REGULATION (EC) NO 1272/2008 (CLP REGULATION),

ANNEX VI, PART 2

Proposal for Harmonised Classification and Labelling for a biocidal active substance

CLH REPORT

Dinotefuran

EC Number: -

CAS Number: 165252-70-0

Index Number: 612-RST-VW-Y

Contact details of dossier submitter:

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BELGIUM

On behalf of the Belgian Biocidal unit

Version number: 2 Date: October 2022

Table of Contents

STATEMENT

This CLH report is the first proposal for an harmonised Classification & labelling for the Active Substance "Dinotefuran" (CAS: 165252-70-0).

However, it is important to note that a large majority of the parameters/endpoints described in this document had already been determined in the context of the Assessment Report of Dinotefuran prepared by the previous evaluating competent authority, United Kingdom, and approved on 1st June 2015. Following the departure of the United Kingdom from the European Union, Belgium has taken over the function of evaluating competent authority for the Dinotefuran dossier and more precisely for the renewal of the assessment report for Dinotefuran for product type 18.

SUMMARY

1 PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Table 1-1: Main constituent(s)

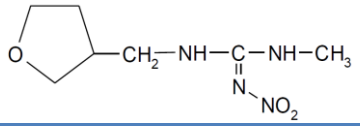
Main constituent(s)	
ISO name	Dinotefuran
IUPAC or EC name	(*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
EC number	-
CAS number	165252-70-0
Index number in Annex VI of CLP	612-RST-VW-Y
Minimum purity / content	991 g/kg
Structural formula	

Table 1-2: Relevant impurities and additives

There are no relevant impurities in the active substance Dinotefuran, as per the definition of relevant impurities.

1.2 INTENDED USES AND EFFECTIVENESS

Table 1-3: Use of the active substance

Product type	Product Type 18 : Insecticide
Intended use pattern(s)	Insecticide for indoor use only as a spot or crevice and crack treatment at / near locations where target pests gather.
Users	Professional, trained professional and non-professional

Table 1-4: Effectiveness of the active substance

Function	PT 18 Insecticide
Organisms to be controlled	Adult and nymph cockroaches: Oriental cockroach (*Blatta orientalis*) German cockroach (*Blattella germanica*)
Limitation of efficacy including resistance	None
Mode of action	Contact and ingestion: Nicotinic acetylcholine receptor (nAChR) competitive modulator (IRAC sub-group 4A)

2. PROPOSED HARMONISED CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE ACCORDING TO THE CLP CRITERIA

2.1 PROPOSED HARMONISED CLASSIFICATION AND LABELLING FOR THE ACTIVE

Table 2-1: Proposed harmonised classification and labelling of the substance

For substance with no current entry in Annex VI of CLP

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	-	165252-70-0	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09, Warning	H400 H410		Acute: M=10 Chronic: M= 10	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	TBD	dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	-	165252-70-0	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09, Warning	H400 H410		Acute: M=10 Chronic: M= 10	

Table 2-2: Reason for not proposing harmonised classification and labelling and the status under CLH consultation

Hazard class	Reason for not proposing classification and labelling	Within the scope of consultation *(please select YES or NO from the drop down list)* (yes/no)
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable (e.g. physical state or chemical structure)	No
Oxidising gases	Hazard class not applicable (e.g. physical state or chemical structure)	No
Gases under pressure	Hazard class not applicable (e.g. physical state or chemical structure)	No
Flammable liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances and mixtures	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances and mixtures	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable (e.g. physical state or chemical structure)	No
Corrosive to metals	Hazard class not applicable (e.g. physical state or chemical structure)	No
Desensitised explosives	Hazard class not applicable (e.g. physical state or chemical structure)	No
Acute toxicity via oral route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	Data conclusive but not sufficient for classification	Yes
Skin sensitisation	Data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes

Carcinogenicity	Data conclusive but not sufficient for classification	Yes
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	Hazard class not applicable (e.g. physical state or chemical structure)	Yes
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

2.1.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no current harmonised classification for the active substance dinotefuran according to Annex VI of Regulation (EC) no 1272/2008. The UK CA, who was the evaluating CA for the approval of dinotefuran, did not submit a CLH report to ECHA and RAC in light of other compounds being of a higher priority for completion ahead of EU exit.

2.2 PROPOSED CLASSIFICATION AND LABELLING AND PACKAGING FOR THE REPRESENTATIVE PRODUCT(S)

Not applicable for the CLH report

Table 2-3: Proposed Classification and Labelling according to Regulation (EC) No 1272/2008

Table 2-4: Packaging of the biocidal product

2.3 DATA SOURCES

See the reference list in the Appendix V of this CLH report and the IUCLID dossier (UUID : 911cc350-f1ca-4503-ab3b-034ffa29c3fa). All the relevant data from REACH dossier have been included.

3. SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

Not applicable for the CLH report

3.1 SUMMARY OF THE ASSESSMENT OF EFFECTS ON HUMAN HEALTH

Table 3-1: Summary of the assessment of effects on human health

Not applicable for the CLH report

3.2 REFERENCE VALUES

Table 3-2: Reference values

Not applicable for the CLH report

3.3 RISK CHARACTERISATION

Not applicable for the CLH report

Table 3-3: Summary of exposure scenarios

Not applicable for the CLH report

Table 3-4: Conclusion of risk characterisation for industrial user

Not applicable for the CLH report

Table 3-5: Conclusion of risk characterisation for professional user

Not applicable for the CLH report

Table 3-6: Conclusion of risk characterisation for non-professional user

Not applicable for the CLH report

Table 3-7: Conclusion of risk characterisation for indirect exposure

Not applicable for the CLH report

4. SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

Not applicable for the CLH report

4.1 FATE AND BEHAVIOUR IN THE ENVIRONMENT

Table 4-1: Summary table on compartments exposed and assessed

Not applicable for the CLH report

Table 4-2: Summary table on relevant metabolites/degradants

Not applicable for the CLH report

Table 4-3: Summary table on relevant physico-chemical and fate and behaviour parameter of the active substance

Property	Value	Unit	Remarks
Molecular weight	202.2	g/mol	
Vapour pressure (25°C)	5E-05	Pa	
Solubility in water (20°C)	39830	mg/L	
Log Octanol/water partition coefficient (Log Kow)	-0.549	Log 10	25°C, pH 7 [redacted] (2000a)
Organic carbon/water partition coefficient (Koc)	25.4	l/kg	Geometric mean, according to GBPR (p. 58)
Henry's Law Constant (20°C) **(30°C)**	8.30E-08 <3.89E-09	$Pa/m^3/mol$	ST4.0 default, as the Henry's Law Constant could not be determined due to lack of vapour pressure Calculated based on VAP30°c pure water and solubility 30°C
Biodegradability	Not ready biodegradable	-	
DT_{50} water-sediment (total system – 12 °C)	37.6	d	[redacted] 2020a & ENV WG-V-2019
DT_{50} for hydrolysis in surface water	365	d	[redacted] 1998
DT_{50} for photolysis in surface water	0.9	d	[redacted] 2002e
DT_{50} for degradation in soil (12°C)	32.4	d	Geometric mean
DT_{50} for degradation in air	2.4	h	Calculated, AOPWIN, version 1.92
Bioconcentration, aquatic	0.068	L/kg (wwt)	Calculated, IUCLID 9.1.7
Bioconcentration, terrestrial	0.843	L/kg (wwt)	Calculated, IUCLID 9.6

4.2 EFFECTS ASSESSMENT

Table 4-4: Summary table on calculated PNEC values

Not applicable for the CLH report

4.3 EXPOSURE ASSESSMENT

Table 4-5: Summary table on calculated PEC values

Not applicable for the CLH report

4.4 RISK CHARACTERISATION

Table 4-6: Summary table on calculated PEC/PNEC values

Not applicable for the CLH report

5. ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

Not applicable for the CLH report

Table 5-1: Assessment of exclusion criteria, substitution criteria and POP

Not applicable for the CLH report

A Assessment of intrinsic properties and effects of the active substance

A.1 General substance information

A.1.1 Identity of the Substance

Table A-1: Summary table on substance identity

Summary table on substance identity	
Common name (ISO name, synonyms)	Dinotefuran
Chemical name (EC name, CA name, IUPAC name)	IUPAC name:(*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine CA name:N-methyl-N′-nitro-N″-[(tetrahydro-3-furanyl)methyl]guanidine
EC number	-
CAS number	165252-70-0
other CAS numbers (e.g. deleted, related, preferred, alternate)	CIPAC number: 749
Molecular formula	$C_7H_{14}N_4O_3$
Molecular weight or molecular weight range	202.2 g/mole
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Determination of the optical rotation of dinotefuran shows that the value of angular rotation (α) is zero. This demonstrates that dinotefuran is not optically active, but it is isolated as racemic mixture; in a 1:1 ratio (IUCLID 2.9).
Description of the manufacturing process and identity of the source (for UVCB substances only)	This information can be found in confidential annex, Table 92.
Degree of purity (%)*	>=99.1% (w/w)

Table A-2: Structural formula

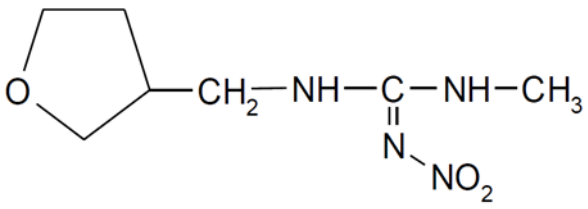
Structural formula


Table A-3: Origin of the natural active substance or precursor(s) of the active substance

Not applicable for the CLH report

Table A-4: Method of manufacture

Not applicable for the CLH report

A.1.2 Composition of the substance (reference specifications)

Table A-5: Main constituent(s)

Constituent (chemical name)	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
(RS)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	≥99.1	≥99.1 ≤100	None	H400 H410	None

Table A-6: Impurities

Constituent (chemical name)	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
Impurities do not contributes to the classification. Additionnal information can be found in the confidential annex, Table 93.					

Table A-7: Additives

Constituent (chemical name)	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
Dinotefuran contains no additives.					

Table A-8: Concentration of constituents (main constituents, impurities, additives) in batches used for (eco)toxicity studies and proposed specification

Not applicable

Table A-9: Concentration of constituents (main constituents, impurities, additives) in batches used for (eco)toxicity studies and proposed specification

See Confidential Annex, Table 94

A.1.3 Physical and chemical properties of the active substance

Table A-10: Physical and chemical properties of the active substance

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Aggregate state at 20°C and 101.3 kPA	Solid (99.6%)	Visual method	none	[redacted] (1999a)
Physical state (appearance) at 20°C and 101.3 kPA	Solid (crystalline) (99.6%)	Visual method	none	[redacted] (1999a)
Colour at 20°C and 101.3 kPA	White (99.6%)	Visual method	none	[redacted] (1999b)
Odour at 20°C and 101.3 kPA	Odourless (99.6%)	Functional method	none	[redacted] (1999c)
Melting / freezing point	107.5°C (99.7%)	OECD TG 102 (DSC), EU Annex IIA Point #2.1.1, OPPTS 830.7200	none	[redacted] (2000a) Report no. 011098-1
Boiling point at Granulometry	Does not boil (99.7%)	OECD TG 103 (DSC), EU Annex IIA Point #2.1.2, OPPTS 830.7220	Decomposition before boiling (at 208.3°C, 100.2 kPa)	[redacted] (2000a) Report no. 011098-1
Vapour pressure	<1.7 x 10^{-6} Pa at 30 °C (99.7%)	OECD TG 104, EU Annex IIA Point #2.3.1, OPPTS 830.7950	none	[redacted] (2000a) Report no. 011098-1
	5.0 x 10^{-5} Pa at 25°C (99.5%)	OECD TG 104, EEC A.4	-	[redacted] (1996) Report no MTO097/980159
Henry's law constant	-	-	Could not be determined at 20 °C. Extrapolation by linear regression was not possible due to the lack of experimentally determined data points at other temperatures.	
Surface tension	Dinotefuran is not surface active	OECD TG 115 (Ring tensiometer), EEC A.5	none	[redacted] (2001c) Report no. 780208

	72 mN/m at 20.2 °C ± 0.2 °C (99.2 %, 0.1 % solution)			
Water solubility at 20 °C	pH 6.98 = 39.83 g/L (99.7%)	OECD TG 105, EU Annex IIA Point #2.6, OPPTS 830.7840	none	[redacted] (2000a) Report no. 011098-1
	pH 5 = 52.3 g/L pH 7 = 54.5 g/L pH 9 = 51.2 g/L Purified water: 10°C = 39.0 g/L 20°C = 54.3 g/L 30°C = 89.7 g/L (99.5%)	OECD TG 105, EEC A.6		[redacted] (1996) Report no. MTO097/ 980159
Partition coefficient (n-octanol/water) and its pH dependency	Log K_{OW} Mean = -0.549 at 25°C (i.e. K_{OW} = 0.283) (99.7%)	OECD TG 107 (shake flask), EU Annex IIA Point #2.8, OPPTS 830.7550	none	[redacted] (2000a) Report no. 011098-1
Thermal stability and identity of breakdown products	Thermally stable (99.7%)	OECD TG 113, EU Annex IIA Point #2.14.14, OPPTS 830.6313	none	[redacted] (2000a) Report no. 011098-1
Reactivity towards container material	Stable for at least 12 months at 25°C, 60% relative humidity (98.9%)	OPPTS 830.6317, OPPTS 830.6320, GIFAP No. 17	none	[redacted] (2003) Report no. 828865
Dissociation constant	pKa:12.6 (pH range 11.6-12.8) (99.7%)	OECD TG 112, EU Annex IIA Point #2.9.4, OPPTS 830.7370	none	[redacted] (2000a) Report no. 011098-1
	No dissociation (pH range 1.4-12.3) (99.5%)	OECD TG 112		[redacted] (1996) Report no. MTO097/ 980159
Viscosity	-	-	Not applicable for solids	
Solubility in organic solvents, including effect of temperature on solubility	solubility at 20 °C, (99.7%): Hexane=9.0 µg/L Heptane=10.5 µg/L Xylene=71.85 mg/L Toluene=148.6 mg/L Dichloromethane = 60.86 g/L Acetone = 57.84 g/L Methanol = 57.18 g/L Ethanol = 19.37 g/L Ethyl acetate=5.17 g/L	OECD TG 105, EU Annex IIA Point #2.7, OPPTS 830.7840	none	[redacted] (2000a) Report no. 011098-1

Stability in organic solvents used in biocidal products and identity of relevant degradation products	Not required as the active substance as manufactured does not include an organic solvent.

A.1.3.1 Physical hazards and respective characteristics

Table A-11: Physical hazards and respective characteristics

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
Explosives	EEC A.14,	Thermal sensitivity Mechanical sensitivity (shock) Mechanical sensitivity (friction) (99.2%)	Not explosive. Furthermore, according to the UN-MTC, 7th revised edition Appendix 6 and CLP Annex I, Part 2, paragraphs 2.1.4.2 and 2.1.4.3, "neither a series 1 type (a) propagation of detonation test nor a series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g" and following screening procedure "the acceptance procedure for explosives need not be applied... (c) for the organic substance or a homogeneous mixture of organic substances containing chemical group (or groups) associated with explosive properties when the exothermic decomposition energy is less than 500 J/g and the	[redacted] (2001) Report no. 780197

			onset of exothermic decomposition is below 500 ºC". Dinotefuran contains chemical groups associated with explosive properties other than oxygen and both, decomposition energy and decomposition onset temperature are < 500 under the conditions of the test conducted according to EU Annex IIA Point #2.1.2, OPPTS 830.7220 and OECD 103, boiling point (report no. 011098-1 [redacted], 2000a; calculated exothermic decomposition energy 423.6 J/g; extrapolated decomposition onset temperature 208.3°C, is below 500ºC). Accordingly, criterion (c) is fulfilled and the acceptance procedure for Class 1 explosives does not need to be applied.	
Flammable gases	-	-	Not applicable for a solid	
Flammable aerosols	-	-	Not applicable for a solid	
Oxidising gases	-	-	Not applicable for a solid	
Gases under pressure	-	-	Not applicable for a solid	
Flammable liquids	-	-	Not applicable for a solid	
Flammable solids	EEC A.10, equivalent to UN MTC N.1	Ignition (99,2%)	Non-flammable	[redacted] (2001a) Report no 780175
Self-reactive substances and mixtures	-	-	Test method EEC A.16 (autoignition; [redacted], 2000; report no. 780186) showed no exotherms up to the melting temperature of 107.5 °C; the broad	

			exothermic peak observed above 200°C in test method OECD 103, OPPTS 830.7220, EU Annex IIA Point #2.1.2 (boiling point; [redacted], 2000a; report no. 011098-1) is assigned to decomposition of the test substance. Test method EEC A.10 equivalent to UN Test N.1 (flammability; [redacted], 2001a; report no. 780175) indicated no ignition after a two-minute exposure of the test substance to a flame. Test method EEC A.14 (explosive properties; [redacted], 2001; report no. 780197) indicated no explosive properties. Considering the chemical structure of dinotefuran and the above information on the physicochemical properties, there is no evidence that dinotefuran is a self-reactive substance. Therefore, the criteria for classification are not met.	
Pyrophoric liquids	-	-	Not applicable for a solid	
Pyrophoric solids	-	-	CLP Regulation Annex I, 2.10.4, indicates that the classification procedure need not be applied when the substance is known to be stable at room temperature for prolonged periods of time (days). Furthermore, the classification procedure for	

			pyrophoric solids need not be applied as experience in manufacture and handling of dinotefuran shows that the substance does not ignite spontaneously on coming into contact with air at normal temperatures.	
Self-heating substances and mixtures	-	-	CLP Regulation Annex I indicates substances with melting point <160ºC do not need to be considered for classification as self-heating. The melting point of dinotefuran is 107.5ºC (this criterion is only applicable if the substance is completely molten up to 160°C as is the case of dinotefuran)	
Substances and mixtures which in contact with water emit flammable gases	-	-	According to the UN -MTC, 7th revised edition, Appendix 6, Screening procedures, the classification of dinotefuran does not need to be applied as dinotefuran does not contain metals or metalloids in the structure; in production the substance does not react with water (is washed with water) and is soluble in water. In addition, the hydrolysis study (OECD TG 111; [redacted], 1998; report no. 95/MTO098/1216) conducted with dinotefuran in water at five pH intervals concluded that	

			dinotefuran is hydrolytically stable under acid, neutral and weakly basic conditions, although unstable under more strongly basic conditions.	
Oxidising liquids	-	-	Not applicable for a solid	
Oxidising solids	UN MTC Test O.1	Burning times of mixtures or reference substance to cellulose	In both the 4:1 and 1:1 sample-to-cellulose ratio (by mass) tested, exhibited mean burning times greater than that of a 3:7 mixture (by mass) of potassium bromate and cellulose, therefore dinotefuran does not fulfil criteria to be classified as a oxidising substance.	[redacted] (2004) No report n°.
Organic peroxides	-	-	Not applicable based on chemical structure, the substance does not fall under the definition of organic peroxides according to GHS and the relevant UN MTC.	
Corrosive to metals	-	-	CLP regulation Annex I, 2.16 indicates that only substances for which the application of UN Test C1 is relevant need to be considered (liquids and solids that may become liquids). Dinotefuran is a solid with a melting point higher than 55°C and that may not become liquid during transport. On the basis of expert judgement, the study does not need to be conducted. The pH is not extreme and dinotefuran does not	

			contain acidic or basic functional groups, it does not contain halogens, and it is not able to form complexes with metals.	
Desensitised explosives			Test method EEC A.16 (autoignition; [redacted], 2000; report no. 780186) showed no exotherms up to the melting temperature of 107.5 °C; the broad exothermic peak observed above 200°C in test method OECD 103, OPPTS 830.7220, EU Annex IIA Point #2.1.2 (boiling point; [redacted], 2000a; report no. 011098-1) is assigned to decomposition of the test substance. Test method EEC A.10 equivalent to UN Test N.1 (flammability; [redacted], 2001a; report no. 780175) indicated no ignition after a two-minute exposure of the test substance to a flame. Test method EEC A.14 (explosive properties; [redacted], 2001; report no. 780197) indicated no explosive properties. Considering the chemical structure of dinotefuran and the above information on the physicochemical properties, there is no evidence that dinotefuran is a self-reactive substance. Therefore, the criteria for classification are not met.	

