FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

DINOTEFURAN

(*EZ*)-(*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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DINOTEFURAN

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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 agricultural 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) and amended with the supplement of this manual (2006), which is available only on the internet through the FAO and WHO web sites. 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). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the 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 plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

PART TWO: **The Evaluation Report(s)** of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the "Manual on the development and use of FAO specifications for plant protection products" 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 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 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.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/agriculture/crops/core-themes/theme/pests/en/).

PART ONE

SPECIFICATIONS

DINOTEFURAN

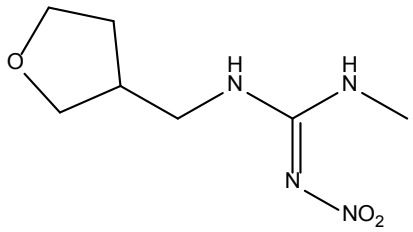
INFORMATION

ISO common name
Dinotefuran (ISO 1750 published)

Chemical names
IUPAC *(EZ)-(RS)*-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
CA N-methyl-N'-nitro-N''-[(tetrahydro-3-furanyl)methyl]guanidine

Synonym
MTI-446

Structural formula



Molecular formula
$C_7H_{14}N_4O_3$

Relative molecular mass
202.21 g/mole

CAS Registry number
165252-70-0

CIPAC number
749

Identity tests
IR, retention time in reversed-phase HPLC

DINOTEFURAN TECHNICAL MATERIAL

FAO Specification 749 / TC (March 2013*)

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 (749/2011). It should be applicable to TC produced by 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 TC produced by other manufacturers. The evaluation report (749/2011), as PART TWO, forms an integral part of this publication.

1. Description

The material shall consist of dinotefuran together with related manufacturing impurities and shall be a white crystalline powder free from visible extraneous matter and added modifying agents.

2. Active Ingredient

2.1 Identity tests (749/TC/M/-, CIPAC Handbook L, p.67, 2006)
The active ingredient shall comply with an identity test and, where the identity remains in doubt with at least one additional test.

2.2 Dinotefuran content (749/TC/M/-, CIPAC Handbook L, p.67, 2006)
The dinotefuran content shall be declared (not less than 991 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

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

PART TWO

EVALUATION REPORTS

DINOTEFURAN

DINOTEFURAN

FAO/WHO EVALUATION REPORT 749/2011

Recommendations

The Meeting recommended that the new specification for dinotefuran TC, proposed by Mitsui Chemicals Agro Inc., and as amended, should be adopted by FAO

Appraisal

Dinotefuran is a systemic neonicotinoid insecticide, in the nitroguanidine sub-class. It is used to control a wide range of pests, such as whiteflies, thrips, leafhoppers, aphids, mealy bugs, stink bugs, leaf miners, ants, cockroaches, fleas, flies, crickets and gnats.

Dinotefuran is under patent in many countries including USA, Australia, China, Switzerland, EU, Indonesia, and Japan.

Dinotefuran has been evaluated by the FAO/WHO JMPR in 2012 for toxicity and residues. Dinotefuran has not been evaluated by WHO/IPCS

The meeting considered the data on dinotefuran, submitted by Mitsui Chemicals Agro in support of a proposed new FAO specification for dinotefuran TC.

Dinotefuran is a solid that is soluble in water and highly soluble in medium polarity organic solvents like dichloromethane, acetone, methanol and ethyl acetate. It is stable to hydrolysis at all pH ranges. It is susceptible to fairly rapid photolysis. It has a $pK_a > 12$ and hence shows basic properties.

The meeting were provided with commercially confidential information on the manufacturing process and manufacturing specification for purity and impurities, supported by 5 batch analysis data. Mass balances were between 990 and 1006 g/kg and no unidentified impurities ≥ 1 g/kg were reported. A statement was provided by the EPA confirming that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were the same as those submitted to the national regulatory authority of the USA.

When comparing the data submitted to the FAO with the data submitted to US EPA it was noted that 2 additional impurities were sought in the 5 batches submitted to the USA, although these were detected at levels < 1 g/kg and hence were not declared in the manufacturing specification submitted to US EPA. The company clarified that these 2 impurities are not in the manufacturing specification but confirmed they were also analysed in the batches submitted to FAO and found below the limit of detection.

The analytical data provided indicated that a further two impurities were present at levels < 1 g/kg in the analytical data and were declared in the specification. Their inclusion in the manufacturing specification was questioned by the Meeting because of the generic threshold level for non-relevant impurities of 1 g/kg according to the FAO/WHO Manual. The company responded that they would prefer these two impurities to be kept in their manufacturing specification to remain in-line with the currently approved specification in national regulatory authorities (Japan and USA).

