4 weeks	NOAEL = 6000 mg/kg bw/day, Noel et al, 1965
rabbits	subacute oral	4 weeks	NOAEL = 100 mg/kg bw/day, Harper et al, 1965
cats	subacute oral	4 weeks	NOAEL = 900 mg/kg bw/day, Hunter et al, 1965
rats, males and females	subacute, dermal	3 weeks	NOAEL = 200 mg/kg bw/day, DuBois et al, 1963
rats, males and females	chronic feeding study	24 months, 0, 500, 2000, 8000 ppm	NOAEL = 2000 ppm, Bomhard, Löser & Janda, 1982
mice, males and females	chronic feeding study	104 weeks, 0, 200, 1000, 5000 ppm-	NOAEL = 200 ppm, Brune & Deutsch-Wenzel, 1983
as above	carcinogenicity	as above	the above mentioned chronic feeding studies with rats and mice did not reveal any evidence of carcinogenic potential of niclosamide
rabbits, female	reproduction, developmental toxicity and teratogenicity	oral administration of 1000mg/kg bw. for 3-4 consecutive days on days 7 to 10, 10 to 12 and 13 to 6 of gestation	the concentration was acutely toxic to mothers, but there was no evidence of embryotoxic or teratogenic effects in the litter, Harper & Palmer, 1965
rabbits, female	reproduction, developmental toxicity and teratogenicity	oral administration of 1000mg/kg bw. for 3-4 consecutive days on days 4-6, 7-9, 10-12 of gestation	the concentration was acutely toxic to mothers, but there was no evidence of embryotoxic or teratogenic effects in the cesarian-delivered fetuses, Lorke, 1964
rabbits, female	reproduction, developmental toxicity and teratogenicity	oral administration of up to 1500mg/kg bw., 25 dams	no evidence of embryotoxic or teratogenic effects in the litter, Renhof, 1985

Because niclosamide is not an organophosphorus compound, sub-chronic delayed neurotoxicity studies were not conducted.

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

Species	Test	Conditions	Result
Salmonella microsome test (SMT)	<i>in vitro</i>	not stated	pos/neg, 1977
SMT	<i>in vitro</i>	not stated	pos, 1979
SMT	<i>in vitro</i>	not stated	neg, 1982
SMT	<i>in vitro</i>	not stated	pos, 1998
Point mutation / eucaryotes (PM/E)	<i>in vitro</i>	not stated	neg, 1982
Micronucleus test (MNT)	<i>in vivo</i>	not stated	neg, 1981
Dominant lethal test (DLT)	<i>in vivo</i>	not stated	neg, 1975

Table 6. Ecotoxicology profile of the technical material

Species	Test	Duration and conditions	Result
golden orfe	acute; 84.3% acid equivalent	96h, static	TIm = ca. 0.1 mg/l Hermann, 1978
golden orfe	acute	96h, static	TIm = 0.1-0.2 mg/l (at pH 7.8) TIm = >0.2 mg/l (at pH 8.5) Hermann, 1978
rainbow trout	acute	96h, 12°C	LC <sub>50</sub> = 0.05 mg/l Marking & Hogan, 1967
rainbow trout	acute test with 70 WP	96h, 13°C	LC <sub>50</sub> = 0.34 mg/l Johnson & Finley, 1980
goldfish	acute	96h, 17°C	LC <sub>50</sub> = 0.23 mg/l Marking & Hogan, 1967
carp	acute	96h, 12°C	LC <sub>50</sub> = 0.139 mg/l Marking & Hogan, 1967
<i>Daphnia magna</i> (water flea)	acute test with 70 WP	48h, 21°C test in hard water	EC <sub>50</sub> = 0.19 mg/l, Johnson & Finley, 1980
<i>Daphnia magna</i> (water flea)	acute, test with 250 EC	48h, static 48h, semistatic	EC <sub>50</sub> = 0.224 mg product/l EC <sub>50</sub> = 0.208 mg product/l Heimbach, 2000
<i>Gammarus pseudolimnaeus</i> (scud)	acute test with 70 WP	96h, 21°C test in hard water	LC <sub>50</sub> = 2.4 mg/l Johnson & Finley, 1980
<i>Chironomus</i> (midge)	acute test with 70 WP	48h, 21°C test in hard water	EC <sub>50</sub> = 1.6 mg/l Johnson & Finley, 1980
<i>Scenedesmus subspicatus</i> (green alga)	effect on growth, static water	not stated	EC <sub>50</sub> = 5mg /l LOEC = 2 mg/l Holz & Hawa, 1963
Earthworm	acute toxicity	not stated	not applicable
<i>Apis mellifera</i> (honey bee)	acute oral toxicity	not stated	not applicable
Bobwhite quail	acute oral test with 70 WP	single dose	LD <sub>50</sub> >2000 mg/kg b.w. Hudson, publ., ref. 90248
Mallard duck	acute oral test with 70 WP	single dose	LD <sub>50</sub> >2000 mg/kg b.w. Hudson, publ., ref. 90248
Mallard duck	acute oral toxicity	single dose	LD <sub>50</sub> =>2000 mg/kg bw
Mallard duck	acute oral	single dose	NOEC ≥500 mg/kg bw Nelson & Anderson, 1969
Ring-billed gull	acute oral test with 70 WP	single dose	LD <sub>50</sub> = 500 mg/kg b.w. Hudson, publ., ref. 90248
Red-winged blackbird	subacute toxicty	18 days feeding study	LD <sub>50</sub> =>60 mg/kg bw

Data from WHO data sheet on pesticides, no.63, WHO/VBC/DS/88.63

## **Hazard Summary**

Niclosamide was evaluated by WHO in 1988 and published in "Data Sheet on Pesticides, No. 63, Niclosamide" (WHO/VBC/DS/88.63). Further information on the pesticide and its formulations is available in the WHO documents WHO/SMT/8, WHO/SMT/4.R1, WHO/SMT/4.R2, WHO/SMF/2R2 and WHO/SMF/1.R3.