Auto-ignition temperature (liquids and gases)	-	-	The study does not need to be conducted because the substance is solid having a melting point <=160 ºC.	
B.3.2.1 Relative self-ignition temperature for solids	EEC A.16	Exothermic reaction (99.2%)	Not auto-flammable, melting at 107.5 ºC and decomposing at 208ºC.	[redacted] (2000) Report no 780186
Dust explosion hazard	-	-	Dinotefuran is not an oxidising substance (IUCLID 4.4, Seki (2004)), therefore it is exempt from testing according to BPR Guidance, Vol I, Parts A+B+C, Version 2.0, May 2018. Furthermore, dinotefuran is a solid, does not contain metals or metalloids, experience in production and handling shows that the substance does not react with water (the substance is manufactured with water or washed with water), and dinotefuran is soluble in water forming a stable mixture.	

A.1.3.2 Assessment of physical hazards according to the CLP criteria

Not applicable for the CLH report.

A.1.3.3 Explosives

Table A-12: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Determination of the explosive properties according to EEC Guideline A.14; Thermal sensitivity test (equivalent to Koenen test), mechanical sensitivity test (shock, equivalent to BAM Fallhammer) and mechanical sensitivity test (friction, equivalent to BAM friction apparatus)	Dinotefuran was not explosive when subjected to thermal or physical shock, nor with respect to friction. Steel tubes were unchanged.	Criterion (c) is fulfilled and the acceptance procedure for Class 1 explosives does not need to be applied. Additionally, the submitted study concluded that dinotefuran is not an explosive item as no explosion occurred during the test series.	[redacted] (2001) Report no. 780197

A.1.3.3.1 Short summary and overall relevance of the provided information on explosive properties

The test substance did not exhibit any thermal or mechanical (shock and friction) sensitivity under the conditions of the test.

Furthermore, according to the UN-MTC, 7th revised edition Appendix 6 and CLP Annex I, Part 2, paragraphs 2.1.4.2 and 2.1.4.3, "neither a series 1 type (a) propagation of detonation test nor a series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g" and following screening procedure "A substance or mixture shall not be classified as explosive if:... (c) when the organic substance or a homogeneous mixture of organic substances contains chemical groups associated with explosive properties but the exothermic decomposition energy is below 500 J/g".

Dinotefuran contains chemical groups associated with explosive properties other than oxygen. Decomposition energy and decomposition onset temperature are < 500 under the conditions of the test conducted according to EU Annex IIA Point #2.1.2, OPPTS 830.7220, and OECD TG 103 (boiling point; [redacted], 2000a; report no. 011098-1; calculated exothermic decomposition energy 423.6 J/g; extrapolated decomposition onset temperature 208.3 °C). Accordingly, criterion I is fulfilled and the acceptance procedure for Class 1 explosives does not need to be applied.

A.1.3.3.2 Comparison with the CLP criteria

A substance is considered for classification as an explosive substance where a positive result is obtained in the test series indicated in Figure 2.1.2 of Annex I of the CLP regulation. Dinotefuran was not found to be sensitive to the effects of heat, shock, or friction.

Furthermore, according to the screening criteria in Annex I of the CLP Regulation, section 2.1.4.2, dinotefuran meets the third criteria i.e. broad pair of exotherms with high enthalpy 2300 J/g.

Consequently, dinotefuran does not meet the criteria for classification as an explosive substance.

A.1.3.3.3 Conclusion on classification and labelling for explosive properties

Dinotefuran is not classified as explosive.

A.1.3.4 Flammable gases (including chemically unstable gases)

Table A-13: Summary table of studies on flammable gases (including chemically unstable gases)

Not applicable, dinotefuran is a solid not a gas.

A.1.3.5 Flammable aerosols and aerosols

Table A-14: Summary table of studies on flammable aerosols and aerosols

Not applicable, dinotefuran is a solid and not provided as an aerosol.

A.1.3.6 Oxidising gases

Table A-15: Summary table of studies on oxidising gases

Not applicable, dinotefuran is a solid not a gas.

A.1.3.7 Gases under pressure

Table A-16: Summary table of studies on gases under pressure

Not applicable, dinotefuran is a solid not a gas.

Table A-17: Summary table of studies on flammable liquids

Not applicable, dinotefuran is a solid not a liquid.

A.1.3.8 Flammable solids

Table A-18: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
Conducted according to EEC Guideline A.10. Methodology equivalent to UN Test N.1.	Dinotefuran is not flammable. It could not be ignited during the preliminary test after contact with the ignition	No further test was performed according to the result of the preliminary test.	[redacted] (2001a) Report no 780175

	source for about 2 minutes. Dinotefuran melted smokeless and a turbid melt remained.		

A.1.3.8.1 Short summary and overall relevance of the provided information on flammable solids

According to UN MTC 7th revised edition Part III section 33, "a preliminary screening test is performed to determine if, on ignition by a gas flame, propagation by burning with flame or smouldering occurs" and follows "If in the screening test, the substance does not ignite and propagate combustion either by burning with flame or smouldering, it is not necessary to perform the complete burning rate test as the substance is not a flammable solid".
During the preliminary test, dinotefuran melted when in contact with the ignition source for two minutes and could not be ignited (flammability; [redacted] 2001a; Report no. 780175). Consequently, the main test was not performed.

A.1.3.8.2 Comparison with the CLP criteria

A substance (non-metal powders) is classified as a flammable solid when the burning time is < 45 seconds or the burning rate is > 2.2 mm/s. Dinotefuran could not be ignited, therefore the classification criteria are not met.
Dinotefuran could not be ignited during the preliminary screening test after contact with the ignition source for about 2 minutes. In contact with the ignition source, dinotefuran melted smokeless and a turbid melt remained. Therefore, the submitted study fulfils the data requirements, unequivocally demonstrating that dinotefuran is not a flammable solid.

A.1.3.8.3 Conclusion on classification and labelling for flammable solids

Dinotefuran is not a flammable solid.

A.1.3.8.4 Self-reactive substances

Table A-19: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
ECC A.16	The test methods showed no exotherms up to the melting temperature of 107.5°C.	Given the results of the tests, and the structure of the active substance, it is not expected that dinotefuran is a self-reactive substance.	autoignition; [redacted] 2000; report no. 780186
OECD TG 103	Broad exothermic peak was observed above 200°C.		boiling point; [redacted] 2000a; report no. 011098-1
EEC A.10	no ignition after a two-minute exposure of the test substance to a flame		flammability; [redacted] 2001a; report no. 780175
EEC A.14	Tests indicate no explosive properties		explosive properties; [redacted] 2001; report no. 780197

A.1.3.8.5 Short summary and overall relevance of the provided information on self-reactive substances

Test method ECC A.16 (autoignition; [redacted], 2000; report no. 780186) showed no exotherms up to the melting temperature of 107.5 °C; the broad exothermic peak observed above 200°C in test method OECD 103, EU Annex IIA Point #2.1.2 and OPPTS 830.7220 (boiling point; [redacted], 2000a; report no. 011098-1) is assigned to decomposition of the test substance. Test method EEC A.10

(flammability; [redacted], 2001a; report no. 780175) indicated no ignition after a two-minute exposure of the test substance to a flame. Test method EEC A.14 (explosive properties; [redacted], 2001; report no. 780197) indicated no explosive properties.

Considering the chemical structure of dinotefuran and the above information on the physicochemical properties, there is no evidence that dinotefuran is a self-reactive substance. Therefore, the criteria for classification are not met.

A.1.3.8.6 Comparison with the CLP criteria

Dinotefuran presents none of the characteristic or criteria to be classified as a self-reactive substance. As per the CLP criteria, most self-reactive substance can decompose with a strong exothermic reaction at or below 75°C. However, Dinotefuran can be heated to higher temperatures (including up to and above its melting point) without any issues. Dinotefuran also does not exhibit any behaviour that could be considered as being explosive properties. Even exposed to a flame, Dinotefuran show thermal stability, and therefore demonstrate clearly that he does not meet the criteria to be considered as being a self-reactive substance.

A.1.3.8.7 Conclusion on classification and labelling for self-reactive substances

Dinotefuran is not a self-reactive substance.

A.1.3.9 Pyrophoric liquids

Not applicable, dinotefuran is a solid not a liquid.

A.1.3.10 Pyrophoric solids

Table A-20: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference
Conducted according to EEC Guideline A.10. Methodology equivalent to UN Test N.1.	Dinotefuran is not flammable. It could not be ignited during the preliminary test after contact with the ignition source for about 2 minutes. Dinotefuran melted smokeless and a turbid melt remained. It therefore also can't be considered as being pyrophoric.	No further test was performed according to the result of the preliminary test.	[redacted] (2001a) Report no 780175

A.1.3.10.1 Short summary and overall relevance of the provided information on pyrophoric solids

CLP Regulation Annex I, 2.10.4, indicates that the classification procedure need not be applied when the substance is known to be stable at room temperature for prolonged periods of time (days); as is the case for dinotefuran.
Furthermore, the classification procedure for pyrophoric solids need not be applied as experience in manufacture and handling of dinotefuran shows that the substance does not ignite spontaneously on coming into contact with air at normal temperatures.
It is also important to take into account the fact that most pyrophoric solids are either metals or organo-metallic compounds, which is not the case for dinotefuran, who does not exhibit any specific function that would lead to such a classification. Furthermore, as dinotefuran does not meet the criteria to be classified as a flammable solid, he certainly does not meet the criteria for being a

pyrophoric solid.

A.1.3.10.2 Comparison with the CLP criteria

A solid substance that spontaneously ignites in contact with air (in five minutes or less) is considered to be pyrophoric. This is not the case for dinotefuran.

A.1.3.10.3 Conclusion on classification and labelling for pyrophoric solids

Dinotefuran is not a pyrophoric solid.

A.1.3.11 Self-heating substances

Table A-21: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
Conducted according to EEC Guideline A16	Substance is not self heating. Dinotefuran is melting at 107.5 ºC and decomposing at 208ºC.	Substance melted before completion of the experiment	[redacted] (2000)

A.1.3.11.1 Short summary and overall relevance of the provided information on self-heating substances

No self-ignition was detected at < 400 °C in a standard EEC A.16 (self-ignition; [redacted] (2000); study no. 780186), Dinotefuran has a melting point of 107.5 °C and melted before the end of the experiment. Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) further indicate that the substance decomposes at approximately 208 °C.

A.1.3.11.2 Comparison with the CLP criteria

According to CLP Guidance, substances or mixtures with a low melting point (< 160 °C) should not be considered for classification in this class being this criterion only applicable if the substance or mixture is completely molten up to this temperature. According to UN-MTC, 7th revised edition Appendix 6, Screening Procedures "the classification procedure for self-heating substances need not to be applied if the results of a screening test can be adequately correlated with the classification test and an appropriate safety margin is applied".
A substance is classified as self-heating when a positive result is obtained in the test method outlined in subsection 33.3.1.6 of the UN RTDG Manual of Tests and Criteria. No data are available using this method, but in an A.16 study, no self-ignition was detected at temperatures below 400 °C. Dinotefuran is not self-igniting, melts at 107.5 ºC and decomposes at 208ºC.

A.1.3.11.3 Conclusion on classification and labelling for self-heating substances

Dinotefuran is not a self-heating substance.

A.1.3.12 Substances which in contact with water emit flammable gases

According to the UN -MTC, 7th revised edition, Appendix 6, Screening procedures, the classification of "substance which in contact with water emit flammable gases" does not need to be applied as dinotefuran does not contain metals or metalloids in the structure; in production the substance does not react with water (is washed with water) and is soluble in water. In addition, the hydrolysis study (OECD TG 111; [redacted], 1998; report no. 95/MTO098/1216) conducted with dinotefuran in water at five pH intervals concluded that dinotefuran is hydrolytically stable under acid, neutral and weakly basic conditions, although unstable under more strongly basic conditions.

A.1.3.13 Oxidising liquids

Not applicable, Dinotefuran is not a liquid.

A.1.3.14 Oxidising solids

Table A-22: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
Equivalent to O.1, Part III, 34.4.1 UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria	The test substance does not display oxidising properties.	In both the 4:1 and 1:1 sample-to-cellulose ratio (by mass) tested, exhibited mean burning times greater than that of a 3:7 mixture (by mass) of potassium bromate and cellulose, therefore dinotefuran does not fulfil criteria to be classified as a oxidising substance-	[redacted] (2004) No report no

A.1.3.14.1 Short summary and overall relevance of the provided information on oxidising solids

In the study performed by [redacted] (2004), conducted according to the method specified in Annex I of the CLP Regulation, conical piles are ignited, and potassium bromate is used as the reference substance. Whilst the study was not to GLP, it was well reported and sufficient information was provided in the study report to determine that it was conducted in accordance with the test guidelines and it is therefore considered to be reliable and relevant in the consideration of classification. The results of this study show that none of the tested samples, nor their averages, burned faster than the potassium bromate-to-cellulose reference mixture. The substance is not considered to be an oxidising solid in the context of this study.

Results of the oxidising solids study ([redacted], 2004)

Burning time		
Run Number	1:1 (Dinotefuran:Cellulose)	4:1 (Dinotefuran:Cellulose)
1	10 min. 55 sec.	10 min. 34 sec
2	11 min. 51 sec.	9 min. 36 sec.
3	10 min. 54 sec.	9 min. 22 sec.
4	9 min. 30 sec.	9 min. 33 sec.
5	9 min. 18 sec.	10 min. 16 sec.
Average	10 min. 30 sec.	9 min. 52 sec.
Minimum	9 min. 52 sec.	
Run Number	2:3 (Potassium Bromate:Cellulose)	3:7 (Potassium Bromate:Cellulose)
1	1 min. 7 sec.	3 min. 15 sec.
2	1 min. 5 sec.	3 min. 8 sec.
3	1 min. 8 sec.	3 min. 28 sec.
4	1 min. 9 sec.	3 min. 10 sec.
5	1 min. 4 sec.	3 min. 4 sec.
Average	1 min. 7 sec.	3 min. 13 sec.

A.1.3.14.2 Comparison with the CLP criteria

A substance is classified as an oxidising solid when the burning time of a 1:1 or 4:1 ratio of sample-to-cellulose mixture is less than or equal to the burning time of the appropriate reference sample. In the study, the burning time of 1:1 and 4:1 mixtures of dinotefuran-to-cellulose were greater than the burning time of 2:3 and 3:7 mixtures of potassium bromate-to-cellulose. Therefore, dinotefuran is a non-oxidising.

A.1.3.14.3 Conclusion on classification and labelling for oxidising solids

Dinotefuran is not an oxidising solid.

A.1.3.15 Organic peroxides

Not applicable as the chemical structure of the active substance does not exhibit a peroxide moiety.

A.1.3.16 Corrosive to metals

CLP Regulation Annex I, 2.16 indicates that only substances for which the application of UN Test C.1 is relevant need to be considered (liquids and solids that may become liquids). Dinotefuran is a solid with a melting point higher than 55°C and that may not become liquid during transport. On the basis of expert judgement, the study does not need to be conducted. The pH is not extreme and dinotefuran does not contain acidic or basic functional groups, it does not contain halogens, and it is not able to form complexes with metals.

A.1.3.17 Desensitised explosives

Table A-23: Summary table of studies on the hazard class desensitised explosives

Method	Results	Remarks	Reference
Determination of the explosive properties according to EEC Guideline A.14; Thermal sensitivity test (equivalent to Koenen test), mechanical sensitivity test (shock, equivalent to BAM Fallhammer) and mechanical sensitivity test (friction, equivalent to BAM friction apparatus)	Dinotefuran was not explosive when subjected to thermal or physical shock, nor with respect to friction. Steel tubes were unchanged. As Dinotefuran is not classified as explosive, the classification of desensitised explosive cannot be applied to it.	Criterion (c) is fulfilled and the acceptance procedure for Class 1 explosives does not need to be applied. Additionally, the submitted study concluded that dinotefuran is not an explosive item as no explosion occurred during the test series.	[redacted] (2001) Report no. 780197

A.1.3.17.1 Short summary and overall relevance of the provided information on the hazard class desensitised explosives

The test substance did not exhibit any thermal or mechanical (shock and friction) sensitivity under the conditions of the test.
Furthermore, according to the UN-MTC, 7th revised edition Appendix 6 and CLP Annex I, Part 2, paragraphs 2.1.4.2 and 2.1.4.3, "neither a series 1 type (a) propagation of detonation test nor a series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g" and following screening procedure "A substance or mixture shall not be classified as explosive if:... (c) when the organic substance or a homogeneous mixture of organic substances contains chemical groups associated with explosive properties but the

exothermic decomposition energy is below 500 J/g".
Dinotefuran contains chemical groups associated with explosive properties other than oxygen. Decomposition energy and decomposition onset temperature are < 500 under the conditions of the test conducted according to EU Annex IIA Point #2.1.2, OPPTS 830.7220, and OECD TG 103 (boiling point; [redacted], 2000a; report no. 011098-1; calculated exothermic decomposition energy 423.6 J/g; extrapolated decomposition onset temperature 208.3 °C). Accordingly, criterion I is fulfilled and the acceptance procedure for Class 1 explosives does not need to be applied.

A.1.3.17.2 Comparison with the CLP criteria

A substance is considered for classification as an explosive substance where a positive result is obtained in the test series indicated in Figure 2.1.2 of Annex I of the CLP regulation. Dinotefuran was not found to be sensitive to the effects of heat, shock, or friction.
Furthermore, according to the screening criteria in Annex I of the CLP Regulation, section 2.1.4.2, dinotefuran meets the third criteria i.e. broad pair of exotherms with high enthalpy 2300 J/g.
Consequently, dinotefuran does not meet the criteria for classification as an explosive substance.

A.1.3.17.3 Conclusion on classification and labelling for desensitised explosives

As dinotefuran does not fit the classification for being an explosive substance, it is also not a desensitised explosive.

A.1.4 Analytical methods for detection and identification

Not applicable for the CLH report

Table A-24: Analytical methods

Not applicable for the CLH report

A.2 Effects against target organisms

Not applicable for the CLH report

A.2.1 Intended uses

Not applicable for the CLH report

Table A-25: Summary table of intended uses

Not applicable for the CLH report

A.2.2 Summary on efficacy

Not applicable for the CLH report

A.2.2.1 Efficacy

Table A-26: Experimental data on the efficacy of the active substance against target organism(s)

Not applicable for the CLH report

A.2.2.2 Mode of action

Not applicable for the CLH report

A.2.2.3 Resistance

Not applicable for the CLH report

A.2.2.4 Conclusion on efficacy

Not applicable for the CLH report

A.3 Assessment of effects on Human Health

There are no concerns regarding the technical equivalence of the batches of material used in the mammalian toxicology studies to material that matches the technical specification. This is because all of the named impurities in the proposed technical specification have maximum limits of 1 g/kg (i.e. none are considered to be 'significant impurities') and none are of known toxicological concern (i.e. none are 'relevant impurities'). Material matching the technical specification is relatively clean, such that there are no concerns that impurities could be present in the technical material that have not been adequately covered by the mammalian toxicity testing. Thus, the mammalian toxicology testing fully supports the material that will be placed on the market.