In considering the commercially confidential information on the manufacturing process the Meeting raised concerns about the potential formation of nitrosamines. The company clarified that reactions of secondary amines with nitrite salts, or reduction reactions of N-nitro compounds did not occur in the starting materials or during the manufacture of technical dinotefuran therefore the formation of nitrosamines could be excluded. This explanation was accepted by the Meeting.

The Meeting noted that dinotefuran could actually consist of possible *E* and *Z* isomers at the nitroguanidine moiety and an optical isomerism at the furan moiety and questioned the consequences for the unambiguous assessment of the identity and of the active ingredient and for the analytical determination of the compound by HPLC. The company provided further information to demonstrate that the starting material containing the furan moiety was present as a racemate and that there were no reaction conditions during the method of manufacture that could lead to preferential formation of one enantiomer over the other. The company therefore concluded that dinotefuran itself is present as a racemate. Furthermore dinotefuran showed no net rotation in polarimetric measurements further supporting the presence of a racemate.

In addition, further analytical data in the form of NMR analysis at different temperatures were provided. The hypothetical presence of a significant amount of *Z*-isomer was expected to show up in these NMR experiments. The data provided indicated that at lower temperatures (-40°C) tautomerisation is slowed sufficiently to allow the detection of the presence of the *E* and *Z* isomers. At 0 °C however the signals attributable to the E and Z isomer show coalescence, indicating a rapid interchange of the *E* and *Z* isomer. Interestingly, the IUPAC name refers to the racemate and includes both the *E* and *Z* isomers. Therefore, on the basis of the explanations provided by the company it was accepted by the Meeting that *E* and *Z* isomers are not stable at room temperature and do not need to be taken into account in practice.

The data provided supported a minimum dinotefuran content of 991 g/kg. No relevant impurities were identified by the company and the Meeting agreed. The analytical methods for determination of impurities are based on reversed HPLC and were acceptably validated.

The draft specification contained clauses on pH and acetone insolubles. The Meeting questioned the need for these clauses in the specification for TC and it was agreed with the company that they could be removed. On request the proposer provided a more detailed description of the TC taking into account its colour and physical state.

At the request of the meeting the proposer provided revised hazard summary tables giving classifications according to the GHS: The GHS category 5 applies for acute oral, dermal and inhalation toxicity. Dinotefuran does not require classification under GHS for skin irritation, eye irritation or skin sensitization.

The revised data and information provided for the technical material supports the specification for the TC as proposed.

The Meeting noted that in addition to dinotefuran TC the proposer also produces water soluble granule (SG) and wettable powder (WP) formulated products. The proposer clarified that their products are wettable powders rather than soluble powders (SP) as additional co-formulants are added to prevent caking. The proposer informed the Meeting that they will be applying for FAO specifications for their products in the future once their internal specifications have been standardised.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 749/2011

EXPLANATION

The data for dinotefuran were evaluated in support of a new FAO specification. Dinotefuran is currently under patent in many countries Dinotefuran has been evaluated by the FAO/WHO JMPR in 2012, but was not evaluated by WHO/IPCS.

USES

Dinotefuran is a neonicotinoid insecticide, in the nitroguanidine sub-class. It is systemic, with contact and stomach action and it affects the central nervous system of insects. Dinotefuran is a nicotinic acetylcholine receptors agonist. It is used in agriculture, horticulture, animal health and public health to control a wide range of pests, such as whiteflies, thrips, leafhoppers, aphids, mealy bugs, stink bugs, leaf miners, ants, cockroaches, fleas, flies, crickets and gnats.

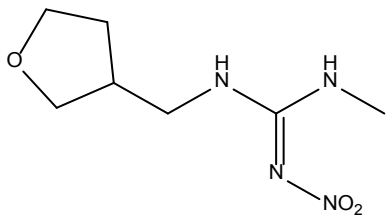
IDENTITY OF THE ACTIVE INGREDIENT

ISO common name
Dinotefuran (ISO 1750 published)

Chemical names
IUPAC *(EZ)-(RS)*-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
CA N-methyl-N'-nitro-N''-[(tetrahydro-3-furanyl)methyl]guanidine