Hazard classification of niclosamide:

- irritating to eyes
- very toxic to aquatic organisms
- do not breathe dust
- classification: Xi: irritant
- N: dangerous for the environment

WHO hazard classification: "Unlikely to present acute hazard in normal use."

## **Formulations**

The main formulation types available are EC, WP and SC. These formulations are registered and sold in China, Taiwan, Philippines, Thailand, Malaysia, Indonesia and the Dominican Republic.

## **Methods of analysis and testing**

The analytical method for the active ingredient (including identity tests) is a full CIPAC method (CIPAC 599, Handbook J, pages 84-91, 2000). Niclosamide is determined by reversed-phase HPLC, using UV detection at 236 nm and external standardisation.

The method for determination of impurities (Bayer method 2201-0313801-98) is based on reversed-phase LC, using UV detection and external standardisation. The components are separated by HPLC with isocratic elution. The quantitative evaluation is carried out after UV detection by means of the peak areas with external standard by comparison with reference substances. Alternatively the by-products can be determined with substance-specific area correction factors referring to the calibration of the main component, niclosamide. Validation reports were not available.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA, EC, 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 EC, SC, WP formulations, comply with the requirements of the FAO Manual (5<sup>th</sup> edition).

## **Containers and packaging**

No special requirements for containers and packaging were identified.

## **Expression of the active ingredient**

The active ingredient is expressed as niclosamide (free acid).

## Appraisal

Niclosamide was evaluated by WHO and FAO in 1988. WHO specifications for the TC, TK, WP and EC were last revised 10 December 1999. A data package on niclosamide, its salts (ethanolamine and piperazine) and hydrate was published in "Data Sheet on Pesticides, No. 63, Niclosamide" (WHO/VBC/DS/88.63).

The data submitted in support of the specifications were in accordance with the requirements of the FAO Manual (5<sup>th</sup> edition).

Niclosamide is a single compound. It has very low solubility in water at pH 4, with the solubility slightly increasing as the pH increases. The compound is stable in sterile water at pH 5 to 8.7, but subject to photolysis by long wavelength ultraviolet light. The vapour pressure of niclosamide is very low. It is very quickly metabolized in water and does not exhibit a long-term effect.

Niclosamide is a lampricide and molluscicide, formulated as the EC, SC or WP from the TC or TK (olamine salt). It is distributed in Asia and the Dominican Republic. It is registered (olamine salt only and formulations) under data supplied to the U.S. Fish and Wildlife Service (U.S. Department of the Interior).

The meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1g/kg. None of the impurities was considered to be relevant, except water in the free acid TC (because it is used to prepare the EC), while unknowns ranged from 0.2 to 0.3%. In the five batch analyses, mass balances were 98.6 to 100.2%. These data were declared to be essentially identical to those submitted in China, Taiwan, Thailand, Philippines, Indonesia, Malaysia and the Dominican Republic.

Niclosamide exhibits low acute oral, dermal and inhalation toxicity, as indicated by the data package submitted. The compound is irritating to the skin, especially at high doses, and strongly irritating to the eye. Skin sensitization observations vary from low to moderate.

Mutation study results from *Salmonella* microsome tests have been both positive and negative, while studies in other test systems (point mutation/eucaryotes, micronucleus and dominant lethal) have all been negative. Summary study results provided indicate no evidence for carcinogenicity, embryo toxicity or teratogenicity.

Niclosamide technical and formulations are analyzed by the full CIPAC HPLC method (CIPAC 599), which is applicable to TC (acid and salt), EC and WP. The proposer has validated the extension of the method to the SC. Identity tests are HPLC retention time and IR spectrum. The olamine salt can be distinguished from the free acid by the IR method.

The persistent foam test (MT 47.2) for the 70 WP gives results (85 ml after 1 min) above the FAO guideline but many years of field experience by WHO with this product have indicated no problems in practice. The test of stability of the SC at elevated temperature is carried out at 40°C (MT 46.3); however, actual use has not resulted in complaints and no limit on use in hot climates has been found to

be necessary. Crystal growth, not niclosamide degradation, is the problem at 54°C. Thus, although crystal growth might result in an adverse wet sieve test after storage at 54°C, blockage of sprayer filters and nozzles has not been reported in actual field use over many years in tropical countries.

Impurities are analyzed by isocratic HPLC, although validation reports were available at the time of evaluation. No relevant impurities other than water in the TC were identified by the meeting.

### **Recommendations**

The meeting recommended adoption of the proposed specifications for niclosamide TC, niclosamide olamine TC, EC, SC and WP as new FAO specifications and recommended adoption of the specifications for niclosamide TC, niclosamide olamine TC, EC and WP as revised WHO specifications.

### **References**

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