A.3.1 Toxicokinetics

The toxicokinetics of dinotefuran have been investigated in two in vivo absorption, distribution, metabolism and excretion studies, one in adult rats, the other in neonates and in an in vivo dermal absorption study. An additional oral study investigating the transfer of dinotefuran to the milk of lactating rats is also available.

Table A-27: Summary table of toxicokinetic studies

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Biokinetics and metabolism, EPA-FIFRA, Subdivision F, § 85-1 JMAFF 59 NohSan no. 4200, GLP, Reliability 1, Key study	Rat, [redacted]:CD(SD) BR (male and female), [redacted](SD)CVF (male and female bile duct-cannulated rats), no. of animals per group is group dependent	dinotefuran ([F-^{14}C]), >98% purity. dinotefuran ([G-^{14}C]), >99% purity. 0.5% carboxymethyl cellulose (0.5% CMC) for oral administration, or 0.9% saline for intravenous administration. 0, 50, 1000 mg/kg bw. Up to 15 days exposure	Radioactivity derived from orally administered [^{14}C]-dinotefuran is rapidly and almost completely absorbed from the GI tract into the general circulation, and is widely distributed throughout the tissues and fluids of the body. Elimination is rapid, predominantly by urinary excretion and almost complete within 7 days after administration. [^{14}C]-dinotefuran is rapidly transferred to the foetus *in utero* and to maternal milk *post-partum*, but is rapidly	None	Report no. 6648-136 [redacted], 2000a IUCLID no. 8.8.1 Amendment 1 [redacted], 2000b Amendment 2 [redacted], 2001

			eliminated from them. More than 90% of orally and intravenously administered dinotefuran is eliminated as unchanged parent molecule, which is also the major radioactive component in plasma, milk, bile and most tissues. Unchanged dinotefuran accounted for 92.5 – 97.2% of total urine radioactivity. The major route of metabolism appeared to be via initial hydroxylation of the furan ring to form isomers of PHP. Further oxidation, reduction, and acetylation of PHP produced additional metabolites. Other routes of metabolism involved desmethylation, nitro reduction, and deamination at various stages, producing numerous additional metabolites. A small degree of cleavage at the C-N bond also appeared to occur.		
Metabolism in neonatal rats, EPA-FIFRA, Subdivision F, § 85-1 **JMAFF 59 NohSan no. 4200,** **GLP,** **Reliability 1,** **Key study**	Rat, [redacted]:CD(SD) BR, males and females, 25 pups/sex/group and 3 pups/sex/group for whole-body autoradiographic analysis (WBA)	dinotefuran ([G-^{14}C]), >99% purity, 0.5% carboxymethyl cellulose (0.5% CMC), 50 mg/kg bw by gavage, single exposure.	Absorption of [G-^{14}C]-dinotefuran from the neonatal gastrointestinal tract is rapid and extensive. It undergoes a wide distribution within the body tissues and is eliminated predominantly in the urine. [G-^{14}C]-dinotefuran undergoes minimal metabolism in the neonatal rat. The absorption, distribution, metabolism and elimination is not affected by the sex of the neonate. The absorption, distribution, metabolism and elimination of [G-^{14}C]-dinotefuran are similar in neonatal and young adult rats.	None	Report no. 6648-141 [redacted], 2000c IUCLID no. 8.8.1 Amendment 1 [redacted], 2000d

			However, absorption and elimination in the neonate proceed at a slower rate than in young adults, and although metabolite profiles are similar, fewer metabolites are formed in the neonate.		
Dermal absorption in the rat, EPA OPPTS 870.7600 (1998), GLP, Reliability 1, Key study	Rat, Sprague Dawley, 24 males/6 subgroups/group	dinotefuran ([G-^{14}C]), 98.5% purity, applied as solution, 3.2, 30 and 302 µg/cm^2, 24 hours exposure	A large proportion of the dermally applied dinotefuran (60.7 – 93.3%) remained on the surface of the skin and could be dislodged by washing and was not available for absorption into the skin or systemic circulation. Therefore, systemic absorption of dinotefuran was very low at all time points for all dose levels.	No	Report no. A25975, [redacted], 2006b, IUCLID no. 8.8.2
Oral Milk transfer Non-Guideline GLP	Rat SD 6 lactating females / test group	dinotefuran ([G-^{14}C]) Single oral dose: 50 & 500 mg/kg bw	The concentrations of radiolabel in blood/plasma and milk (% applied dose data not available) 0.5 hours after administration of 50 mg/kg bw G-14C-dinotefuran were 30.1 – 35.2 ppm and 55.2 - 62.9 ppm dinotefuran equivalents respectively across all sampling times from day 2 to day 12 of lactation. Within 1.5 hours after administration, the concentrations in blood and plasma had declined to about half the levels determined after 0.5 hours, and were within the range 13.9 – 17.5 ppm dinotefuran equivalents throughout the study. The concentrations in milk were within the range 26.4 – 36.9 ppm dinotefuran equivalents at all sampling times.	no	[redacted], 2006a, Report no. A29136, August 9, 2006. IUCLID no. 8.13.2-03

			In the high dose group, the absorption and depletion profiles resembled those observed for the low dose level although the concentrations in blood and plasma were only approximately 4 times higher for a 10-fold increase in dose level. Two hours after administration the concentrations in blood and plasma were within the range 104 - 144 ppm dinotefuran equivalents, and the concentrations in milk were 160-199 ppm dinotefuran equivalents, on all sampling occasions from day 2 to day 12 of lactation. Four hours after administration, the concentrations in blood and plasma had declined to 70 – 96 ppm dinotefuran equivalents. Milk concentrations had declined to 114 – 196 ppm on all sampling occasions from day 2 to day 12 of lactation.		

A.3.1.1 Short summary and overall relevance of the provided toxicokinetic information

A comprehensive evaluation of the absorption, distribution, metabolism and excretion of [^{14}C]-dinotefuran has been performed in young adult male and female rats using an approximate 1:1 mixture of tetrahydrofuran- (F) and guanidine-labelled (G) material at dose levels of 50 and 1000 mg/kg bw. The placental transfer at approximately day 18 of gestation, the transfer to maternal milk at approximately 12 days *post-partum* and the absorption, distribution, metabolism and excretion in 12-day old neonatal rats have also been investigated using a single dose of 50 mg/kg bw [^{14}C]- dinotefuran.

[redacted] (2000a) demonstrated in young adult rats that the distribution of radioactivity between urine, faeces and carcass was similar for both F- and G-radiolabelled forms of dinotefuran, and that radioactivity in expired air is ≤ 0.05% administered dose. Therefore, the main study in young adult rats was performed using a 1:1 mixture of the radiolabelled forms. Expired air was not collected. [redacted] (2000c) used G-radiolabelled dinotefuran to investigate the absorption, distribution, metabolism and excretion in 12-day old neonatal rats.

Radioactivity derived from orally administered [^{14}C]-dinotefuran is rapidly and almost completely absorbed into the general circulation of young adult rats. Calculated T_{max} values are 0.25 - 0.63 hours for single and multiple doses of 50 mg/kg bw and 2.00 - 2.10 hours for a single dose of 1000 mg/kg bw. The recovery of radioactivity 168 hours after single doses of 50 or 1000 mg/kg bw and multiple doses of 50 mg/kg bw range from 87.7 to 99.8% of administered dose in urine and 1.06 to 3.16% in faeces. Intravenous administration of a single dose of 50 mg/kg bw results in the recovery of 96.6 to 96.7% administered dose in urine and 1.06 to 1.26% administered dose in faeces. Elimination is rapid, predominantly by urinary excretion and almost complete within 7 days of administration. The elimination half-life ($T_{1/2}$) ranged from 3.64 to 16.1 hours for single and multiple oral doses of 50mg/kg. A single oral dose of 1000 mg/kg bw gives $T_{1/2}$ values of 13.8 - 15.2 hours. Comparison of calculated AUC values for a single oral dose of 50 mg/kg bw (83.3 / 110 ppm.hour, males / females) and 1000 mg/kg bw (2660 / 2370 ppm.hour, males / females) indicate an approximate linear relationship between administered oral dose and systemic availability.

In young adult rats, radioactivity is widely distributed in all tissues 0.5 hours after a single oral dose of 50 mg/kg bw. At this time, only the concentrations in the kidneys (79.4 ppm), stomach (67.3 ppm) and urinary bladder (45.8 ppm) are higher than in plasma (40.6 ppm). Tissue concentrations decline quickly and at 168 hours after dosing, all tissues with the exception of male skin (0.05 ppm), kidneys (0.01 ppm) and mammary gland (0.02 ppm), are below the limits of detection (0.001 ppm). With the exceptions of male and female skin (0.007 and 0.014 ppm), female bone (0.004 ppm), female intestinal tract (0.003 ppm) and female mammary gland (0.018 ppm), all tissues are below the limit of detection 168 hours after 15 oral doses of 50 mg/kg bw/day. Tissue distribution is similar after a single oral dose of 1000 mg/kg. Whole body autoradiographic results after single oral doses of 50 or 1000 mg/kg bw are consistent with the results obtained for the tissue distribution groups. Tissue radioactivity derived from [^{14}C]-dinotefuran is widely distributed and highest at the first sampling interval, 0.5 hours and 1.5 hours, for 50 and 1000 mg/kg bw, respectively. Thereafter, levels of radioactivity decline 1.5 hours after administration of 50 mg/kg bw and 8 hours after administration of 1000 mg/kg bw. Elimination is almost complete after 24 hours (50 mg/kg bw), and 72 hours after 1000 mg/kg bw no detectable radioactivity is apparent in either sex.

Radioactivity is rapidly transferred to foetuses and rapidly distributed to the foetal tissues. Maximum foetal concentrations occur in all tissues examined within 0.5 hours of maternal treatment but decline rapidly to low levels within 4 hours. Similar concentrations occur in maternal and foetal blood suggesting a rapid equilibration and similar tissue distribution in maternal and foetal tissues. Radioactivity is

rapidly transferred from maternal blood to the milk of lactating animals at day 12 *post-partum*. C_{max} values for maternal plasma and milk are 29.3 and 34.8 μg equivalents/g, respectively, 0.5 hours after treatment. Concentrations in milk decline rapidly within 4 hours. The elimination $T_{1/2}$ is 1.39 hours in milk, indicating that within 14 hours of administration the expected concentration of radioactivity would be lower than the limit of detection.

More than 90% of orally and intravenously administered dinotefuran is eliminated as unchanged parent molecule, which is also the major radioactive component in plasma, milk, bile and most tissues of young adult rats. No individual metabolite accounts for 10% or more of the administered dose. Initially, enzymatic hydroxylation on the tetrahydrofuran ring occurs to form PHP isomers, followed by further oxidation, reduction and acetylation of PHP to produce 446-DO and its isomers, 446-CO, 446-DO-Ac, 446-OH-Ac and 446-OH+COOH. Other routes of metabolism involve demethylation to FNG, nitro-reduction to 446-NH2 and further hydrolysis to DN and UF.

[redacted] (2000a) concludes that, with the exception of the linear relationship between applied dose and AUC, the absorption, distribution, metabolism and elimination of [^{14}C]-dinotefuran are unaffected by sex, dose level and treatment regimen in young adult rats. Absorption of G-radiolabelled dinotefuran from the neonatal gastrointestinal tract is also rapid and extensive. It undergoes a wide distribution within neonatal body tissues and is eliminated predominantly in the urine. G-radiolabelled dinotefuran undergoes minimal metabolism in the neonatal rat. The absorption, distribution, metabolism and elimination is not affected by the sex of the neonate.

[redacted] (2000c) concludes that the absorption, distribution, metabolism and elimination of G-radiolabelled dinotefuran are similar in neonatal and young adult rats. However, absorption and elimination in the neonate proceed at a slower rate than in young adults, and although metabolite profiles are similar, fewer metabolites are formed in the neonate.

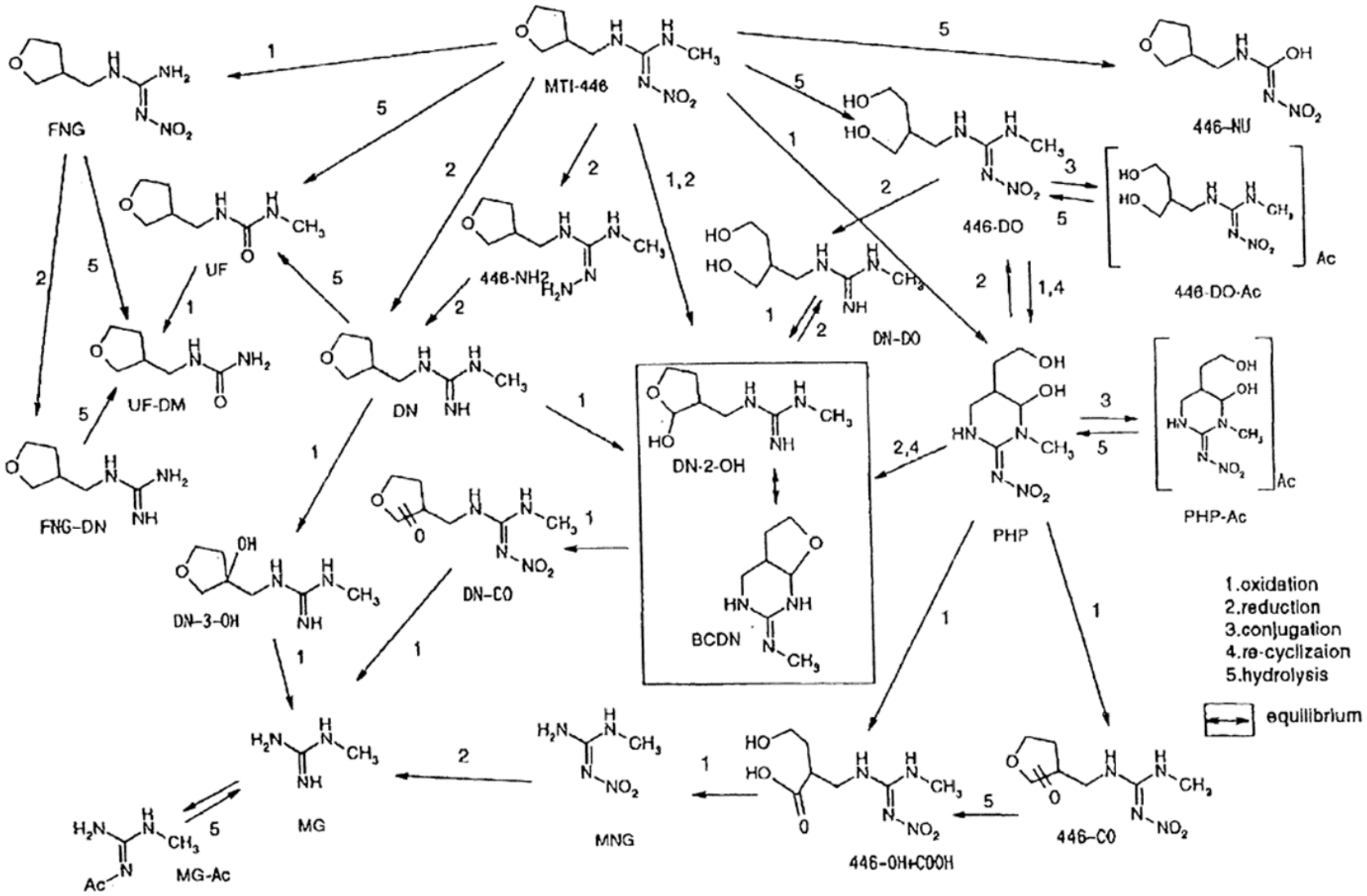


Figure A-3-1: Proposed metabolic pathway for dinotefuran in the rat

An *in vivo* dermal absorption study of [^{14}C]-dinotefuran has been performed in the rat according to the EPA-OPPTS guideline ([redacted], 2006b; Section 8.8.2). Nominal dose levels of 3.2, 30 and 302 µg/cm^2 were applied for up to 24 hours. The high dose reflected the maximum solubility of dinotefuran in water.

A large proportion of the dermally applied dinotefuran (60.7 – 93.3%) is not available for absorption into the skin or systemic circulation. Therefore, systemic absorption of dinotefuran is very low at all time points from 0.5 – 24 hours for all dose levels and was less than or equal to 2.1% of the applied dose. The calculated rates of dermal penetration into the systemic circulation increased with dose level from 0.0011 µg.cm^{-2}.hr^{-1} at the lowest dose through 0.0060 µg.cm^{-2}.hr^{-1} (middle dose) to 0.1309 µg.cm^{-2}.hr^{-1} at the highest dose.

The extent of indirect absorption (into the stratum corneum) increases with increasing dose dilution, up to 35% for the low dose, 26% for the middle dose and 9% for the high dose, within 24 hours. However, only a very small fraction is found in the deeper skin layers indicating most material in the stratum corneum is not available for systemic absorption during the first 24 hours of exposure.

A.3.1.2 Values and conclusions used for the risk assessment

Not applicable for the CLH report

A.3.2 Acute toxicity / STOT SE

A.3.2.1 Acute oral toxicity

Table A-28: Summary table of animal studies on acute oral toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Type of administration (gavage, in diet, other)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rat [redacted]:CD[SD]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000, 3000, 4000 and 5000 mg/kg bw; single dose; 14-days post exposure period	Deaths occurred in females treated at ≥2000 mg/kg bw and in males treated at ≥3000 mg/kg bw. Treatment-related clinical signs were apparent at dose levels of ≥2000 mg/kg bw and included hypoactivity, staggering gait, hunched posture, prostration, red-stained face, miosis, lacrimation, salivation, tachypnea, dyspnea, soft feces, yellow staining of the uro-genital area, tonic or clonic convulsions and tremors.	LD50: 2450 mg/kg bw (2804 mg/kg bw males; 2000 mg/kg bw females; 2450 mg/kg bw sexes combined)	none	Report no. CHW 6648-118 [redacted], 1997a IUCLID 8.7.1
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Mouse [redacted]:CD1[ICR]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000 and 3000 mg/kg bw; single dose; 14-days post exposure period	Deaths occurred at dose levels of ≥2000 mg/kg bw but not at 1000 mg/kg bw. Transient clinical signs of toxicity, on the day of treatment only, were apparent at dose levels of ≥2000 mg/kg bw and included hypoactivity, staggering gait, dyspnea, tonic convulsions and tremors.	LD50: 2371 mg/kg bw 2450 mg/kg bw males; 2275 mg/kg bw females; 2371 mg/kg bw sexes combined)	none	Report no. CHW 6648-119 [redacted], 1997b IUCLID 8.7.1 Amendment 1 [redacted], 2000

Table A-29: Summary table of human data on acute oral toxicity

No data is available.

Table A-30: Summary table of other studies relevant for acute oral toxicity

No data is available.