Synonym
MTI-446

Structural formula



Molecular formula
$C_7H_{14}N_4O_3$

Relative molecular mass
202.21 g/mole

CAS Registry number
165252-70-0

CIPAC number
749

Identity tests
IR spectrum, retention time in reversed-phase HPLC

Table 1 Physico-chemical properties of pure dinotefuran

Parameter	Value(s) and conditions	Purity%	Method reference (and technique if the reference gives more than one)	Study Reference
Vapour pressure	< 1.7 x 10^{-6} Pa at 30 °C	99.7	OECD 104, OPPTS 830.7950 Gas saturation method	1
Melting point	107.5 °C	99.7	OECD 102, OPPTS 830.7200 DSC method	1
Temperature of decomposition	208 °C	99.7	OECD 103 OPPTS 830.7220 DSC method	1
Solubility in water	39.8 g/l at 20 °C (at pH 6.98)	99.7	OECD 105 OPPTS 830.7840 Flask solubility method	1
Octanol/water partition coefficient	log P_{OW} = -0.549 at 25 °C [2]	99.7	OECD 107 OPPTS 830.7550 Shake flask method	1
Hydrolysis characteristics	Half-life ≥ 1 year at 25°C at pH 4 Half-life ≥ 1 year at 25°C at pH 7 Half-life ≥ 1 year at 25°C at pH 9	99.6	JMAFF, 9 Nohsan No. 5089 OECD 111	2
Photolysis characteristics	Conditions: aqueous solution with artificial sunlight. Half-life = 1.80 days at 40°N in Summer	99.6	Directives 95/36/EEC and 94/37/EEC SETAC March 1995 OPPTS 835.2210	3
Dissociation characteristics	pK_a = 12.6	99.7	OECD 112 OPPTS 830.7370 Spectrophotometric method	1
Solubility in organic solvents	9.0 x 10^{-6} g/l hexane at 20°C 10.5 x 10^{-6} g/l heptane at 20°C 71.8 x 10^{-3} g/l xylene at 20°C 148.6 x 10^{-3} g/l toluene at 20°C 60.9 g/l dichloromethane at 20°C 57.8 g/l acetone at 20°C 57.2 g/l methanol at 20 °C 19.4 g/l ethanol at 20°C 5.17 g/l ethyl acetate at 20°C	99.7	OECD 105 OPPTS 830.7840 Shake flask method	1

[2] In deviation to the Test Guideline OECD 111, no buffer system was used. Instead the Pow was determined at two different concentrations and with several different ratios of octanol & water. In all cases the P_{ow} measured was consistently low indicating the low lipophilicity of dinotefuran.

Table 2: Chemical composition and properties of dinotefuran technical (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 100-100.6%. No unknowns were identified
Declared minimum [a.i.] content	991 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study reference
Melting temperature range of the TC and/or TK	Not available. See Table 1 for data on pure active ingredient			
Solubility in organic solvents	Not available. See Table 1 for data on pure active ingredient			

HAZARD SUMMARY

The JMPR (2012) summarized the hazard of dinotefuran as follows:
The LD_{50} in rats treated orally with dinotefuran was 2450 mg/kg bw. The dermal LD_{50} in rats was greater than 2000 mg/kg bw, and the inhalation LC_{50} in rats was greater than 4.09 mg/L. Dinotefuran was not a skin irritant in rabbits, was slightly irritating to the eye of rabbits and was not a skin sensitizer in the maximization test in guinea-pigs.
Although dinotefuran is neurotoxic in insects, neurotoxicity in mammals was not a critical effect after repeated exposure. No specific target organs were clearly identified in any species following short-term or long-term oral exposure, despite the administration of very high doses of up to 10 635, 3156 and 862 mg/kg bw per day for 13 weeks in mice, rats and dogs, respectively. In all species, the NOAELs were based on decreases in body weight and/or body weight gain as the critical effect. At higher dose levels, a number of minor e fects on clinical chemistry parameters, without histopathological correlates, occurred in all species and comprised increased serum albumin concentration and reduced urinary pH in mice, increased serum cholesterol and urea nitrogen concentrations and reduced serum glucose and protein concentrations in rats, and reduced urinary pH in dogs.

(...) The Meeting concluded that dinotefuran is not carcinogenic in mice or rats.
Dinotefuran was tested for genotoxicity in vitro and in vivo in an adequate range of assays. It was not found to be genotoxic. The Meeting concluded that dinotefuran is unlikely to be genotoxic. In view of the lack of genotoxicity and the absence of carcinogenicity in rats and mice, the Meeting concluded that dinotefuran is unlikely to pose a carcinogenic risk to humans.

FORMULATIONS

Dinotefuran is not co-formulated with other pesticides.The main formulation types available are SG, GR, SL, WP (agricultural use) and bait, ready to use, fogger, spot-on (public health formulations).