A.3.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an OECD-compliant study, groups of 5 male and 5 female rats were exposed to dinotefuran by gavage followed by a 14-day observation period ([redacted] 1997a). Doses were based on the results of a range-finding study in which one male and one female were exposed to 500, 1000, 3000 and 5000 mg/kg bw dinotefuran. In Phase I of the main study, males were exposed to 5000 mg/kg bw and females to 1000, 3000 and 5000 mg/kg bw dinotefuran. In Phase II, males and females were exposed to 1000, 2000 and 3000 mg/kg bw dinotefuran with an additional group of males exposed to 5000 mg/kg bw dinotefuran and an additional group of females exposed to 4000 mg/kg bw dinotefuran. Deaths occurred in both females exposed to 3000 and 5000 mg/kg bw dinotefuran in the range finding study and following exposure to 2000 (3/5 deaths), 3000 (4/5 deaths) and 4000 (5/5 deaths) mg/kg bw dinotefuran in Phase II of the main study. Males exposed to 3000 (3/5) and 5000 (5/5) mg/kg bw dinotefuran in Phase II also died. Most deaths occurred on the day of treatment or on day 1. No deaths were recorded in the Phase I study. This difference between the results from Phase I and II, given the doses were the same or higher in Phase I, may be associated with the lower treatment volume used in Phase I. LD_{50} values of 2804, 2000 and 2450 mg/kg bw dinotefuran were identified for males, females and for the sexes combined respectively. Clinical signs were generally transient and included red staining of the face from 1000 mg/kg bw dinotefuran and hypoactivity, staggering gait, hunched posture, prostration miosis, lacrimation, salivation, tachypnoea, dyspnoea, soft faeces, convulsions and tremors at dose levels ≥ 2000 mg/kg bw dinotefuran. All survivors, except 1 female exposed to 5000 mg/kg bw in Phase I, gained weight during the observation period. No treatment-related gross lesions were observed at necropsy in any animal.

In a second OECD-compliant study, groups of 5 male and 5 female mice were exposed to dinotefuran by gavage followed by a 14-day observation period ([redacted] 1997b, 2000). Doses were based on the results of a range-finding study in which one male and one female were exposed to 500, 1000, 3000 and 5000 mg/kg bw dinotefuran. In the main study, males and females were exposed to 1000, 2000 and 3000 mg/kg bw dinotefuran. Deaths occurred in males and females exposed to ≥ 2000 mg/kg bw dinotefuran; in the range finding study 1/1 male died following exposure to 3000 mg/kg bw and both male (1/1) and female (1/1) mice exposed to 5000 mg/kg bw dinotefuran died. In the main study, male and female mice died following exposure to 2000 (1/5 males, 2/5 females) and 3000 (4/5 males and females) mg/kg bw dinotefuran. All deaths occurred on the day of treatment. LD_{50} values of 2450, 2275 and 2371 mg/kg bw dinotefuran were identified for males, females and for the sexes combined respectively. Clinical signs were apparent on the day of treatment only and included hypoactivity, staggering gait, dyspnoea, convulsions and tremors at dose levels ≥ 2000 mg/kg bw dinotefuran. Slight weight loss was recorded in 4 females exposed to 1000 mg/kg bw but all other survivors gained weight during the observation period. No treatment-related gross lesions were observed at necropsy in any animal.

Addition information on acute oral toxicity in the rat is available in a standard acute neurotoxicity

study in rats summarised in Section A.3.12 ([redacted], 2001a). A single gavage dose of 0 (0.5 % CMC vehicle only), 325, 750 or 1500 mg/kg bw was administered. The only treatment related change reported was a reduction in motor activity score at the highest dose level in the assessments conducted 3 hours after dosing. Based on this observation, a study NOAEL of 750 mg/kg bw is identified for acute toxicity in the rat.

Standard rabbit developmental toxicity studies summarised in Section A.3.10.2 provide information on acute oral toxicity in the rabbit. In the first study, gavage dose levels of 0 (0.5 % CMC vehicle), 52, 125 and 300 mg/kg bw/day were administered to NZW rabbits ([redacted] 1998e). Clinical signs were obseved at 300 mg/kg bw/day from the first day of dosing, which included hypoactivity, prone position, panting, flushed nose and ears, and tremors. In a second study, gavage dose levels of 0 (0.5 % CMC vehicle), 60, 175 and 500 mg/kg bw/day were administered to Kbl:JW strain rabbits ([redacted] 2013). Clinical signs of tachypnoea were observed at 500 mg/kg bw/day on the first day of dosing. Based on these clinical signs, a NOAEL of 175 mg/kg bw/day is identified for acute toxicity in NZW rabbits.

A.3.2.1.2 Comparison with the CLP criteria

Dinotefuran does not fulfil the CLP classification criteria as the LD50 is >2000 mg/kg bw.

A.3.2.1.3 Conclusion on classification and labelling for acute oral toxicity

The acute toxicity estimate (ATE) of dinotefuran via the oral exposure route is 2371 mg/kg bw, therefore dinotefuran is not classified for acute oral toxicity.

A.3.2.1.4 Conclusion on acute oral toxicity related to risk assessment

Not applicable for the CLH report

A.3.2.2 Acute dermal toxicity

Table A-31: Summary table of animal studies on acute dermal toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Surface area	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
Dermal toxicity, OECD TG 402 (1987), EPA 81-2 (1982), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rat [redacted]:CD[SD]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, 0.5% (w/v) solution of carboxymethylcellulose in distilled water, 2000 mg/kg bw, 16 cm², 24 h exposure, 14-days post-exposure period.	All animals survived to the end of the study. No treatment-related clinical signs of toxicity. All male animals gained weight throughout the study, but 4 females during the first week and 2 females during the second week showed minor weight losses of up to 9 g. Transient slight to moderate erythema, associated with slight edema in one animal, occurred in 8 of the 10 animals on the day of patch removal. Slight erythema persisted in 2 animals until day 7.	LD50: > 2000 mg/kg bw (both sexes combined)	None	Report no. CHW 6648-120 [redacted], 1997c IUCLID 8.7.3

Table A-32: Summary table of human data on acute dermal toxicity

No data is available.

Table A-33: Summary table of other studies relevant for acute dermal toxicity

No data is available.

A.3.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In an OECD-compliant study, 5 male and 5 female rats were exposed to the limit dose of 2000 mg/kg bw dinotefuran via the dermal route for 24 h followed by a 14-day observation period ([redacted] 1997c). No deaths were observed during or post-exposure, and therefore the dermal LD_{50} was estimated to be > 2000 mg/kg bw in both male and female rats. There were no treatment-related clinical signs of systemic toxicity although 2 females did exhibit red-stained faces on the day of treatment. All males gained weight during the study but minor weight losses were observed in 4 females during week 1 and 2 females during week 2. In terms of local toxicity, slight to moderate erythema was observed in all males and 3/5 females on day 1 post-exposure with slight erythema persisting in all 5 males and 1 female up to day 3 and in 2 males up to day 7 post-exposure. In addition, slight oedema was observed in 1/5 males on day 1 and 2/5 males on day 3. No other effects were observed and there was no evidence of macroscopic changes at necropsy.

A.3.2.2.2 Comparison with the CLP criteria

Dinotefuran does not fulfil the CLP classification criteria as the LD50 is >2000 mg/kg bw.

A.3.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

The acute toxicity estimate (ATE) of dinotefuran via the oral exposure route is >2000 mg/kg bw, therefore dinotefuran is not classified for acute dermal toxicity.

A.3.2.2.4 Conclusion on acute dermal toxicity related to risk assessment

Not applicable for the CLH report

A.3.2.3 Acute inhalation toxicity

Table A-34: Summary table of animal studies on acute inhalation toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), form (gas, vapour, dust, mist) and particle size (MMAD) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LC50	Remarks (e.g. major deviations)	Reference
Inhalation (nose-only), OECD TG 403 (1981), EEC B.2. (1992), OPPTS 870.1300 (1998), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1 Key study	Rat [redacted]:WI[Glx/BRL/Han]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, MMAD 4.74 µm + GSD 2.79. Nominal concentration 29.1 mg/L, analytical concentration 4.09 mg/L, nose only, 4 h exposure, 14-days post exposure period.	No deaths occurred during the exposure or observation periods, and no treatment-related clinical signs of an adverse reaction to treatment were apparent. Body weight gains were not affected by exposure to dinotefuran. Necropsy and *post mortem* examination did not reveal any treatment-related lesions in either sex. The group mean absolute and relative lung weights were considered to be unaffected by treatment.	LC50: >4.09 mg/L (both sexes combined)	None	Report no. 1300/3-D6154 [redacted], 1999 IUCLID 8.7.2 Amendment 1 [redacted], 2000a Amendment 2 [redacted], 2000b

Table A-35: Summary table of human data on acute inhalation toxicity

No data is available.

Table A-36: Summary table of other studies relevant for acute inhalation toxicity

No data is available.

A.3.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an OECD-compliant study, groups of 5 male and 5 female rats were exposed to 0 or 4.09 mg/L dinotefuran via the inhalation route (nose only) for 4 h followed by a 14-day observation period ([redacted] 1999, 2000a, b). The analytical concentration of 4.09 mg/L dinotefuran was reported to be the maximum attainable concentration. The MMAD of dinotefuran in the test atmosphere was reported to be 4.74 µm ± 2.79 µm as the GSD, which is above the optimal respirable size range of 1-4 µm; the study authors stated that this was the minimum attainable MMAD. [It is noted that a smaller MMAD of 2 µm was produced in the sub-acute inhalation study but at a concentration of 2.1 mg/L or below]. No deaths were observed during or post-exposure, therefore an inhalation LC_{50} value was not identified from this study but it was estimated to be > 4.09 mg/L in both male and female rats. No treatment-related clinical signs of toxicity were observed and body weight gains were not affected by treatment. There was no evidence of any treatment-related lesions in either sex at necropsy.

A.3.2.3.2 Comparison with the CLP criteria

Although the 4-hour LC_{50} value falls within the classification category of Category 4, higher aerosol concentrations of dinotefuran in the respirable range are not technically feasible. Therefore, dinotefuran does not require hazard classification for acute inhalation toxicity.

A.3.2.3.3 Conclusion on classification and labelling for 250 acute inhalation toxicity

Dinotefuran does not fulfil the CLP classification criteria as higher concentrations in the respirable range are not technically feasible.

A.3.2.3.4 Conclusion on acute inhalation toxicity related to risk assessment

Not applicable for the CLH report

A.3.2.4 Specific target organ toxicity – single exposure Category 1 and 2 (STOT SE 1 and 2)

Table A-37: Summary table of animal studies on Specific Target Organ Toxicity STOT SE 1 and 2

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (including target organ and the effect levels)	Remarks (e.g. major deviations)	Reference
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rat [redacted]:CD[SD]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000, 3000, 4000 and 5000 mg/kg bw; single dose; 14-days post exposure period	Sprague-Dawley rats were treated via oral gavage at 1000, 2000, 3000, 4000 and 5000 mg/kg bw with a single dose (Glaza, 1997a). Treatment-related clinical signs were apparent at dose levels of ≥2000mg/kg bw and included hypoactivity, staggering gait, hunched posture, prostration, red-stained face, miosis, lacrimation, salivation, tachypnea, dyspnea, soft feces, yellow staining of the uro-genital area, tonic or clonic convulsions and tremors. Clinical signs were generally	LD50: 2450 mg/kg bw (2804 mg/kg bw males; 2000 mg/kg bw females; 2450 mg/kg bw sexes combined)	Report no. CHW 6648-118 [redacted], 1997a IUCLID 8.7.1

			transient but occasionally persisted for up to 3 days after treatment.		
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Mouse [redacted]:CD1[ICR]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000 and 3000 mg/kg bw; single dose; 14-days post exposure period	Transient clinical signs of toxicity (on the day of treatment only) were apparent at dose levels of ≥2000 mg/kg bw and included hypoactivity, staggering gait, dyspnea, tonic convulsions and tremors.	LD50: 2371 mg/kg bw 2450 mg/kg bw males; 2275 mg/kg bw females; 2371 mg/kg bw sexes combined)	Report no. CHW 6648-119 [redacted], 1997b IUCLID 8.7.1 Amendment 1 Glaza, 2000
Acute neurotoxicity, 14 days exposure, oral dietary, OECD TG 424, OPPTS 870.6200, GLP, Reliability 1, Key study	Rat, [redacted]:CD®(SD) IGS BR, males/females, 10/sex/group	Dinotefuran, 98.9%, 0.5% CMC vehicle, single administration of 0, 325, 750, 1500 mg/kg bw	The only treatment related change reported was a reduction in motor activity score at the highest dose level in the assessments conducted 3 hours after dosing. Based on this observation, a study NOAEL of 750 mg/kg bw is identified. However, this transient minor change is considered to be a manifestation of general toxicity, and because no neuropathological changes were detected it can be concluded that dinotefuran is not acutely neurotoxic.	Males and females at 1500 mg/kg bw had statistically significantly lower motor activity on day 1, transient and not other correlating changes therefore not adverse nor treatment related.	Report no. 6648-147 [redacted] (2001a) IUCLID 8.13.2
Dermal toxicity, OECD TG 402	Rat [redacted]:CD[SD]BR (SPF)	Dinotefuran, 99.1% purity, 0.5% (w/v)	There were no treatment-related	LD50: > 2000 mg/kg bw	Report no. CHW 6648-120

(1987), EPA 81-2 (1982), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Males and females 5/sex/group	solution of carboxymethylcellulose in distilled water, 2000 mg/kg bw, 16 cm², 24 h exposure, 14-days post-exposure period.	clinical signs of toxicity although 2 females did exhibit red-stained faeces on the day of treatment. Slight to moderate erythema and slight oedema were noted in some treated animals.	(both sexes combined)	[redacted], 1997c IUCLID 8.7.3
Inhalation (nose-only), OECD TG 403 (1981), EEC B.2. (1992), OPPTS 870.1300 (1998), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1 Key study	Rat [redacted]:WI[Glx/BRL/Han]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, MMAD 4.74 µm + GSD 2.79. Nominal concentration 29.1 mg/L, analytical concentration 4.09 mg/L, nose only, 4 h exposure, 14-days post exposure period.	No treatment-related clinical signs of toxicity were observed. There was no evidence of any treatment-related lesions in either sex at necropsy.	LC50: >4.09 mg/L (both sexes combined)	Report no. 1300/3-D6154 [redacted], 1999 IUCLID 8.7.2 Amendment 1 [redacted], 2000a Amendment 2 [redacted], 2000b

Table A-38: Summary table of human data on Specific Target Organ Toxicity STOT SE 1 or 2

No data is available.

Table A-39: Summary table of other studies relevant for Specific Target Organ Toxicity STOT SE 1 and 2

No data is available.

A.3.2.4.1 Short summary and overall relevance of the provided information on STOT SE 1 and 2

The single dose toxicity of dinotefuran has been thoroughly investigated in a series of standard studies. Acute studies via the oral route were performed in rats and mice, while studies via the inhalation and dermal routes were performed in rats. Additionally, an oral neurotoxicity study in rats is available. No target organ toxicity has been observed in these studies.

A.3.2.4.2 Comparison with the CLP criteria

As dinotefuran did not induce target organ toxicity in animal studies after single exposure and no relevant human evidence is available, classification in Category 1 or Category 2 is not justified.

A.3.2.4.3 Conclusion on classification and labelling for STOT SE 1 and 2

Not classified.

A.3.2.5 Specific target organ toxicity – single exposure Category 3 (STOT SE 3)

Table A-40: Summary table of animal studies on STOT SE 3

No data is available.

Table A-41: Summary table of human data on STOT SE 3

No data is available.

Table A-42: Summary table of other studies relevant for STOT SE 3

No data is available.

A.3.2.5.1 Short summary and overall relevance of the provided information on STOT SE 3

Category 3 classification is required for substances that induce transient target organ effects, specifically narcotic effects and respiratory tract irritation.

Since no relevant human evidence is available, the results from animal acute toxicity studies and animal developmental toxicity studies are used.

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (including target organ and the effect levels)	Remarks (e.g. major deviations)	Reference
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rat [redacted]:CD[SD]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000, 3000, 4000 and 5000 mg/kg bw; single dose; 14-days post exposure period	Sprague-Dawley rats were treated via oral gavage at 1000, 2000, 3000, 4000 and 5000 mg/kg bw with a single dose (Glaza, 1997a). Treatment-related clinical signs were apparent at dose levels of ≥2000mg/kg bw and included hypoactivity, staggering gait, hunched posture, prostration, red-stained face, miosis, lacrimation, salivation, tachypnea, dyspnea, soft feces, yellow staining of the uro-genital area, tonic or clonic convulsions and tremors. Clinical signs were generally transient but occasionally persisted for up to 3 days after treatment. All these effects are considered to be a manifestation of general toxicity.	LD50: 2450 mg/kg bw (2804 mg/kg bw males; 2000 mg/kg bw females; 2450 mg/kg bw sexes combined)	Report no. CHW 6648-118 [redacted], 1997a IUCLID 8.7.1
Oral gavage, OECD TG 401 (1982), EPA 81-1 (1987), JMAFF 59 Nohsan 4200	Mouse [redacted]:CD1[ICR]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, in water, gavage administration, 1000, 2000 and 3000 mg/kg bw; single dose; 14-days post exposure	Transient clinical signs of toxicity (on the day of treatment only) were apparent at dose levels of ≥2000 mg/kg bw and included hypoactivity, staggering gait, dyspnea, tonic convulsions and tremors. All these effects are considered to be a manifestation of general toxicity.	LD50: 2371 mg/kg bw 2450 mg/kg bw males; 2275 mg/kg bw females; 2371 mg/kg	Report no. CHW 6648-119 [redacted], 1997b IUCLID 8.7.1

(1985) GLP, Reliability 1, Key study		period		bw sexes combined)	Amendment 1 Glaza, 2000
Acute neurotoxicity, 14 days exposure, oral dietary, OECD TG 424, OPPTS 870.6200, GLP, Reliability 1, Key study	Rat, [redacted]:CD®(SD) IGS BR, males/females, 10/sex/group	Dinotefuran, 98.9%, 0.5% CMC vehicle, single administration of 0, 325, 750, 1500 mg/kg bw	The only treatment related change reported was a reduction in motor activity score at the highest dose level, in the assessments conducted 3 hours after dosing. This effect was reported only during the first 10 minutes after administration. Beyond 10 minutes, no change was observed regarding the motor activity. Based on this observation, a study NOAEL of 750 mg/kg bw is identified. However, this transient minor change is considered to be a manifestation of general toxicity.	Males and females at 1500 mg/kg bw had statistically significantly lower motor activity on day 1, transient and not other correlating changes therefore not adverse nor treatment related.	Report no. 6648-147 [redacted] (2001a) IUCLID 8.13.2
Dermal toxicity, OECD TG 402 (1987), EPA 81-2 (1982), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rat [redacted]:CD[SD]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, 0.5% (w/v) solution of carboxymethylcellulose in distilled water, 2000 mg/kg bw, 16 cm^2, 24 h exposure, 14-days post-exposure period.	No relevant effect for STOT SE 3	LD50: > 2000 mg/kg bw (both sexes combined)	Report no. CHW 6648-120 [redacted], 1997c IUCLID 8.7.3
Inhalation (nose-only), OECD TG 403 (1981), EEC B.2. (1992), OPPTS 870.1300 (1998),	Rat [redacted]:WI[Glx/BRL/Han]BR (SPF) Males and females 5/sex/group	Dinotefuran, 99.1% purity, MMAD 4.74 µm + GSD 2.79. Nominal concentration 29.1 mg/L, analytical concentration 4.09 mg/L, nose only, 4 h exposure, 14-days post exposure period.	No relevant effect for STOT SE 3	LC50: >4.09 mg/L (both sexes combined)	Report no. 1300/3-D6154 [redacted], 1999 IUCLID 8.7.2 Amendment 1

<table>
<tr>
<td>JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1 Key study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[redacted], 2000a
Amendment 2 [redacted], 2000b</td>
</tr>
<tr>
<td>Developmental toxicity, oral gavage, OECD TG 414, GLP, reliability 1, Key study</td>
<td>Rabbit, NSW, 22 mated females per group</td>
<td>Dinotefuran purity 99.1%, 0.5% CMC vehicle, nominal concentrations 52, 125, 300 mg/kg bw/d, daily exposure for gd 6-18, 10-day post-exposure period</td>
<td>Nature and incidence of clinical signs at dose 300 mg/kg (21 rabbits)
<table>
<tr><td>Day of administration</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>9</td></tr>
<tr><td>Hypoactivity</td><td>21</td><td>19</td><td>19</td><td>15</td><td>11</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>Prone position</td><td>19</td><td>17</td><td>18</td><td>12</td><td>6</td><td>1</td><td>1</td><td>0</td></tr>
<tr><td>Panting</td><td>17</td><td>15</td><td>15</td><td>10</td><td>5</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Tremor</td><td>7</td><td>4</td><td>2</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
The clinical signs disappeared in the 5-9 days of administration.

Since there is no lack of coordination or ataxia observed, the lethargy alone cannot be imputable to a narcotic effect.</td>
<td>NOAEL (maternal toxicity) 300 mg/kg bw/d
NOAEL (developmental toxicity) 1000 mg/kg/d</td>
<td>Report no. H-97166
[redacted] (1998e)
IUCLID 8.10.1</td>
</tr>
<tr>
<td>Developmental toxicity, oral gavage, OECD TG 414 (2001), OPPTS 870.3700 (1998), JMAFF 59</td>
<td>Rabbit, Kbl:JW, 25 mated females per group</td>
<td>Dinotefuran purity 99.6%, 0.5% CMC vehicle, nominal concentrations 60, 175, 500 mg/kg bw/d, daily exposure for gd 6-27, 10-day post-exposure period</td>
<td>No relevant effect for STOT SE 3</td>
<td>NOAEL (maternal toxicity) 175 mg/kg bw/d
NOAEL (developmental toxicity) 500 mg/kg bw/d</td>
<td>Report no. SR12005
[redacted] (2013)
IUCLID 8.10.1</td>
</tr>
</table>

Nohsan 4200 (2000, 2011), GLP, reliability 1, Key study					
Developmental toxicity, oral gavage, OECD TG 414, GLP, reliability 1, Key study	Rat, [redacted]:CD(SD) IGS (SPF), 24 mated females per group	Dinotefuran purity 99.1%, 0.5% CMC vehicle, nominal doses 100, 300, 1000 mg/kg bw/d, daily exposure for gd 6-15, 5-day post-exposure period	No relevant effect for STOT SE 3	NOAEL (maternal toxicity) 300 mg/kg bw/d NOAEL (developmental toxicity) 1000 mg/kg/d	Report no. H-97163 [redacted] (1998b) IUCLID 8.10.1
Developmental neurotoxicity, Oral, dietary OECD TG 426, OPPTS 870.6300, GLP Reliability 1, Key study	Rat, [redacted]:CD(SD), 25 mated females F0/sex/group	Dinotefuran purity 99.5%, no vehicle, nominal doses 0, 1000, 3000, 10000 ppm, (equivalent to 0, 79, 237, 784 mg/kg bw/day) daily exposure on Day 6 of gestation until Day 21 of lactation	No relevant effect for STOT SE 3	NOAEL (maternal): 237 mg/kg bw/day NOAEL (neonatal toxicity and developmental neurotoxicity): 784 mg/kg bw/day	Report no. SRY00002 [redacted] (2010) IUCLID 8.13.2

A.3.2.5.2 Comparison with the CLP criteria

As dinotefuran did not induce transient target organ effects (such as narcotic effects or respiratory tract irritation) after single exposure and no relevant human evidence is available, classification in Category 3 is not justified.

A.3.2.5.3 Conclusion on classification and labelling for STOT SE 3

Not classified.

A.3.2.5.4 Overall conclusion on acute toxicity related to risk assessment

Not applicable for the CLH report

A.3.3 Skin corrosion and irritation

Table A-43: Summary table of in vitro studies on skin corrosion/irritation

No in vitro data is available.

Table A-44: Summary table of animal studies on skin corrosion/irritation

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results Average score for erythema/eschar and oedema (24, 48, 72 h) per animal, observations and time point of onset, reversibility, other adverse local/systemic effects, histopathological findings	Remarks (e.g. major deviations)	Reference
Skin irritation, OECD TG 404 (1992), EPA 81-5 (1982), JMAFF 59 Nohsan 4200 (1985), GLP, Reliability 1, Key study	Rabbit, New Zealand White ([redacted]:(NZW)SPF), 5 males and 1 female	Dinotefuran, 99.1% purity, 0.5 g in 0.3 mL distilled water applied to shaved intact dorsal and/or flank skin (2.5 x 2.5 cm), 4h exposure, semi-occlusive dressing	No dermal response in 5/6 rabbits at 24, and 6/6 rabbits at 48 and 72 hours, 1/6 showed erythema score of 1 at 24h which had reversed by 48 hours. Mean erythema score of 0.17 at 24 hours.	None	Report no. 6648-121, [redacted], 1998a, IUCLID no. 8.1.1.

Table A-45: Summary table of human data on skin corrosion/irritation

No human data is available.

A.3.3.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

An OECD-comparable skin irritation study is available ([redacted] 1998a). Dinotefuran (0.5 g in 0.3 ml water) was applied to the skin (6.25 cm^2) of 5 male and 1 female rabbit for 4 hours. Very slight erythema was observed on the treated skin of 3/6 rabbits 30 minutes post-exposure. At 24 hours post-exposure very slight erythema was observed in 1 male rabbit only. Erythema was not observed in any animal at 48 hours or 72 hours post-exposure. Oedema was not observed in any animal at any time point.

Animal	**Individual erythema / edema scores at:**			**EU index score****
	24 hours	**48 hours**	**72 hours**	
1	0 / 0	0 / 0	0 / 0	0.0
2	0 / 0	0 / 0	0 / 0	0.0
3	0 / 0	0 / 0	0 / 0	0.0
4	0 / 0	0 / 0	0 / 0	0.0
5	0 / 0	0 / 0	0 / 0	0.0
6	1 / 0	0 / 0	0 / 0	0.33

** EU index score = total erythema & edema score at the 24, 48 and 72hr intervals / no. of observation intervals

A.3.3.2 Comparison with the CLP criteria

The mean erythema score at 24 hours was 0.17, which is <2.3. Together with reversibility of effect, and no persistent inflammation, dinotefuran does not fulfil the classification criteria for a skin irritant.

A.3.3.3 Conclusion on classification and labelling for skin corrosion/irritation

Dinotefuran is not classified as a skin irritant.

A.3.3.4 Overall conclusion on skin irritation and corrosivity related to risk assessment

Not applicable for the CLH report

A.3.4 Serious eye damage and Eye irritation

Table A-46: Summary table of in vitro studies on serious eye damage and eye irritation

No in vitro data is available.

Table A-47: Summary table of animal studies on serious eye damage and eye irritation

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results Average score for corneal opacity, iritis, conjunctival redness and conjunctival oedema (24, 48, 72 h) per animal, observations and time point of onset, reversibility	Remarks (e.g. major deviations)	Reference
Eye irritation, OECD TG 405 (1987), EPA 81-4 (1982), JMAFF 59 Nohsan 4200 (1985) GLP, Reliability 1, Key study	Rabbit New Zealand White ([redacted]:(NZW)SPF), 6 males and 3 females, 3 rabbits per washed group, 6 rabbits per unwashed group	Dinotefuran, 99.1% purity, applied neat, single application of 0.1 g, Group 1 animal eyes remained unflushed after treatment, Group 2 animal eyes were flushed with water for one minute after 30 sections of test material instillation.	Mean scores; corneal opacity 0.7 at 24h, 0.2 at 48 and 72h; iris lesion 0.3 at 24h, 0.2 at 48h and 0.0 at 72h; Erythema 2.0 at 24h, 1.3 at 48h, 0.8 at 72h; oedema 1.5 at 24h, 1.2 at 48h, 0.3 at 72h All effects fully reversibly at day 14.	None	Report no. 6648-122, [redacted], 1998b, IUCLID no. 8.1.2
Acute eye irritation study in rabbits, OPPTS 870.2400 (1998), GLP, Reliability 1,	Rabbit New Zealand White, 1 male and 2 females	Dinotefuran, 98.9% purity, 0.1mL by volume (37.8mg) dry dinotefuran solid, No unwashed group	Mean scores; corneal opacity 0 at 24h, 0 at 48 and 72h; iris lesion 0 at 24h, 0 at 48h and 0 at 72h;	None	Report no. 8394-04, [redacted], 2004 IUCLID no. 8.1.2

Key study			Erythema 0 at 24h, 0 at 48h, 0 at 72h; oedema 0 at 24h, 0 at 48h, 0 at 72h All effects fully reversibly at 24h.		

Table A-48: Summary table of human data on serious eye damage and eye irritation

No human data is available.

A.3.4.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

An eye irritation study that is comparable to OECD guideline 405 is available ([redacted] 1998b). Dinotefuran (0.1 g) was instilled directly into one eye of 9 rabbits. The eyes of 3 of these rabbits were washed for 1 minute with water 30 seconds after exposure. The eyes of the remaining 6 animals were not washed. The animals were observed for 14 days and eye irritation scores recorded at 1, 24, 48, 72 and 96 hours and on days 7 and 14. Sodium fluorescein examinations were performed to assist the visualisation of possible corneal lesions at 24, 48, 72 and 96 hours or until a negative response was evident. Dinotefuran was slightly irritating to the eyes of all rabbits tested. The average scores for effects on the cornea, iris and conjunctiva for each animal over 24, 48 and 72 hours are presented in Table below. The irritant effects observed in both the unwashed and washed groups were no longer apparent on day 14.

Individual eye irritation scores – Group 1 (unwashed) – Corneal opacity

Animal number	1h	24h	48h	72h	96h	Day 7	Day 14	Score (24, 48, 72h)
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	1[a]	0	0	0	0	0	0.3
4	1	1[a]	0	0	0	0	0	0.3
5	0	1[a]	0	0	0	0	0	0.3
6	0	1[a]	1[a]	1[a]	1	1	0	1

[a] *corneal epithelial peeling*

A second eye irritation study following guideline OPPTS 870.2400 ([redacted], 2004) is available. This study was conducted on three albino rabbits. The test substance, 0.1 mL by volume (37.8 mg), was placed into the conjunctival sac of the right eye of each animal selected for testing. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24 hour observation.

A.3.4.2 Comparison with the CLP criteria

The mean scores for corneal opacity did not exceed ≥1, iritis did not exceed ≥1, conjunctival redness did not exceed ≥2 and conjunctival oedema did not exceed ≥2 at 24, 48 and 72 hours after instillation of dinotefuran. The effects seen fully reversed within an observation period of <21 days (14 days).

In the second study, the mean scores for corneal opacity, iris lesion, erythema and oedem were 0

at 24h, 0 at 48h, 0 at 72h. All effects were fully reversibly at 24h.

A.3.4.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Dinotefuran does not fulfil the classification criteria for eye irritation.

A.3.4.4 Overall conclusion on eye irritation and corrosivity related to risk assessment

Not applicable for the CLH report

A.3.5 Skin sensitisation

Table A-49: Summary table of animal studies on skin sensitisation

Method, Duration of study, Route of exposure (e.g. topical/intradermal, induction/challenge if relevant), Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (e.g. EC3-value or amount of sensitised animals at induction dose)	Remarks (e.g. major deviations)	Reference
Guinea pig maximisation test, intradermal inductions and topical challenge, OECD TG 406 (1992), EPA 81-6 (1982), Magnusson & Kligman (1970), JMAFF 59 Nohsan 4200 (1985), GLP, Reliability 1, Key study	Albino guinea pig, [redacted]:[HA]BR, 20 male animals per group	Dinotefuran, 99.1% purity, a) for induction: A series of 3 preparations for dinotefuran for <u>intradermal induction</u> was prepared as follows: 1. 1:1 dilution of FCA in sterile water, without dinotefuran 2. 5% suspension of dinotefuran in 0.5% CMC/distilled water 3. 1:1 dilution of 10% suspension of dinotefuran in 0.5% CMC/distilled water and FCA 4. topical application was performed with 25% w/w mixture of test substance in petrolatum. b) <u>for challenge</u>: A 25% (w/w) mixture of dinotefuran in petrolatum	Not sensitising No skin reactions in any of the test animals or negative controls. Positive controls demonstrated the sensitivity of the test system.	None	Report no. 6648-123, [redacted], 1997d IUCLID no. 8.3.1

Table A-50: Summary table of human data on skin sensitisation

No human data is available.

Table A-51: Summary table of other studies relevant for skin sensitisation

No other studies are available.

A.3.5.1 Short summary and overall relevance of the provided information on skin sensitisation

A skin sensitisation study of dinotefuran is available in guinea pigs ([redacted] 1997d). A preliminary irritation test was performed on 2 groups of 4 guinea pigs in which intradermal injections of 1, 5, 10 and 15 % dinotefuran were applied to one group and topical applications of 5, 10, 15 and 25 % dinotefuran for 24 hours were administered to the other group. Dermal reactions were evaluated after 24 and 48 hours post-exposure. Dermal irritation was observed 24 and 48 hours after all intradermal applications; Intradermal injection of 1 % dinotefuran caused mild erythema, 5 % resulted in mild-moderate diffuse erythema and 10 and 15 % dinotefuran caused moderate-diffuse to intense erythema. No dermal reactions were observed following topical exposure to ≤ 25 % dinotefuran.

In the main study, the induction phase for the test group of 20 guinea pigs included intradermal injections with 5 % dinotefuran (with and without FCA) and a 48 h topical application of 25 % dinotefuran. A group of 20 control animals were not exposed to dinotefuran at this stage. A single 24 h challenge application of 25 % dinotefuran was applied to both groups on day 22 and dermal reactions assessed 24 and 48 hours later. Dinotefuran did not induce skin sensitisation in any of the animals tested as dermal reactions were not observed in any of the test or control animals. A positive control study performed within 6 months of the dinotefuran study produced the appropriate response.

As the preliminary study did not identify the irritation threshold for topical application of dinotefuran, the challenge concentration of 25 % dinotefuran may not be the highest non-irritant concentration (as recommended in the OECD guideline). This raises concern that the full sensitisation potential of dinotefuran has not been assessed. However, the company owning the data has stated that the original Magnusson and Kligman procedure includes an approach to incorporate the pulverized solid test item into petrolatum at a concentration not exceeding 25 % w/w, based on the rationale that solid test item concentrations greater than 25 % w/w in petrolatum are generally not homogeneous and do not allow for good contact of the test item with animal skin under the conditions of the test. Good contact of the test item with animal skin is necessary to ensure potential absorption into the skin. Additionally, the company owning the data states that dinotefuran technical is a powder with low solubility in organic solvents and therefore 25 % w/w dinotefuran in petrolatum is the maximum technically achievable concentration possible to prepare as a homogeneous mixture. Taking account of the company statement, the RMS concludes that the skin sensitisation potential of dinotefuran has been adequately tested.

A.3.5.2 Comparison with the CLP criteria

In an adjuvant type skin sensitisation study, a ≥ 30% response in tested animals is considered to be a positive result. As no adverse skin reactions were observed in any of the tested animals in the GPMT, the criteria for classification are note met.

A.3.5.3 Conclusion on classification and labelling for skin sensitisation

Dinotefuran does not fulfil the classification criteria for skin sensitisation.

A.3.5.4 Overall conclusion on skin sensitisation related to risk assessment

Not applicable for the CLH report

A.3.6 Respiratory sensitisation

Table A-52: Summary table of animal data on respiratory sensitisation

No animal data is available.

Table A-53: Summary table of human data on respiratory sensitisation

No human data is available.

Table A-54: Summary table of other studies relevant for respiratory sensitisation

No other studies are available.

A.3.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No data.

A.3.6.2 Comparison with the CLP criteria

No data.

A.3.6.3 Conclusion on classification and labelling for respiratory sensitisation

No data.

A.3.6.4 Overall conclusion on respiratory sensitisation related to risk assessment

Not applicable for the CLH report

A.3.7 Repeated dose toxicity/STOT RE

A.3.7.1 Short term repeated dose toxicity

A.3.7.1.1 Short-term oral toxicity

Table A-55: Summary table of oral short-term animal studies (usually 28-day studies)

<table>
<tr><th>Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study</th><th>Species, Strain, Sex, No/Group</th><th>Test substance (including purity), Vehicle, Dose levels, Duration of exposure</th><th>NOAEL, LOAEL</th><th>Results (all dose levels including severity and magnitude of all effects, including also target organs)</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr>
<td>OECD TG 407 (1995), equivalent to EU B.7, 4-week oral dietary administration, GLP, Reliability 1, Key study</td>
<td>Rat, [redacted]:CD® [SD]BR VAF/Plus®, males and females, 5 animals per sex per dose</td>
<td>Dinotefuran, 99.1% purity, no vehicle, 0, 5000, 25000, 50000 ppm administered continuously for 4 weeks</td>
<td>NOAEL 50000 ppm equivalent to 3720 and 4222 mg/kg bw/d, M/F respectively</td>
<td>Summary of bodyweight gain and food consumption
<table>
<tr><th>Sex</th><th>Dose level (ppm)</th><th>Overall group mean weight gain (g)</th><th>Group mean terminal body weight (g)</th><th>Overall mean food consumption (g/wk)</th></tr>
<tr><td>Male</td><td>0</td><td>177</td><td>404.0</td><td>193</td></tr>
<tr><td></td><td>5000</td><td>173</td><td>403.1</td><td>193</td></tr>
<tr><td></td><td>25000</td><td>139*</td><td>378.6</td><td>173</td></tr>
<tr><td></td><td>50000</td><td>94*</td><td>335.5*</td><td>159</td></tr>
<tr><td>Female</td><td>0</td><td>67</td><td>199.2</td><td>119</td></tr>
<tr><td></td><td>5000</td><td>53</td><td>197.6</td><td>120</td></tr>
<tr><td></td><td>25000</td><td>50</td><td>188.2</td><td>111</td></tr>
<tr><td></td><td>50000</td><td>34*</td><td>172.6</td><td>99</td></tr>
</table>
* p < 0.05; a statistical analysis not performed on overall group mean data

Treatment related effects on serum clinical chemistry - Week 5
<table>
<tr><th>Sex</th><th>Dose level (ppm)</th><th>Group mean serum glucose</th><th>Group mean serum cholesterol</th></tr>
</table>
</td>
<td>The applicant would have liked to review the NOAEL from 5000 ppm to 50000 ppm attributing the reduced BW gain at dose 25 000 and 50 000 to the unpalatability. (Report no. 15-LKC-10, Gale and Ishikawa,</td>
<td>Report no. CHW 6648-125, [redacted], 1997a IUCLID no. 8.9.5.1</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td></td><td>concentration (mg/dL)</td><td>concentration (mg/dL)</td></tr>
<tr><td>Male</td><td>0</td><td>118</td><td>56</td></tr>
<tr><td></td><td>5000</td><td>119</td><td>52</td></tr>
<tr><td></td><td>25000</td><td>111</td><td>70*</td></tr>
<tr><td></td><td>50000</td><td>101*</td><td>80*</td></tr>
<tr><td>Female</td><td>0</td><td>105</td><td>85</td></tr>
<tr><td></td><td>5000</td><td>105</td><td>70</td></tr>
<tr><td></td><td>25000</td><td>103</td><td>83</td></tr>
<tr><td></td><td>50000</td><td>100</td><td>86</td></tr>
</table>
* p < 0.05
No target organ toxicity was observed
</td>
<td>2022, IUCLID no. 8.13.6).