These formulations are registered and sold in many countries throughout the world.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is CIPAC Method 749 and includes submethods for TC, WP and SG, respectively. The dinotefuran content is determined by reverse phase HPLC with UV detection using external standardisation. Test methods for determination of physical-chemical properties of the technical active ingredient were OECD, EC or OPPTS as indicated.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as dinotefuran.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

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

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result	Study reference
Crl:CD[SD]BR rat, male and female	Acute oral	96.5[a]	OECD 401, FIFRA, Subdivision F, § 81-1, JMAFF 59 NohSan No. 4200 1000, 2000, 3000, 4000, 5000 mg/kg	LD_{50} = 2450 mg/kg bw (sexes combined)	4
Crl:CD1[ICR]BR mice, male and female	Acute oral	96.5[a]	OECD 401, FIFRA, Subdivision F, § 81-1, JMAFF 59 NohSan No. 4200 1000, 2000, 3000 mg/kg	LD_{50} = 2371 mg/kg bw (sexes combined)	5
Crl:CD[SD]BR rat, male and female	Acute dermal	96.5[a]	OECD 402, FIFRA, Subdivision F, § 81-2, JMAFF 59 NohSan No. 4200 2000 mg/kg	LD_{50} > 2000 mg/kg bw (sexes combined)	6
Crl:WI[Glx/BRL/Han]BR rat, male and female	Acute inhalation	93.0[b]	92/69/EEC, method B2, OECD 403, OPPTS 870.1300, JMAFF 59 NohSan no. 4200 4.09 ± 0.87mg/L (analytical) at MMAD ± GSD of 4.74 ± 2.79 µm Nose only, 4-hour exposure	LC_{50} > 4.09 mg/L (sexes combined)	7
New Zealand White (Hra:(NZW) rabbit, 5 males and 1 female	Skin irritation	96.5[a]	OECD 404, FIFRA, Subdivision F, § 81-5, JMAFF 59 NohSan No. 4200 0.5 g/animal 4-hour semi-occlusive application	Non-irritant	8

[a] 96.5% + 2% water, purity of dried material 99.1%
[b] 93.0% + 7.6% water, purity of dried material 98.9%

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

Table 3: Toxicology profile of dinotefuran technical material, based on acute toxicity, irritation and sensitization (cont.)

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study reference
New Zealand White (Hra:(NZW) rabbit, 6 males and 3 females	Eye irritation	96.5[a]	OECD 405, FIFRA, Subdivision F, § 81-4, JMAFF 59 NohSan No. 4200 0.1 g/ eye 3 rabbits: treated eye flushed with water 30 seconds after instillation 6 rabbits: treated eye unwashed.	Mean primary eye irritation scores according to the method of Kay & Calandra were greatest at 24 hours (14.8 and 14.7 in unwashed and washed groups, respectively) and had declined to zero in both groups by day 14. According to the GHS rules dinotefuran does not require classification for eye irritation.	9
New Zealand White rabbits, 1 male and 2 females	Eye irritation	98.9± 0.163[c]	OPPTS No. 870.2400, FIFRA 7 USC 136, TSCA 15 USC 2601 0.1 mL by volume (37.8 mg)/animal	Based on the Maximum Average Irritation Score of 2.7, dinotefuran is rated minimally irritating. No “positive” effects were observed during the study. No irritation was observed in any eyes at 24 hours.	10
Crl:[HA]BR guinea pig, male	Skin sensitisation	96.5[a]	OECD 406, FIFRA, Subdivision F, § 81-6, JMAFF 59 NohSan No. 4200 Maximisation test 25% concentrations	Non-sensitizer	11

[a] 96.5% + 2% water, purity of dried material 99.1%
[b] 93.0% + 7.6% water, purity of dried material 98.9%
[c] Four replicate determinations

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

Table 4: Toxicology profile of dinotefuran technical material based on repeated administration (subacute to chronic)

Species	Test	Purity % Note[5]	Guideline, duration, doses and	Result	Study reference
Beagle dog (Marshall beagle), male and female	Sub-acute, feeding, dose range finder	92.9[a]	No applicable guideline 1 week 0, 1250, 5000, 20000, 30000, 40000 ppm One dog/sex/group	NOAEL = 40000 ppm, equivalent to 770 / 924 mg/kg bw/d (males/females) LOEL not available	12
Beagle dog (Marshall beagle), male and female	Sub-acute, gavage, dose range finder	92.9[a]	No applicable guideline 1 week 0, 30, 100, 300 mg/kg/d One dog/sex/group	NOAEL = 100 mg/kg bw/d (both sexes) LOEL = 300 mg/kg bw/d (both sexes)	13
Crl:CD® [SD]BR VAF/Plus ® rat, male and female	Sub-acute, feeding	96.5[b]	OECD 407 4 weeks 0, 5000, 25000, 50000 ppm	NOAEL = 50000 ppm, equivalent to 3720 / 4222 mg/kg bw/d (males/females) LOEL not available	14
Crl:CD1®[ICR]BR VAF/Plus® mouse, male and female	Sub-acute, feeding	96.5[b]	OECD 407 4 weeks 0, 5000, 25000, 50000 ppm	NOAEL = 50000 ppm, equivalent to 10303/12289 mg/kg bw/d (males/females) LOEL not available	15
Crl:CD® [SD]BR VAF/Plus ® rat, male and female	Sub-acute, feeding	96.5[b]	OECD 408, FIFRA, Subdivision F, § 82-,1 JMAFF 59 NohSan No. 4200 13 weeks 0, 500, 5000, 25000, 50000 ppm	NOAEL = 25000 ppm, equivalent to 1623/1871 mg/kg bw/d (males/females) LOEL = 50000 ppm, equivalent to 3156 / 3616 mg/kg bw/d (males/females)	16
Crl:CD1®[ICR]BR VAF/Plus® mouse, male and female	Sub-acute, feeding	96.5[b]	OECD 408, FIFRA, Subdivision F, § 82-,1 JMAFF 59 NohSan No. 4200 13 weeks 0, 500, 5000, 25000, 50000 ppm	NOAEL = 25000 ppm, equivalent to 4442 / 5414 mg/kg bw/d (males/females) LOEL = 50000 ppm, equivalent to 10635 / 11560 mg/kg bw/d (males/females)	17