Since the unpalatability of Dinotefuran was proved at dose 20 000 & 50 000 ppm in the provided study (Report no. MCW0059,

Arrowsmith, 2015, IUCLID no. 8.13.6), BE eCA agrees to consider a NOAEL of 50 000.</td>
<td></td>
</tr>
<tr>
<td>OECD TG 407 (1995), equivalent to EU B.7, 4-week oral dietary administration,
GLP,
Reliability 1,
Key study</td>
<td>Mouse, [redacted]:CD1®(ICR)BR VAF/Plus®, males and females, 10 animals per sex per dose</td>
<td>Dinotefuran, 99.1% purity, no vehicle, 0, 5000, 25000, 50000 ppm administered continuously for 4 weeks</td>
<td>NOAEL 5000 ppm equivalent to 901 and 1043 mg/kg bw/d, M/F respectively</td>
<td>Treatment related effects on group mean body weight and overall weight gain
<table>
<tr><td rowspan="2">Week of study</td><td colspan="4">Males treated at (ppm):</td><td colspan="4">Females treated at (ppm):</td></tr>
<tr><td>0</td><td>5000</td><td>25000</td><td>50000</td><td>0</td><td>5000</td><td>25000</td><td>50000</td></tr>
<tr><td>1</td><td>30.7</td><td>32.1</td><td>32.6</td><td>32.8</td><td>25.5</td><td>26.1</td><td>26.5</td><td>26.0</td></tr>
<tr><td>2</td><td>33.1</td><td>33.7</td><td>32.9</td><td>30.9</td><td>27.0</td><td>27.5</td><td>27.0</td><td>24.9*</td></tr>
<tr><td>3</td><td>34.9</td><td>35.3</td><td>34.0</td><td>32.0*</td><td>28.4</td><td>29.0</td><td>27.9</td><td>26.0*</td></tr>
<tr><td>4</td><td>35.4</td><td>35.7</td><td>34.1</td><td>33.3</td><td>28.9</td><td>29.0</td><td>28.3</td><td>27.0</td></tr>
</table>
</td>
<td>The applicant would have liked to review the NOAEL from 5000 ppm to 50000 ppm attributing the reduced BW gain at dose 25 000 and 50</td>
<td>Report no. CHW 6648-124, [redacted], 1997b IUCLID no. 8.9.5.1</td>
</tr>
</table>

				5	36.2	37.0	35.4	33.6	29.4	30.4	28.6	27.8	000 to the unpalatability. (Report no. 15-LKC-10, Gale and Ishikawa, 2022, IUCLID no. 8.13.6). However, in this study there is no decrease of FC in the 2 highest doses; thus the BWG decrease cannot be imputable to the unpalatability. Therefore, BE eCA is the opinion that the NOAEL should remain 5000 ppm.	
				Over all gain (g)	5.5	4.9	2.8	0.8	3.9	4.3	2.1	1.8		

* p < 0.05

Treatment related serum clinical chemistry findings – week 5

Sex	Dose level (ppm)	Mean serum total protein ± SD (g/dL)	Mean serum albumin ± SD (g/dL)
Male	0	4.7 ± 0.23	3.2 ± 0.13
	5000	4.8 ± 0.26	3.2 ± 0.30
	25000	5.0 ± 0.25	3.3 ± 0.18
	50000	5.1* ± 0.18	3.6* ± 0.23
Female	0	4.8 ± 0.15	3.5 ± 0.13
	5000	5.0 ± 0.22	3.4 ± 0.26
	25000	5.1 ± 0.14	3.7 ± 0.09
	50000	4.9 ± 0.20	3.5 ± 0.13

* p < 0.05

No target organ toxicity was observed

OPPTS 870.4100, 7-day oral capsule administrati	Dog, Marshall beagle, males and females, one animal per sex per dose	Dinotefuran, 99.1% purity, no vehicle, 0, 30, 100,	NOAEL 100 mg/kg bw/d	Selected absolute and relative organ weights					None	Report no. H-97326 , [redacted],

Organ weight	Treatment rate (mg/kg bw/day):			
	0	30	100	300
Testes (g) (males)	6.869	4.325	5.289	3.290

<table>
<tr>
<td>on,
Not GLP,
Reliability 2,
Supportive study</td>
<td></td>
<td>300 mg/kg bw/d, administered daily for 7 days</td>
<td></td>
<td>
<table>
<tr><td>Testes (g/10kg bw) (males)</td><td>6.604</td><td>4.081</td><td>5.086</td><td>3.163</td></tr>
<tr><td>Prostate (g) (males)</td><td>2.999</td><td>2.053</td><td>1.333</td><td>1.795</td></tr>
<tr><td>Prostate (g/10kg bw) (males)</td><td>2.884</td><td>1.937</td><td>1.282</td><td>1.726</td></tr>
<tr><td>Uterus (g) (females)</td><td>0.894</td><td>0.788</td><td>1.238</td><td>0.488</td></tr>
<tr><td>Uterus (g/10kg bw) (females)</td><td>1.118</td><td>1.037</td><td>1.290</td><td>0.567</td></tr>
</table>
Diarrhoea and/or vomiting were observed 300 mg/kg bw/day. Fluctuations in the weight of both male and female genital organs were considered attributable to sexual immaturity of the subjects.
No target organ toxicity was observed
</td>
<td></td>
<td>1998a IUCLID no. 8.9.5.1</td>
</tr>
<tr>
<td>OPPTS 870.4100, 7-day oral dietary administration,
Not GLP,
Reliability 2,
Supportive study</td>
<td>Dog, beagle, males and females, one animal per sex per dose</td>
<td>Dinotefuran, 99.1% purity, no vehicle, 0, 1250, 5000, 20000, 30000, 40000 ppm, administered continuously for 7 days</td>
<td>NOAEL 770 and 924 mg/kg bw/d, M/F respectively</td>
<td>
Body weights and overall mean food consumption
<table>
<tr><td rowspan="2">Body weight (kg)</td><td colspan="4">Males treated at (ppm):</td><td colspan="4">Females treated at (ppm):</td></tr>
<tr><td>0/ 40000</td><td>1250/ 30000</td><td>5000</td><td>20000</td><td>0/ 40000</td><td>1250/ 30000</td><td>5000</td><td>20000</td></tr>
<tr><td>- day 0</td><td>9.2</td><td>9.0</td><td>9.6</td><td>9.4</td><td>8.8</td><td>8.4</td><td>9.2</td><td>8.6</td></tr>
<tr><td>- day 2</td><td>9.2</td><td>9.0</td><td>9.8</td><td>9.4</td><td>9.0</td><td>8.4</td><td>9.4</td><td>8.6</td></tr>
<tr><td>- day 4</td><td>9.4</td><td>9.0</td><td>10.0</td><td>9.8</td><td>9.2</td><td>8.4</td><td>9.4</td><td>8.8</td></tr>
<tr><td>- day 7</td><td>9.0</td><td>8.8</td><td>10.0</td><td>9.8</td><td>9.0</td><td>8.6</td><td>9.4</td><td>8.4</td></tr>
<tr><td>- day 10</td><td>9.4</td><td>9.0</td><td>-</td><td>-</td><td>9.0</td><td>8.6</td><td>-</td><td>-</td></tr>
<tr><td>- day 14</td><td>8.8</td><td>9.0</td><td>-</td><td>-</td><td>8.8</td><td>8.2</td><td>-</td><td>-</td></tr>
<tr><td>Food consumption (g/d):
- week 1
- week 2</td><td>400
181</td><td>357
257</td><td>400
-</td><td>400
-</td><td>339
208</td><td>400
231</td><td>400
-</td><td>265
-</td></tr>
</table>
</td>
<td>None</td>
<td>Report no. H 97327, [redacted], 1998b IUCLID no. 8.9.5.1</td>
</tr>
</table>

Table A-56: Summary table of human data on short-term oral toxicity

No human data is available.

A.3.7.1.2 Short-term dermal toxicity

Table A-57: Summary table of dermal short-term animal studies (usually 28-day studies)

<table>
<tr><th>Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study</th><th>Species, Strain, Sex, No/Group</th><th>Test substance (including purity), Vehicle, Dose levels, Surface area, Duration of exposure</th><th>NOAEL, LOAEL</th><th>Results (all dose levels including severity and magnitude of all effects, including target organs)</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr><td>OECD TG 410 (1981), equivalent to EU B.9, OPPTS 870.3200 (1998), 4-week dermal toxicity, GLP, Reliability 1, Key study</td><td>Rat, [redacted]:CD®(SD)IGS BR, males and females, 10 animals per sex per dose</td><td>Dinotefuran, 98.9% purity, no vehicle, 0, 40, 200, 1000 mg/kg bw/d administered daily for 6-7 hours per day for 4 weeks</td><td>NOAEL >1000 mg/kg bw/d, M/F</td><td>Incidence of selected histopathological alterations
<table>
<tr><th rowspan="3">Organ: finding</th><th colspan="8">Incidence of lesion in:</th></tr>
<tr><th colspan="4">Males treated at (mg/kg bw/day):</th><th colspan="4">Females treated at (mg/kg bw/day):</th></tr>
<tr><th>0</th><th>40</th><th>200</th><th>1000</th><th>0</th><th>40</th><th>200</th><th>1000</th></tr>
<tr><td>Treated skin:</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>- no. examined</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>- inflammation</td><td>2</td><td>0</td><td>0</td><td>2</td><td>3</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>-acanthosis/ hyperkeratosis</td><td>1</td><td>1</td><td>0</td><td>10</td><td>2</td><td>0</td><td>0</td><td>8</td></tr>
<tr><td>Untreated skin:</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>- no. examined</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>- inflammation</td><td>8</td><td>0</td><td>0</td><td>4</td><td>8</td><td>0</td><td>1</td><td>7</td></tr>
<tr><td>- fibrosis</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>- ulceration</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>- acanthosis/ hyperkeratosis</td><td>0</td><td></td><td></td><td></td><td>1</td><td></td><td></td><td></td></tr>
</table>
No target organ toxicity was observed</td><td>None</td><td>Report no. 6648-149, [redacted], 2001b IUCLID no. 8.9.5.3</td></tr>
</table>

Table A-58: Summary table of human data on short-term dermal toxicity

No human data is available.

A.3.7.1.3 Short-term inhalation toxicity

Table A-59: Summary table of inhalation short-term animal studies (usually 28-day studies)

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Form (gas, vapour, dust, mist) and particle size (MMAD), Actual and nominal concentration, Type of administration (nose only / whole body/ head only), Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
OECD TG 412, equivalent to EU B.8, OPPTS 870.3465, JMAFF 59 Nohsan 4200 4-week inhalation toxicity, GLP, Reliability 1, Key study	Rat, [redacted]:WI(Glx/BRL/Han)BR, males and females, 10 animals per sex per dose	Dinotefuran, 99.1% purity, air used as vehicle, 0, 0.22, 0.66, 2.08 mg/L air administered daily for 6 hours per day for 29 or 30 days	For males: LOAEC of 0.22 mg/L For females : NOAEC is 2.08 mg/L	**0.22 mg/L:** ↓ bodyweight gain (M 36 %) & food cons (M 6 %) week 1 only **0.66 mg/L:** ↓ bodyweight gain (M 40 %) & food cons (M 5 %) week 1 only **2.08 mg/L:** ↓ bodyweight gain	The applicant proposed to not consider the LOAEL of 0.22 mg/L for males and to set a NOAEC at 2.08 mg/L for both sexes. Since this value was already discussed in WG and since there is	Report no. 719/16, [redacted], 2002 IUCLID no. 8.9.5.2

				(M 46 %) & food cons (M 11 %) week 1 only	no new data, eCA decided to refuse this proposal.	

Table A-60: Summary table of human data on short-term inhalation toxicity

No human data is available.

A.3.7.1.4 Overall conclusion on short-term repeated dose toxicity related risk assessment

Not applicable for the CLH report

A.3.7.2 Sub-chronic repeated dose toxicity

A.3.7.2.1 Sub-chronic oral toxicity

Table A-61: Summary table of oral sub-chronic animal studies (usually 90-day studies)

<table>
<tr><th>Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study</th><th>Species, Strain, Sex, No/Group</th><th>Test substance (including purity), Vehicle, Dose levels, Duration of exposure</th><th>NOAEL, LOAEL</th><th>Results (all dose levels including severity and magnitude of all effects, including also target organs)</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr>
<td>OECD TG 408 (1981), equivalent to EU B.26, EPA 82-1, Japan MAFF (1985), 13-week oral dietary administration, GLP, Reliability 1, Key study</td>
<td>Rat, [redacted]:CD® [SD]BR VAF/Plus® males and females, 10 animals per sex per dose</td>
<td>Dinotefuran, 99.1% purity, no vehicle, 0, 500, 5000, 25000, 50000 ppm administered continuously for 90 days</td>
<td>NOAEL 50000 ppm equivalent to 3156 mg/kg bw/d for males and 3616 mg/kg bw/d for females</td>
<td>Summary of body weight gain and food consumption
<table>
<tr><th>Sex</th><th>Dose level (ppm)</th><th>Overall group mean weight gain (g)</th><th>Group mean terminal body weight (g)</th><th>Overall mean food consumption (g/wk)a</th></tr>
<tr><td>Male</td><td>0</td><td>315</td><td>531</td><td>208</td></tr>
<tr><td></td><td>500</td><td>316</td><td>528</td><td>204</td></tr>
<tr><td></td><td>5000</td><td>295</td><td>512</td><td>201</td></tr>
<tr><td></td><td>25000</td><td>257*</td><td>478*</td><td>184</td></tr>
<tr><td></td><td>50000</td><td>190*</td><td>412*</td><td>157</td></tr>
<tr><td>Female</td><td>0</td><td>141</td><td>314</td><td>160</td></tr>
<tr><td></td><td>500</td><td>131</td><td>298</td><td>146</td></tr>
<tr><td></td><td>5000</td><td>118*</td><td>290*</td><td>146</td></tr>
<tr><td></td><td>25000</td><td>96*</td><td>263*</td><td>131</td></tr>
<tr><td></td><td>50000</td><td>67*</td><td>238*</td><td>121</td></tr>
</table>
* p < 0.05; a statistical analysis not performed on overall group mean data</td>
<td>The NOAEL has been reviewed from 500 ppm to 50 000 ppm attributing the reduced BW gain at dose 5000, 25 000 & 50 000 to the unpalatability (Report no. 15-LKC-10, Gale and Ishikawa, 2022, IUCLID no. 8.13.6).</td>
<td>Report no. CHW 6648-127, [redacted], 1997c IUCLID no. 8.9.5.1

Amendment 1, [redacted], 2000a</td>
</tr>
</table>

Treatment related effects on hematology and serum chemistry – week 14

Sex	Dose level (ppm)	Group mean hematology and serum chemistry values: APTT (sec)	UN (mg/dL)	Glu (mg/dL)	Prot (g/dL)	Glob (g/dL)
Male	0	14.4	14	102	7.9	3.1
	500	13.8	13	111	7.7	2.9
	5000	14.8	14	104	7.8	2.9
	25000	13.7	15	98	7.6	2.8
	50000	13.1*	17*	85*	7.5*	2.7*
Female	0	13.2	16	102	8.3	2.6
	500	12.6	16	107	8.3	2.7
	5000	12.8	15	105	8.2	2.5
	25000	12.6	16	98	8.1	2.6
	50000	12.2	19	104	8.0	2.7

Treatment related histopathological alterations in the adrenal cortex

Sex	Dose level (ppm)	Incidence (%) of increased vacuolation in zona glomerulosa	Incidence (%) of increased vacuolation in zona fasciculata
Male	0	0	10
	500	0	0
	5000	30	20
	25000	20	30
	50000	40	50
Female	0	0	0
	500	0	0
	5000	0	0
	25000	60	0
	50000	100	0

No target organs were identified

More information below this table.

OECD TG 408 (1981), EU B.26, EPA 82-1, JMAFF 59 Nohsan 4200 (1985), 13-week oral dietary administration, GLP, Reliability 1, Key study

Mouse, [redacted]:CD1 ® (ICR)BR VAF/Plus® males and females, 10 animals per sex per dose

Dinotefuran, 99.1% purity, no vehicle, 0, 500, 5000, 25000, 50000 ppm administered continuously for 90 days

NOAEL 25000 ppm equivalent to 4442 and 5414 mg/kg bw/d, M/F respectively

Animal assignment and treatment

Group number	Dose level of dinotefuran (ppm)	Number of animals	
		Male	Female
1	0	10	10
2	500	10	10
3	5000	10	10
4	25000	10	10
5	50000	10	10

Summary of body weights, weight gains and food consumption

Interval	Males treated at (ppm):					Females treated at (ppm):				
	0	500	5000	25000	50000	0	500	5000	25000	50000
Group mean body weight (g)										
Week 1	31.0	31.6	30.2	30.1	31.1	26.0	26.1	25.3	26.1	25.6
Week 2	32.7	33.2	32.0	31.2	30.2	27.3	27.2	26.5	26.8	24.0
Week 3	34.4	35.0	33.7	32.9	30.4*	28.9	28.5	27.6	28.0	24.7*
Week 4	34.6	34.9	34.2	32.8	30.9*	29.1	28.5	27.8	28.1	25.1*
Week 8	37.9	38.1	37.0	36.1	33.2*	31.5	30.7	30.0	30.2	26.6*
Week 14	41.7	41.9	40.3	39.1	35.3*	36.5	34.1	32.5*	33.3	28.5*
Overall gain	10.7	10.3	10.1	9.0	4.2*	10.5	8.0	7.2	7.2	2.9*
Group mean food consumption (g/week)**										
Weeks 1 - 4	45.1	43.6	43.6	43.7	49.6	41.4	43.2	43.6	44.5	46.1
Weeks 5 - 8	45.6	44.4	45.1	45.8	51.4	45.0	46.1	45.1	45.9	42.3
Weeks 9 - 13	40.5	40.4	40.2	41.7	45.3	42.6	42.1	42.6	43.7	41.9

* $p < 0.05$
** food consumption of animals not showing substantial food spillage

Treatment related serum and urine clinical chemistry findings –

None

Report no. CHW 6648-126, [redacted], 1997d IUCLID no. 8.9.5.1

Amendment 1, [redacted], 2000b

week 14

Sex	Dose level (ppm)	Mean serum albumin concentration ± SD (g/dL)	Mean urine pH (range)
Male	0	2.9 ± 0.14	7.3 (6.5 - 8.5)
	500	3.1 ± 0.31	7.5 (7.0 - 8.0)
	5000	3.2 ± 0.21	7.5 (7.0 - 8.0)
	25000	3.3 ± 0.18	7.6 (7.0 - 8.5)
	50000	3.4 ± 0.26*	6.9 (6.0 - 8.0)
Female	0	3.4 ± 0.09	7.2 (6.5 - 8.0)
	500	3.4 ± 0.25	7.2 (6.5 - 7.5)
	5000	3.4 ± 0.11	7.2 (6.5 - 8.0)
	25000	3.5 ± 0.38	6.8 (6.5 - 7.5)
	50000	3.6 ± 0.29	6.6* (6.0 - 7.0)

* $p < 0.05$

No target organs were identified

OECD TG 409 (1981), EPA OPP 82-1, JMAFF 59 NohSan no. 4200 (1985), 13-week oral dietary administration, GLP, Reliability 1, Key study

Dog, Beagle, males and females, 4 animals per sex per dose

Dinotefuran, 98.9% purity, no vehicle, 0, 1600, 8000, 24000 ppm administered continuously for 90 days

NOAEL 8000 ppm equivalent to 307 and 323 mg/kg bw/d, M/F respectively

Animal assignment and treatment

Group number	Dose level of dinotefuran (ppm)	Number of animals	
		Male	Female
1	0	4	4
2	1600	4	4
3	8000	4	4
4	24000*	4	4

* Group 4 animals were offered the diet containing 40000 ppm on day 1 through 4; because animals did not readily consume the diet containing 40000 ppm, the high dose was lowered to 30000 ppm on day 5. The animals were offered the diet containing 30000 ppm on day 5 through 11. On day 12, the dose level was again lowered to 24000 ppm because the animals did not readily consume the diet containing 30000 ppm.