[a] 92.9% + 6.9% water; purity of dried material 99.1% / [b] 96.5% + 2% water, purity of dried material 99.1%

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

Table 4: Toxicology profile of dinotefuran technical material based on repeated administration (subacute to chronic) (cont.)

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study reference
Beagle dog, male and female	Sub-acute, feeding	93.0[c]	OECD 409, FIFRA, Subdivision F, § 82-,1 JMAFF 59 NohSan No. 4200 13 weeks 0, 1600, 8000, 40000 – 24000 ppm	NOAEL = 8000 ppm, equivalent to 307 / 323 mg/kg bw/d (males/females) LOEL = 24000 ppm, equivalent to 862 / 950 mg/kg bw/d (males/females)	18
Beagle dog, male and female	Chronic, feeding	93.0[c]	OECD 452, FIFRA, Subdivision F, § 83-,1 JMAFF 59 NohSan No. 4200 52 weeks 0, 640, 3200, 16000 ppm	NOAEL = 16000 ppm, equivalent to 559 / 512 mg/kg bw/d (males/females) LOEL not available	19 and 20
Crl:WI[GlxBRL/Han]BR rat, male and female	Sub-acute, inhalation	99.1	OECD 412 Nose only, 6-hour/day, 28 days 0, 0.22, 0.66, 2.08 mg/L MMAD ± GSD; 2.03 ± 3.31, 1.80 ± 3.60, 1.55 ± 2.96 µm	NOAEL = 2.08 mg/L (both sexes) LOEL not available	21
Crl:CD®(SD)IGS BR rat, male and female	Sub-acute, dermal (dose range finding)	93.0[c]	No applicable EU guideline Semi-occlusive application 6 - 7 hours/day, 14 days 0, 40, 200, 1000 mg/kg/d	NOAEL > 1000 mg/kg/d (both sexes) LOEL not available	22
Crl:CD®(SD)IGS BR rat, male and female	Sub-acute, dermal	93.0[c]	OECD 410, OPPTS 870.3200 Semi-occlusive application 6 - 7 hours/day, 28 days 0, 40, 200, 1000 mg/kg/d	NOAEL > 1000 mg/kg/d (both sexes) LOEL not available	23

[c] 93.0% + 7.6% water, purity of dried material 98.9%

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

Table 4: Toxicology profile of dinotefuran technical material based on repeated administration (subacute to chronic) (cont.)

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result	Study number
Crl:CD®(SD)BR VAF/Plus® rat, male and female	Combined chronic and carcinogenicity, feeding	93.0[c]	OECD 453, FIFRA Subdivision F, §83-2, JMAFF 59 NohSan 4200 104 weeks 0, 60, 200, 2000, 20000 ppm (equivalent to 0, 3, 10, 100, 991 mg/kg bw/d for males – and to 0, 4, 13, 127, 1332 mg/kg bw/d for females)	NOAEL, all effects = 991 / 127 mg/kg bw/d (males/females) NOAEL, carcinogenicity: > 991 / > 1332 mg/kg bw/d (males/females) LOEL, all effects: > 991 / 1332 mg/kg bw/d (males/females) LOEL, carcinogenicity not available	24
Crl:CD-1®(ICR)BR VAF/Plus® mouse, male and female	Carcinogenicity, feeding	93.0[c]	OECD 451, FIFRA, Subdivision F, § 83-2, JMAFF 59 NohSan no. 4200 78 weeks 0, 25, 250, 2500, 25000 ppm (equivalent to 0, 3, 34, 345, 3694 mg/kg bw/d for males – and to 0, 4, 45, 441, 4728 mg/kg bw/d for females)	NOAEL, all effects =345 /441 mg/kg bw/d (males/females) NOAEL, carcinogenicity: > 3694 / > 4728 mg/kg bw/d (males/females) LOEL, all effects = 3694 / 4728 mg/kg bw/d (males/females) LOEL, carcinogenicity not available	25
Hanlbm: WIST rat, male and female	2- generation reproduction, feeding, preliminary	98.9	No applicable EU guideline 0, 10000, 20000 ppm	NOAEL: < 637 / < 2145 mg/kg bw/d (P/F1) LOEL = 637 / 2145 mg/kg bw/d (P/F1)	26
Hanlbm: WIST rat, male and female	2- generation reproduction, feeding	98.9	OECD revised draft guideline 416, EPA OPPTS 870.3800, JMAFF 59 NohSan No. 4200 0, 300, 1000, 3000, 10000 ppm	NOAEL, repro: > 822[d] mg/kg bw/d NOAEL, pup development = 241[d] mg/kg bw/d NOAEL, all effects = 241[d] mg/kg bw/d LOEL, repro: > 822[d] mg/kg bw/d LOEL, pup development = 822[d] mg/kg bw/d LOEL, all effects = 822[d] mg/kg bw/d	27

[c] 93.0% + 7.6% water, purity of dried material 98.9%

[d] values for P generation males (lowest values determined in either sex of either generation)

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

Table 4: Toxicology profile of dinotefuran technical material based on repeated administration (subacute to chronic) (cont.)

Species	Test	Purity % Note[8]	Guideline, duration, doses and conditions	Result	Study reference
Crj:CD(SD) IGS rat, female	Teratogenicity, gavage	92.9[g]	OECD 414, FIFRA, Subdivision F, §83-3, JMAFF 59 NohSan no. 4200 Treatment; from day 6 to day 15 of gestation 0, 100, 300, 1000 mg/kg bw/d	NOAEL, maternal = 300 mg/kg bw/d NOAEL, foetal: > 1000 mg/kg bw/d LOEL, maternal = 1000 mg/kg bw/d LOEL, foetal: not available	28
New Zealand White rabbit, female	Teratogenicity, gavage	92.9[g]	OECD 414, FIFRA, Subdivision F, §83-3, JMAFF 59 NohSan no. 4200 Treatment; from day 6 to day 18 of gestation 0, 52, 125, 300 mg/kg bw/d	NOAEL, maternal = 52 mg/kg bw/d NOAEL, foetal: > 300 mg/kg bw/d LOEL, maternal = 125 mg/kg bw/d LOEL, foetal: not available	29
Crl:CD®(SD) IGS BR rat, male and female	Acute neurotoxicity, gavage	93.0[h]	OECD 424, OPPTS 870.6200 0, 325, 750 and 1500 mg/kg	NOAEL, neuro and all effects: > 1500 mg/kg LOEL not available	30
Crl:CD®(SD) IGS BR rat, male and female	Sub-chronic neurotoxicity, feeding,	93.0[h]	OECD 424, OPPTS 870.6200 13-week 0, 500, 5000, 50000 ppm[i]	NOEL, neurotoxicity: > 3413 / > 3806 mg/kg bw/d (males/females) NOAEL, all effects = 327 / 400 mg/kg bw/d (males/females) LOEL, neurotoxicity: not available LOEL, all effects = 3413 / 3806 mg/kg bw/d (males/females)	31

[g] 92.9% + 6.9% water; purity of dried material 99.1%
[h] 93.0% + 7.6% water, purity of dried material 98.9%
[i] corresponding to overall mean achieved dose levels of 0, 33, 327 and 3413 mg/kg bw/d (males) and 0, 40, 400 and 3806 mg/kg bw/d (females)

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

Table 4: Toxicology profile of dinotefuran technical material based on repeated administration (subacute to chronic) (cont.)

Species	Test	Purity % Note[9]	Guideline, duration, doses and conditions	Result	Study reference
Sprague Dawley rat, male and female	Transfer of [^{14}C]MTI-446 into milk of lactating rats, gavage	[G-^{14}C]; 96.0	No applicable guideline Lactating dams treated on days 2, 4, 8 and 12 of lactation 50 or 500 mg/kg at each administration occasion 6 dams per dose level Determination of concentrations in maternal milk, whole bold and plasma	At both dose levels, dinotefuran and/or metabolites rapidly partitioned into maternal milk on days 2, 4, 8 and 12 of lactation. Concentrations in milk were consistently higher than maternal whole blood and plasma.The study provides evidence of neonatal exposure of suckling pups to dinotefuran and/or metabolites via the maternal milk.	32
Crl:CD(SD) rat, P generation; female, F1 generation; male and female	Developmental neurotoxicity and immunotoxicity, dose-range finder, feeding	99.5	No applicable guideline P generation: from day 6 of gestation until day 21 postpartum F1 generation: 5 weeks following weaning 0, 1000, 3000, 10000 ppm[j]	NOAEL, F1 immunotoxicity: >1043 / >1120 (males/females) NOAEL, maternal toxicity: > 1035 NOAEL, F1 all effects = 311 / 316 (males/females) LOEL, F1 all effects = 1043 / 1120 (males/females)	33 and 34 (analytical method)
Crl:CD(SD) rat, P generation; female, F1 generation; male and female	Developmental neurotoxicity, feeding	99.5	OPPTS 870.6300 P generation: from day 6 of gestation until day 21 postpartum F1 generation: 21 days postpartum 0, 1000, 3000, 10000 ppm[k]	NOEL and NOAEL developmental neurotoxicity = 784 / 1643 (maternal dose during gestation / lactation) NOAEL, all effects = 237 / 501 (maternal dose during gestation / lactation)	35 (draft report)