Selected group mean body weight data

Sex / dose level (ppm)	Mean body weight (kg) at week:					
	1	2	3	4	8	14
Males:						
0	8.1	8.9	9.5	9.9	10.8	11.7
1600	8.0	9.1	9.4	9.9	11.0	11.8

None

Report no. CHW 6648-128, [redacted], 1999a IUCLID no. 8.9.5.1

Amendment 1, [redacted], 1999b

8000	8.2	8.9	9.2	9.6	10.6	11.5				
24000	8.3	7.9*	8.6*	9.1*	10.0*	10.7*				
Females:										
0	7.1	7.9	8.3	8.7	9.8	10.6				
1600	7.0	7.7	8.0	8.2*	8.8*	9.3*				
8000	7.2	7.8	8.2	8.4	9.0*	9.6*				
24000	7.0	6.8*	7.3*	7.8*	8.6*	9.4*				

* p < 0.05

Representative group mean food and water consumption data

Sex	Dose level (ppm)	Mean food consumption (g/week) in week:				
		1	2	4	8	13
Male	0	2951	2919	2875	2958	2990
	1600	2913	2671	2645	2528	2722
	8000	2555	2603	2686	2708	2896
	24000	1394*	2381	2570	2391*	2411*
Female	0	2712	2863	2773	2722	2657
	1600	2406	2311*	2212*	2203*	2102*
	8000	2588	2557	2392*	2350	2631
	24000	869*	2240*	2295*	2207*	2402
		Mean water consumption (g/week) on day:				
		2	10	24	52	86
Male	0	915	1455	1423	1550	1505
	1600	780	958*	1090	980*	1095
	8000	743	1260	1295	1270	1313
	24000	138*	798*	1165	963*	1000*
Female	0	573	1030	945	977	980
	1600	503	903	790	658	833
	8000	390	818	735	683	747
	24000	38*	748	1035	940	1103

* p < 0.05

Treatment related serum clinical chemistry findings

Sex dose level (ppm)	Mean serum ALT activity (IU/L) ± SD in:			Mean urine pH (range) in:		
	Week -1	Week 5	Week 14	Week -1	Week 5	Week 14
Males:						

				0	25 ± 2.9	27 ± 3.3	32 ± 1.0	7.0 (7.0 - 7.0)	8.1 (7.5-8.5)	7.9 (7.0-8.5)	
				1600	30 ± 7.3	24 ± 0.5	27 ± 1.9	6.9 (6.5 - 7.5)	7.5 (6.5-8.5)	7.6 (7.5-8.0)	
				8000	28 ± 5.1	22 ± 6.8	27 ± 4.8	6.9 (6.5 - 7.0)	6.8 (6.0-7.5)	7.8 (7.0-8.5)	
				24000	29 ± 5.5	18* ± 1.6	19* ± 4.3	7.0 (6.5 - 7.5)	6.5 (6.0-7.0)	6.8 (6.0-7.5)	
				Females:							
				0	32 ± 7.7	26 ± 3.5	29 ± 6.7	6.8 (6.5 - 7.5)	6.9 (6.5-7.0)	6.6 (6.5-7.0)	
				1600	28 ± 4.8	27 ± 3.8	26 ± 3.6	7.1 (6.0 - 7.5)	6.8 (6.5-7.0)	7.3 (6.5-8.0)	
				8000	26 ± 5.9	24 ± 5.4	22 ± 4.4	7.1 (7.0 - 7.5)	6.5 (6.0-7.0)	7.1 (7.0-7.5)	
				24000	25 ± 2.6	14* ± 1.5	20* ± 2.1	6.6 (6.5 - 7.0)	6.5 (6.0-7.0)	6.6 (6.0-7.0)	
				* $p < 0.05$ No target organs were identified							

Table A-62: Summary table of human data on sub-chronic oral toxicity

No human data is available.

Setting of the NOAEL for the 13-week oral dietary administration in rat ([redacted], 1997)

The vacuolation of the adrenal cortex comprised slightly increased cytoplasmic vacuolation, which within the context of this study, was considered by the authors as non-adverse since there were no correlating clinical pathology findings indicating functional deficit. There was no increase in adrenal weight.
According to scientific literature, effects on the adrenal gland can arise as a secondary effect of stress rather than as a direct effect. In this 13-week study the stress related response is probably due to the food consumption and body weight gain differences.

Moreover, there was no indication of an effect on the adrenal in other toxicological studies in the rat (4-week oral study, 4-week inhalation study, or in the two-year, long term rat oral study). Also, there was no effect in the mouse (13-week and long term) or dog (13-week and 52-week) oral studies.

Since there is no other change in adrenal gland, a possible stress is identified and no indication in other studies, the vacuolation of the adrenal cortex is considered as non-adverse.

Although the unpalatability of Dinotefuran was not proved at dose 5 000 ppm in [redacted] report (IUCLID no. 8.13.6), since the BWG decrease at 25 000 & 50 000 ppm is linked to the unpalatability of the AS, and that there is no adverse effects, the BWG decrease in females at dose 5000 can also be imputable to this unpalatability.

A.3.7.2.2 Sub-chronic dermal toxicity

Table A-63: Summary table of dermal sub-chronic animal studies (usually 90-day studies)

No animal data is available.

Table A-64: Summary table of human data on sub-chronic dermal toxicity

No human data is available.

A.3.7.2.3 Sub-chronic inhalation toxicity

Table A-65: Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)

No animal data is available.

Table A-66: Summary table of human data on sub-chronic inhalation toxicity

No human data is available.

A.3.7.2.4 Overall conclusion on sub-chronic repeated dose toxicity related risk assessment

Not applicable for the CLH report

A.3.7.3 Long-term repeated dose toxicity

A.3.7.3.1 Long-term oral toxicity

Table A-67: Summary table of oral long-term animal studies

<table>
<tr><th>Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study</th><th>Species, Strain, Sex, No/Group</th><th>Test substance (including purity), Vehicle, Dose levels, Duration of exposure</th><th>NOAEL, LOAEL</th><th>Results (all dose levels including severity and magnitude of all effects, including target organs)</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr>
<td>OECD TG 452, EPA OPP 83-1, JMAFF 59 NohSan no. 4200 (1985), 52-week oral dietary administration, GLP, Reliability 1, Key study</td>
<td>Dog, Beagle, males and females, 4 animals per sex per dose</td>
<td>Dinotefuran, 98.9% purity, no vehicle, 0, 640, 3200, 16000 ppm administered continuously for 90 days</td>
<td>NOAEL 16000 ppm equivalent to 559 and 512 mg/kg bw/d, M/F respectively</td>
<td>Treatment related effects on body weight gain and food consumption
<table>
<tr><th rowspan="2">Treatment

(ppm)</th><th colspan="5">Group mean body weight (kg) in week:</th><th rowspan="2">Overall weight gain (kg)</th><th rowspan="2">Mean food

intake (g/d)</th></tr>
<tr><th>1</th><th>14</th><th>28</th><th>40</th><th>52</th></tr>
<tr><td>Males:
0</td><td>8.7</td><td>11.4</td><td>11.6</td><td>11.7</td><td>11.7</td><td>3.0</td><td>349</td></tr>
<tr><td>640</td><td>8.7</td><td>11.4</td><td>11.7</td><td>11.9</td><td>11.6</td><td>2.9</td><td>330</td></tr>
<tr><td>3200</td><td>8.9</td><td>11.1</td><td>11.5</td><td>12.1</td><td>11.9</td><td>3.0</td><td>368</td></tr>
<tr><td>16000</td><td>8.5</td><td>10.9</td><td>10.7</td><td>11.1</td><td>10.6</td><td>2.1</td><td>363</td></tr>
<tr><td>Females:
0</td><td>8.0</td><td>10.8</td><td>11.3</td><td>12.0</td><td>11.5</td><td>3.5</td><td>350</td></tr>
<tr><td>640</td><td>7.9</td><td>10.2</td><td>10.6</td><td>11.1</td><td>11.4</td><td>3.6</td><td>348</td></tr>
</table>
</td>
<td>The applicant would have liked to review the NOAEL from 640 ppm to 16000 ppm attributing the reduced BW gain at dose 3200 & 16 000 ppm to the unpalatability. (Report no. 15-LKC-10, Gale and Ishikawa, 2022,</td>
<td>Report no. 6648-129, [redacted] 1999c IUCLID no. 8.9.5.1</td>
</tr>
</table>

				3200 16000	7.9 7.9	9.9 * 9.7 *	10.3 10.2	10.4 * 10.2 *	10.1 * 10.2 *	2.3* 2.3*	322 307	IUCLID no. 8.13.6). However the unpalatability of Dinotefuran was only proved at dose 20 000 & 50 000 ppm in the provided study (Report no. MCW0059, Arrowsmith, 2015, IUCLID no. 8.13.6). Therefore, eCA agrees that at dose 16000, the BWG decrease is due do the unpalatability of Dinotefuran. Since there is no adverse effect at this dose, the BWG at dose 3200 is most	

* p < 0.05
No target organs were identified

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>likely also due to the unpalatability of the AS, even if it was not proved.

Moreover, in the conclusion of this study, the NOAEL was set at 16 000 ppm because BWG decrease was not consider as adverse effect.

To conclude, eCA agrees to change the NOAEL from 640 ppm to 16 000 ppm.</td>
<td></td>
</tr>
<tr>
<td>Chronic toxicity and carcinogenicity, OECD TG 453 (1981), EPA OPP 83-2, JMAFF 59 NohSan no. 4200 (1985), 104-week oral dietary</td>
<td>Rat, [redacted]:CD®(SD)BR VAF/Plus®, males and females, 100 animals per sex per dose (control and high dose), 90 animals per sex per dose for other doses, 10</td>
<td>Dinotefuran, 98.9% purity, no vehicle, 0, 60, 200, 2000, 20000 ppm administered continuous</td>
<td>NOAEL 20000 ppm equivalent to 991 and 1332 mg/kg bw/d, M/F respectively</td>
<td>Treatment related effects on body weight, body weight gain and food consumption
<table>
<tr><td rowspan="3">Week of study</td><td colspan="10">Group mean body weight (g) of:</td></tr>
<tr><td colspan="5">Males treated at (ppm):</td><td colspan="5">Females treated at (ppm):</td></tr>
<tr><td>0</td><td>60</td><td>200</td><td>2000</td><td>20000</td><td>0</td><td>60</td><td>200</td><td>2000</td><td>20000</td></tr>
<tr><td>1</td><td>228</td><td>232</td><td>229</td><td>231</td><td>228</td><td>178</td><td>177</td><td>174</td><td>175</td><td>176</td></tr>
<tr><td>26</td><td>685</td><td>694</td><td>692</td><td>702</td><td>638*</td><td>344</td><td>352</td><td>362*</td><td>350</td><td>314*</td></tr>
<tr><td>50</td><td>794</td><td>802</td><td>815</td><td>822</td><td>722*</td><td>411</td><td>418</td><td>439*</td><td>418</td><td>347*</td></tr>
<tr><td>78</td><td>836</td><td>841</td><td>865</td><td>867</td><td>777*</td><td>482</td><td>490</td><td>529*</td><td>497</td><td>377*</td></tr>
</table></td>
<td>The applicant would have liked to review the NOAEL from 2000 ppm to 20000 ppm attributing the</td>
<td>Report no. 6648-131, [redacted], 2000c IUCLID no. 8.9.5.1</td>
</tr>
</table>

<table>
<tr>
<td>administration, GLP, Reliability 1, Key study</td>
<td>animals per sex per dose were sacrificed after 26, 52, 78 weeks</td>
<td>ly for 104 weeks Intake 0, 3/4, 10/13, 100/127, 991/1332 mg/kg/day (M/F)</td>
<td></td>
<td>
<table>
<tr><td>105</td><td>758</td><td>792</td><td>808</td><td>800</td><td>729</td><td>553</td><td>608</td><td>565</td><td>545</td><td>417*</td></tr>
<tr><td>Weight gain (week 1 - 104)</td><td>531</td><td>565</td><td>585</td><td>574</td><td>504</td><td>376</td><td>433</td><td>395</td><td>370</td><td>242*</td></tr>
<tr><td rowspan="3">Interval (weeks)</td><td colspan="10">Group mean food consumption (g/week) of:</td></tr>
<tr><td colspan="5">Males treated at (ppm):</td><td colspan="5">Females treated at (ppm):</td></tr>
<tr><td>0</td><td>60</td><td>200</td><td>2000</td><td>20000</td><td>0</td><td>60</td><td>200</td><td>2000</td><td>20000</td></tr>
<tr><td>1 - 25</td><td>201.3</td><td>197.7</td><td>199.1</td><td>198.1</td><td>182.4[a]</td><td>141.9</td><td>210.8</td><td>139.6</td><td>138.0</td><td>128.9[a]</td></tr>
<tr><td>29 - 49</td><td>202.8</td><td>201.3</td><td>203.5</td><td>209.5</td><td>186.7[a]</td><td>152.7</td><td>151.5</td><td>156.2</td><td>153.7</td><td>143.3[a]</td></tr>
<tr><td>53 - 77</td><td>205.9</td><td>202.7</td><td>207.1</td><td>209.4</td><td>193.7[a]</td><td>164.4</td><td>166.3</td><td>165.6</td><td>168.3</td><td>148.0[a]</td></tr>
<tr><td>81 - 101</td><td>192.7</td><td>199.8</td><td>196.0</td><td>195.2</td><td>186.0</td><td>162.7</td><td>169.2</td><td>160.3</td><td>167.5</td><td>150.5</td></tr>
</table>
* p < 0.05;
[a] p < 0.05 for most weekly values
</td>
<td>reduced BW gain at dose 20 000 to the unpalatability. (Report no. 15-LKC-10, Gale and Ishikawa, 2022, IUCLID no. 8.13.6).

Since the unpalatability of Dinotefuran was proved at dose 20 000 & 50 000 ppm in the provided study (Report no. MCW0059,

Arrowsmith, 2015, IUCLID no. 8.13.6), BE eCA agrees to consider a NOAEL of 20 000 ppm.</td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity, OECD TG 451 (1981), EPA OPP 83-2, JMAFF 59 NohSan no.</td>
<td>Mouse, [redacted]:CD-1®(ICR)BR VAF/Plus®, males and females, 70</td>
<td>Dinotefuran, 98.9% purity, no vehicle, 0, 25, 250, 2500,</td>
<td>NOEL 2500 ppm equivalent to 345 and 441 mg/kg</td>
<td>Treatment related effects in life
<table>
<tr><td rowspan="2">Parameter</td><td colspan="5">Males treated at (ppm):</td><td colspan="5">Females treated at (ppm):</td></tr>
<tr><td>0</td><td>25</td><td>250</td><td>2500</td><td>25000</td><td>0</td><td>25</td><td>250</td><td>2500</td><td>25000</td></tr>
</table>
</td>
<td>None</td>
<td>Report no. 6648-130, [redacted], 2000d</td>
</tr>
</table>

<table>
<tr>
<td>4200 (1985), 78-week oral dietary administration, GLP, Reliability 1, Key study</td>
<td>animals per sex per dose, 10 animals per sex per dose were sacrificed after 52 weeks</td>
<td>25000 ppm administered continuously 78 weeks exposure
Intake 0, 0, 3/4, 34/45, 345/441, 3694/4728 mg/kg/day (M/F)</td>
<td>bw/d, M/F respectively</td>
<td>
<table>
<tr><td>Mean BW gain (g)[a]</td><td>13.4</td><td>14.6</td><td>13.5</td><td>12.6</td><td>11.0*</td><td>13.9</td><td>14.8</td><td>13.4</td><td>13.6</td><td>10.4*</td></tr>
<tr><td>Plt ($10^3/\mu L$)[b] - week 53</td><td>1125</td><td>1138</td><td>1241</td><td>1329</td><td>1147</td><td>1028</td><td>1139</td><td>988</td><td>1063</td><td>1035</td></tr>
<tr><td>Plt ($10^3/\mu L$)[b] - week 79</td><td>1405</td><td>1309</td><td>1545</td><td>1245</td><td>1125*</td><td>1038</td><td>1011</td><td>1021</td><td>966</td><td>857</td></tr>
</table>
[a] Group mean body weight gain weeks 1 - 78;
[b] Group mean platelet count;
* $p < 0.05$
</td>
<td></td>
<td>IUCLID no. 8.9.5.1</td>
</tr>
</table>

Table A-68: Summary table of human data on long-term oral toxicity

No human data is available.

A.3.7.3.2 Long-term dermal toxicity

Table A-69: Summary table of dermal long-term animal studies

No animal data is available.

Table A-70: Summary table of human data on long-term dermal toxicity

No human data is available.

A.3.7.3.3 Long-term inhalation toxicity

Table A-71: Summary table of inhalation long-term animal studies

No animal data is available.

Table A-72: Summary table of human data on long-term inhalation toxicity

No human data is available.

A.3.7.3.4 Overall conclusion on long-term repeated dose toxicity related risk assessment

Not applicable for the CLH report

A.3.7.4 Specific target organ toxicity – repeated exposure (STOT RE)

A.3.7.4.1 Short summary and overall relevance of the provided information on STOT RE

The repeated dose toxicity of dinotefuran has been thoroughly investigated in a series of standard studies. By the oral route, sub-acute studies in rats and mice, sub-chronic studies in rats, mice and dogs and chronic studies in rats and mice are available. Additionally, a sub-acute inhalation study in rats and a sub-acute dermal study in rats are available.

ORAL SUBACUTE

In a standard 28 day oral dietary study in Sprague-Dawley rats, dietary levels 0, 5000, 25000 and

50000 ppm were administered ([redacted], 1997c). There were no treatment related mortalities or clinical signs. Bodyweight gain and food consumption were reduced in a dose related manner in both sexes at 25000 and 50000 ppm. These changes were accompanied minor clinical chemistry changes which may have been secondary to the reduced bodyweight gain, namely increased serum cholesterol at 2500 and 50000 ppm and reduced serum glucose at 50000 ppm. There were no treatment related haematology, ophthalmoscopy, urinalysis, organ weight, macroscopic pathology or histopathology findings or macroscopic pathology findings.