[j] corresponding to overall mean achieved dose levels of 0, 69.5, 212 and 670 mg/kg bw/d (P, gestation); 0, 141, 424 and 1401 mg/kg bw/d (P, lactation); 0, 100, 311 and 1043 (F1 males); 0, 112, 316 and 1120 (F1 females)
[k] corresponding to overall mean achieved dose levels of 0, 79, 237 and 784 mg/kg bw/d (P, gestation); 0, 158, 501 and 1643 mg/kg bw/d (P, lactation)

Table 5: Mutagenicity profile of dinotefuran technical material based on in vitro and in vivo tests

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

Species	Test	Purity % Note[10]	Guideline, duration, doses and conditions	Result [dinotefuran]	Study reference
S. typhi-murium & *E. coli*	Point mutation assay *in vitro*	96.5[a]	OECD proposal for updated guideline 471-472, OPPTS 870.5100/870.5265, JMAFF 59 NohSan no. 4200, JMHW, Part 1, Japan Ministry of Labor, Notification nos. 76 and 77 Pre: 1.2 – 5000 μg/plate (± S9) Main: 313 – 5000 μg/plate (± S9)	Negative (± S9)	36
B. subtilis	DNA repair assay (rec-assay) *in vitro*	96.5[a]	JMAFF 59 NohSan no. 4200 1000 – 16000 μg/disc (± S9)	Negative (± S9)	37
Chinese hamster lung CHL/IU cells	Chromosome aberration assay *in vitro*	96.5[a]	OECD 473, 92/69/EEC (method B.10), OPPTS 870.5375, JMAFF 59 NohSan no. 4200, JMHW, Part 1, Japan Ministry of Labor, Appendix 1, Notification nos. 143 500 – 2000 μg/mL @: 6 hours (± S9), 24 hours (- S9), 48 hours (- S9)	Negative (± S9)	38
L5178Y $tk^{+/-}$ mouse lymphoma cells	Mammalian point mutation assay *in vitro*	99.1	OECD 476, OPPTS 870.5300, UKEMS 400 – 2022 μg/mL for: 3-hr exposure (± S9), 24-hr exposure (- S9), 3-hr exposure (+ S9)	Negative (± S9)	39
BDF1 (C57BL/6 x DBA/2) mouse, male	Micronucleus test *in vivo*	>99%	JMAFF 59 NohSan no. 4200 540 (2 x 270) mg/kg), 1080 (2 x 540) mg/kg, 2160 (2 x 1080) mg/kg 24hr sacrifice after the final treatment	Negative	40

[a] 96.5% + 2% water, purity of dried material 99.1%

Table 6: Ecotoxicology profile of dinotefuran technical material

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

Species	Test	Purity % Note[11]	Guideline, duration, doses and conditions	Result [dinotefuran]	Study reference
Coturnix coturnix japonica Japanese quail	acute oral	97.26	OECD 423, SETAC 14 - 21 days, 200/1000/2000 mg/kg bw, 19 - 25°C	LD50 > 2000 mg/kg bw	41
Colinus virginianus Northern bobwhite	acute oral	94.7	OPPTS 850.2100, 14 days, 22.2 ±0.9°C	LD50 > 2250 mg/kg bw	42
Coturnix coturnix japonica Japanese quail	dietary toxicity	97.26	OECD 205, OPPTS 850.2200, 5 days,	LD50 > 1301 mg/kg bw/day NOEC: 5000 mg/kg diet	43
Anas platyrhynchos Mallard duck	dietary toxicity	99.2	OECD 205, OPPTS 850.2200, 5 days,	LC50 > 997.7 mg/kg bw/day NOEC: 5000 mg/kg diet	44
Anas platyrhynchos Mallard duck	avian reproduction	99.3	FIFRA 71-4, OECD 206, 20 weeks, 22.85 ±0.99°C	NOEL: 2000 mg/kg diet	45
Colinus virginianus Northern bobwhite	avian reproduction	99.3	FIFRA 71-4, OECD 206, ~21 weeks, 23.04 ± 1.86°C	NOEL: 5000 mg/kg diet	46
Oncorhynchus mykiss Rainbow trout	fish acute	97.26	OPPTS 850.1075, EEC C.1, OECD 203, 96 hours, 12-13°C, static	LC50 > 100 mg/L	47
Lepomis macrochirus Bluegill sunfish	fish acute	97.26	OPPTS 850.1075, EEC C.1, OECD 203, 96 hours, 23°C, static	LC50 > 100 mg/L	48
Cyprinus carpio Common carp	fish acute	97.26	OPPTS 850.1075, EEC C.1, OECD 203, 96 hours, 22 - 23°C, static	LC50 > 100 mg/L	49
Oncorhynchus mykiss Rainbow trout	fish early life stage	98.9	OPPTS 850.1400, OECD 210, 94 days, 10 - 12°C, flow-through	Overall NOEC: 10 mg/L	50
Daphnia magna	daphnia acute	97.26	OPPTS 850.1010, EEC C.2, OECD 202, 48 hours, 20 - 21°C, static	EC50 > 1000 mg/L	51
Daphnia magna	daphnia reproduction	97.26	OECD 21, OPPTS 850.1300, 21 days, 20°C, semi-static	NOEC: 100 mg/L EC50, LOEC, MATC > 100 mg/L	52
Pseudokirchneriella subcapitata Green alga	alga growth and growth rate	97.26	EEC C.3, OECD 201, OPPTS 850.5400, 96 hours, 22-23°C, static	EC50/LOEC > 100 mg/L NOEC: 100 mg/L	53

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result [dinotefuran]	Study reference

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

Chironomus riparius	acute test	97.26	OECD 202, EEC C.2, BBA, 1995, OECD 219, draft, 2000, 48 hours, 20°C, static	LC50: 72.1 µg/L, NOEC: 22 µg/L, LOEC: 46 µg/L	54
Chironomus riparius	chronic test	97.26	BBA, 1995, OECD 219 draft 2001, 27 days, 19.4 - 19.8, static, spiked water	NOEC: 3 µg a.i./L, LOEC: 5.9 µg/L $EC50_{emergence\ ratio}$: 14.5 µg/L $EC50_{development\ rate}$: not calculated due to low inhibition rates	55
Lemna Gibba	growth inhibition	99.2	OPPTS 850.4400, OECD 221, 7 days, 24°C, semi-static	NOEC: 110 mg/L LOEC, EC10 and EC50 > 110 mg/L	56
Apis mellifera Honey Bee	acute oral and contact	99.5	OPPTS 850-302, OECD 213/214, 48 hours, 25°C	Contact LD50: 0.056 µg/bee Oral LD50: 0.0223 µg/bee	57
Eisenia foetida Earthworms	acute toxicity	n.a.[13]	OJ L 133, OECD 207, 14 days, 20 - 22°C	LC50: 4.9 mg/ kg dry soil NOEC: 1.7 mg/kg dry soil	58
Eisenia foetida Earthworms	earthworm repro-duction	97.26	ISO 11268-2, BBA part VI, 2-2, 8 weeks	LC50 (28 d, mortality): 5.1 mg/kg dry soil EC50 (28 d, reproduction): 1.2 mg/kg dry soil NOEC (28 d, all effects): 0.2 mg/kg dry soil LOEC (28 d, all effects): 0.5 mg/kg dry soil	59
Soil microbial activity	soil respiration and nitrification	n.a.[14]	SETAC, 28 days	No adverse effect on organic matter turnover and on soil fertility at rates up to ten times the recommended field rate (3 kg dinotefuran/ha)	60
Mysidopsis bahia Saltwater mysid	mysid acute	99.2	OPPTS 850.1035, EPA E.72-3, 96 hours, 25 ± 2°C, flow-through	LC50 (96 h): 0.79 mg/L NOEC: 0.49 mg/L	61
Crassostrea virginica East-ern oyster	oyster acute	Not speci-fied	OPPTS 850.1025, EPA E.72-3, 96 hours, 20 ± 1°C, flow-through	EC50 (96 h): > 141 mg/L NOEC: 141 mg/L	62
Cyprinodon variegatus Sheepshead minnow	fish acute	99.2	OPPTS 850.1075, EPA E.72-3, 96 hours, 22 ± 2°C, flow-through	LC50 (96 h): > 109 mg/L NOEC: 109 mg/L	63

[13] Not applicable (test performed with a 70% WP formulation of dinotefuran) – results expressed as dinotefuran technical
[14] Not applicable (test performed with a 20% SG formulation of dinotefuran)

ANNEX 2

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