Since diet concentrations of 20000 and 50000 ppm in the pair-feeding/palatability investigative study elicited a decrease of 10 and 38/29%, respectively, in overall mean food consumption due to unpalatability, and because mean food consumption at 25000 ppm in the 4-week oral study was reduced by 7 – 11% and by 17% at 50000 ppm, reduced food consumption is considered not to be an expression of non-specific toxicity. Similarly, because reduced body weight gain in the investigative study ([redacted], 2015) was shown to be due entirely to reduced food consumption, reduced body weight gain in the 4-week study can also be ascribed to reduced food consumption alone because the effect at 50000 ppm was less than that seen in the investigative study, and the effect at 25000 ppm was comparable to the effect at 20000 ppm in the investigative study. Moreover, other than during week 1 when food consumption was very low, there was no effect on food conversion efficiency at 50000 ppm. On this basis and in the absence of evidence for functional or anatomical organ toxicity at all dose levels, the NOAEL for the 4-week study should be set at 50000 ppm (3720 / 4222 mg/kg bw/day, M/F).

Supplementary information on repeated dose subacute toxicity in rats is available from a dietary immunotoxicity study, summarised in Section 3.10 ([redacted], 2012). Dietary dose levels 0, 2240, 5600, 14000 ppm were administered for 28 days. A study NOAEL of 5600 ppm (intake 425 mg/kg bw/day in males and 430 mg/kg bw/day in females) for general toxicity was identified, based on the observation of reduced bodyweight gain and food consumption at 14000 ppm.

In a standard 28 day oral dietary study in CD-1 mice, dietary levels of 0, 5000, 25000 and 50000 ppm were administered ([redacted], 1997b). There were no treatment related mortalities or clinical signs. Bodyweight gain was markedly reduced at 25000 and 50000 ppm in both sexes. Excessive food spillage in the 25000 and 50000 ppm groups precluded the measurement of food consumption in these groups, providing evidence that the palatability of the test diets may have been reduced. There was no effect on food consumption at 5000 ppm. The only clinical chemistry difference considered to be treatment related was increased serum protein and albumin concentrations in males at 50000 ppm. There were no treatment related haematology, organ weight, macroscopic pathology or histopathology findings.
On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 28-day study should be set at 50000 ppm for both sexes (10303 / 12289 mg/kg bw/day, M/F).

The developmental toxicity investigations in the rat and rabbit summarised in Section 3.8.1 provide some information on the subacute oral toxicity of dinotefuran following gavage administration. In rats (dose levels 0, 100, 300, 1000 mg/kg bw/day, gd 6-15), dinotefuran elicited maternal toxicity only at 1000 mg/kg/day, observed as reduced bodyweight gain and food consumption during the early part of the dosing period and increased water consumption towards the end of the dosing period. The effects on bodyweight and food consumption are consistent with the findings in the oral dietary studies. A study NOAEL for maternal toxicity of 300 mg/kg bw/day was identified. However, in rabbits the pattern of adverse effects was different from that observed in the dietary studies in rats, mice and dogs. In one rabbit study (dose levels 0, 52, 125, 300 mg/kg bw/day, gd 6-18) reduced bodyweight gain, food consumption and water consumption occurred, accompanied by clinical signs including hypoactivity, prone position, panting, flushed nose and ears, and tremors were observed at the highest dose level. The clinical signs had resolved by gd 14 and bodyweight effects were reversed after treatment was terminated. Less marked maternal toxicity was present at 125 mg/kg bw/day, observed as reduced bodyweight during the early part of the dosing period. Macroscopic necropsy findings of pale brown discolouration of liver and gray-white plaque in fundus of stomach were noted in a number of mothers at 125 and 300 mg/kg bw/day. However, these

tissues were unremarkable on histological examination, and consequently the toxicological significance of the macroscopic necropsy findings is uncertain. A study NOAEL for maternal toxicity of 52 mg/kg bw/day was identified. In a second rabbit developmental toxicity study (dose levels 0, 60, 175, 500 mg/kg bw/day, gd 6-27) clinical signs of tachypnoea in the first two days of dosing, reduced food consumption and reduced bodyweights were observed, but only at the highest dose level tested.

In a 7-day oral capsule administration study in beagle dogs, concentrations of 0, 30, 100, 300 mg/kg bw/day were administered to males and females ([redacted], 1998a). Clinical signs of diarrhoea or vomiting were observed in the 300 mg/kg bw/d group at the beginning of the test period. There were no treatment related mortalities. There were no adverse effects on bodyweight gain or food consumption. There were no treatment related haematology, urinalysis, organ weight changes, macroscopic pathology or histopathology findings. On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOEL for the 7-day capsule administration study should be set at 100 mg/kg bw/day, M/F).

In a 7-day oral dietary study in beagle dogs, dietary levels of 0, 1250, 5000, 20000, 30000, 40000 ppm were administered ([redacted], 1998b). There were no treatment related mortalities. Clinical signs included sporadic observations of loose stool, diarrhoea and vomiting. Loose stool was observed in the control group with similar frequency, diarrhoea and vomiting were transient and considered not to be treatment related. There was a slight reduction in body weight gain and reduced food consumption in the 40000 and the 30000 ppm dose group, suggestive of reduced palatability of the test diets. There were no treatment related haematology, urinalysis, organ weight changes, macroscopic pathology or histopathology findings. 40000 ppm was estimated to be equivalent to 770/924 mg/kg bw/day (M/F) respectively.

On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 7-day oral dietary study should be set at 770/924 mg/kg bw/day, M/F).

Please refer to section A.3.13 for Immunotoxicity studies ([redacted] 2012 & [redacted] 2011)

ORAL SUBCHRONIC

In a standard 13 week oral dietary study in Sprague-Dawley rats, dietary levels 0, 500, 5000, 25000 and 50000 ppm were administered ([redacted], 1997c). There were no treatment related mortalities or clinical signs. Bodyweight gain during the study was reduced in a dose related manner in both sexes at 25000 and 50000 ppm and in females at 5000 ppm. Food consumption was reduced for much of the study in both sexes at the two highest dose levels. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, organ weight or macroscopic pathology findings. Treatment related histopathological finding were limited to the observation of increased cytoplasmic vacuolation of the adrenal cortex in both sexes treated at 25000 and 50000 ppm and in males at 5000 ppm. In most cases the lesion was graded as minimal or slight. The vacuolation was seen in both the zona glomerulosa and zona fasciculata in males but was confined to the zona glomerulosa in females.
According to scientific literature, effects on the adrenal gland can arise as a secondary effect of stress rather than as a direct effect. In this 13-week study the stress related response is probably due to the food consumption and body weight gain differences.

Moreover, this histopathological alteration did not occur at dose levels in excess of 3000 mg/kg bw/day for 4 weeks or after 26, 52, 78 and 104 weeks treatment in an oncogenicity study with interim kills at mean dose levels of at least 991 mg/kg bw/day. Therefore, the adrenal changes were transient and considered not to represent an adverse effect of treatment with dinotefuran.

At 25000 and 50000 ppm, food consumption during the first 4 weeks of the 13- week study was

reduced by up to 16 and 29%, respectively, and body weight gain was reduced by up to 37 and 61%, respectively, which at 50000 ppm included initial body weight loss. However, in the investigative study food consumption was reduced by up to 10 and 38% at 20000 and 50000 ppm, respectively with concomitant decreases in body weight gain of up to 32 and 60%, respectively, including initial body weight loss at 50000 ppm. Since these effects have been shown in the investigative study to be due to unpalatability of the test diets, the effects on food consumption and body weight gain in the 13-week study are also considered to be due to diet palatability and do not therefore represent adverse effects of treatment.

The NOAEL established by the study authors was 25000 ppm (1623 and 1871 mg/kg bw/day in males and females, respectively). However, on the basis of the subsequent pair-feeding/palatability investigative study and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 13-week study should be set ([redacted], 2022) at 50000 ppm (3156 / 3616 mg/kg bw/day, males / females, respectively).

Supplementary information on repeated dose subchronic toxicity in rats is available from a dietary neurotoxicity study in rats, summarised in Section 3.9.1 ([redacted], 2001b). Dietary levels of 0, 500, 5000 and 50000 ppm were administered for 13 weeks. At 50000 ppm only, reduced bodyweight gain and food consumption in both sexes were reported. Thus, a study NOAEL of 5000 ppm (intake 327 mg/kg bw/day for males and 400 mg/kg bw/day for females) is identified for general toxicity.

Supplementary information on repeated dose subchronic toxicity in rats is also available from a dietary 2-generation reproduction study, summarised in Section 3.8.2 ([redacted], 2002). Dietary dose levels 0, 300, 1000, 3000, 10000 ppm were administered. A study NOAEL for general parental toxicity of 3000 ppm (intake of at least 241 and 268 mg/kg bw/day in parental males and females, respectively), was identified, based on the presence of bodyweight and food consumption reductions at 10000 ppm.

In a standard 13 week oral dietary study in CD-1 mice, dietary levels of 0, 500, 5000, 25000 and 50000 ppm were administered ([redacted], 1997b). There were no treatment related mortalities or clinical signs. Bodyweight gain was significantly reduced at 50000 ppm in both sexes. Bodyweight gain for females at 500, 5000 and 25000 ppm was also lower than controls, but the differences did not achieve statistical significance and a strong dose response relationship was not present so this observation was not considered to be treatment-related. Excessive food spillage occurred in the 25000 and 50000 ppm groups in the 1st week and at 50000 ppm for the rest of the study, and provided evidence of reduced palatability of the test diets. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, organ weight, macroscopic pathology or histopathology changes. Thus, based on the bodyweight differences at 50000 ppm, a study NOAEL of 25000 ppm (intake of 4442 mg/kg bw/day in males and 5414 mg/kg bw/day in females) is identified.

On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 13-week study should be set at 25000 ppm for both sexes (4442 / 5414 mg/kg bw/day, M/F).

In a standard 13 week oral dietary study in beagle dogs, dietary levels 0, 1600, 8000 and 40000 ppm were administered ([redacted] 1997c). The highest dose level was progressively reduced to 30000 ppm on day 5 and to 24000 ppm on day 12 following the observation of severe reductions in food consumption and bodyweight loss in both sexes in the early part of the study. There were no treatment related mortalities. Treatment related clinical signs, present only at the highest dose level when receiving 30000 or 40000 ppm, included black, liquid/mucoid, few or no faeces, thinness, slightly reduced activity, pale gums. Bodyweights for both sexes in highest dose recovered after the dose level reductions, though these remained lower that controls for the remainder of the study. Bodyweights were also significantly lower for females at 1600 and 8000 ppm during the second half of the study; although a dose-response relationship was not apparent, similar bodyweight changes were present in females at dietary dose levels of 3200 and 16000 ppm in the 52 week dog study

([redacted], 1999c), and therefore these lower bodyweights were considered to treatment related. After the initial severe effects on food consumption, the amount consumed by the high dose group animals increased when the dietary concentration was changed to 24000 ppm, though consumption remained slightly lower than controls for the rest of the study. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, organ weight, macroscopic pathology or histopathology changes. Based on the bodyweight and food consumption reductions in the high dose group, a study NOAEL for males of 8000 ppm (intake of 307 mg/kg bw/day) was identified. Based on the bodyweight reductions at all dose levels, a study NOAEL in females cannot be identified and an LOAEL 1600 ppm (intake of 58 mg/kg bw/day) is assigned for females.

In the absence of evidence for any other general or specific organ toxicity at all dose levels and on a conservative basis, the NOAEL for the 13-week study was set at 8000 ppm for both sexes (307 / 323 mg/kg bw/day, M/F).

ORAL CHRONIC

In a standard 104 week oral dietary chronic/carcinogenicity study, with interim kills at 26, 52 and 78 weeks, in Sprague-Dawley rats, dietary levels 0, 60, 200, 2000 and 20000 ppm were administered ([redacted], 2000c). There were no treatment related clinical signs or adverse effects on survival. Bodyweight gain during the study was reduced in both sexes at 20000 ppm. Food consumption was also reduced in both sexes at 20000 ppm, notably during the first 77 weeks of the study. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, macroscopic pathology or non-neoplastic histopathology changes. The organ weight analysis revealed a treatment related reduction in liver weight in females at 20000 ppm at the interim week 78 kill, which can be regarded as secondary to the reduced bodyweight gain.

The effect on FC and BWG at 20000 ppm in the 104-week study during the first 4 weeks of treatment was very similar to the effect at 20000 ppm in the investigative study ([redacted], 2015), but the effects tended to persist until termination at 104 weeks, particularly in females. The low overall BWG in females at 20000 ppm (weeks 1 – 104) is considered to reflect the marked retardation of BWG during the early phase of the study which may not be recovered after maturation to adulthood. Since these effects in the investigative study have been shown to be due to unpalatability of the test diets, the effects on FC and BWG in the 104-week study are also considered to be due to diet palatability and do not therefore represent adverse effects of treatment.

On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 104-week study should be set at 20000 ppm for both sexes (991 / 1332 mg/kg bw/day, M/F).

In a standard 78 week oral dietary carcinogenicity study in CD-1 mice, some relevant information on chronic toxicity was generated ([redacted], 2000d,e). Dietary levels 0, 25, 250, 2500 and 25000 ppm were administered. Haematology and histopathology investigations at 53 and 79 weeks were included, but clinical chemistry, urinalysis and ophthalmoscopy were not conducted. There were no treatment related clinical signs or adverse effects on survival. In both sexes, bodyweight gain was reduced throughout most of the study and platelet count was reduced at termination at 25000 ppm. There were no treatment related organ weight changes or non-neoplastic histopathology changes. Thus, a study NOAEL of 2500 ppm (intake of 345 mg/kg bw/day in males and 441 mg/kg bw/day in females) was identified for non-neoplastic effects.

In a standard 52 week oral dietary study in beagle dogs, dietary levels 0, 640, 3200 and 16000 ppm were administered ([redacted], 1999c). There were no treatment related mortalities or clinical signs. A treatment related reduction in mean bodyweight gain was observed in both sexes at 16000 ppm and in females at 3200 ppm throughout the study, though only the changes in females achieved statistical

significance. In females the bodyweight changes were accompanied by reduced cumulative food consumption. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, organ weight, macroscopic pathology or histopathology changes. Thymus weights were reduced in males in all the treated groups; however these changes were not thought to be treatment related based on an analysis of historical control data showing that only one low dose and one high animal had thymus weights outside the historical range and that thymus weights in dogs are highly variable ([redacted] 2005).
On this basis and in the absence of evidence for any other general or specific organ toxicity at all dose levels, the NOAEL for the 52-week study should be set at 16000 ppm for both sexes (559 / 512 mg/kg bw/day, M/F).

DERMAL

In a standard 28 day dermal study in Sprague-Dawley rats, dose levels of 0 (CMC vehicle control), 40, 200 and 1000 mg/kg bw/day were administered ([redacted], 2001b). No evidence of systemic or local toxicity was observed and hence a study NOAEL of 1000 mg/kg bw/day is identified.

INHALATION

In a standard 28 day inhalation study, Wistar rats were exposed nose only to dinotefuran dust atmospheres of 0, 0.22, 0.66, 2.08 mg/L, for 6 h/day ([redacted] 2002). The concentration of 2.08 mg/L was regarded as the highest concentration that could be practically achieved. The MMAD was 2 µm or less for all concentrations. The only treatment-related effect was a reduction in bodyweight gain and food consumption in males only during the 1st week in all the dinotefuran groups (though only the bodyweight differences achieved statistical significance). However, bodyweight gain for weeks 2 to 4 in all treated groups was similar to controls. For males a study NOAEC is not identified, and a LOAEC of 0.22 mg/L can be assigned; for females the study NOAEC is 2.08 mg/L

Neurotoxicity

Please refer to section A.3.12 for neurotoxicity studies.

Table A-73: Effects and corresponding guidance values to assist classification for STOT RE

Adverse target organ effects arising from a repeated exposure to the substance.

A.3.7.4.2 Comparison with the CLP criteria

For the oral (dietary) route, the main effects reported in all species tested (rats, mice and dogs) are minor reductions in bodyweight gain and food consumption for sub-acute, sub-chronic and chronic exposures. A bespoke pair-feeding /palatability study in the rat demonstrated lower food consumption was due to unpalatability. There was no evidence of target organ toxicity at doses relevant for classification.
By the dermal and inhalation routes of exposure, dinotefuran did not cause systemic or local toxicity sufficient to support classification.
Classification for repeated dose toxicity is not appropriate because severe, irreversible, toxicity was not observed below the relevant guidance values for oral, inhalation or dermal exposure.

A.3.7.4.3 Conclusion on classification and labelling for STOT RE

Not classified.

A.3.8 Genotoxicity / Germ cell mutagenicity

A.3.8.1 In vitro

Table A-74: Summary table of in vitro genotoxicity studies

Method, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. organism (e.g. bacteria), cell type, strains)	Results (including cytotoxicity and +/-S9 mix)	Remarks (e.g. major deviations)	Reference
Bacterial reverse mutation assay OECD TG 471 (1994), OECD TG 472 (1994), EU B.14, OPPTS 875.5100, OPPTS 870.5265 GLP, Reliability 1, Key study	Dinotefuran, batch no. 2200110, purity 99.1%. Concentrations (range finder) 0 (solvent DMSO control), 1.2, 4.9, 20, 78, 313, 1250 and 5000 µg/plate, concentrations (definitive test) 0 (solvent DMSO control), 313, 625, 1250, 2500 and 5000 µg/plate with and without metabolic activation.	*S. typhimurium:* TA 98, TA 100, TA 1535, TA 1537 *E. coli* WP2uvrA 1.2 – 5000 µg/plate	-ve +/- S9 An appropriate response was seen in positive control plates. Cytotoxicity or precipitation of test substance in the medium were not observed, but the highest conc. tested was the limit conc. for this type of assay.	None	Report no. CRC3133, [redacted] 1996, IUCLID no. 8.5.1
Bacterial DNA repair assay **Japan MAFF (1985), GLP, Reliability 1, Key study**	Dinotefuran, batch no. 2200110, purity 99.1%. Concentrations 0 (solvent DMSO control), 62.5, 250, 1000, 4000 and 16000 µg/plate, concentrations (definitive test) 0 (solvent DMSO control), 1000, 2000, 4000, 8000 and 16000 µg/plate with and without metabolic	*Bacillus subtilis:* M45 Rec- & H17 Rec+ 62.5 – 16000 µg/disc	-ve +/- S9 An appropriate response was seen in positive control discs.	None	Report no. 4731, [redacted] 1999, IUCLID no. 8.5.2

	activation.				
Chromosomal aberration assay OECD TG 473, EU B.10, OPPTS 870.5375, JMAFF 59 Nohsan 4200 (1985), GLP, Reliability 1, Key study	Dinotefuran, batch no. 2200110, purity 99.1%. Concentrations 0 (vehicle saline control), 500, 1000 and 2000 µg/mL with and without metabolic activation.	Chinese hamster lung cells 500 – 2000 µg/mL (up to ~0.01M)	-ve +/- S9 An appropriate response was seen in positive control cultures. Cytotoxicity or precipitation of test substance in the culture medium were not observed, but the highest concentration tested was the limit concentration for this type of assay.	None	Report no. CRC0076, [redacted] 1996 IUCLID no. 8.5.3
Gene mutation in mammalian cells **OECD TG 476, OPPTS 870.5300,** **GLP, Reliability 1, Key study**	Dinotefuran, batch no. 5400610, purity 99.1%. Concentrations 0 (vehicle saline control), 400, 800, 1200, 1600, and 2022 µg/plate with and without metabolic activation.	Mouse lymphoma L5178Y cells 7.81 (preliminary study) and 400 (main study)– 2022 µg/mL (up to ~0.01M)	-ve +/- S9 An appropriate response was seen in positive control cultures. Cytotoxicity or precipitation of test substance in the culture medium were not observed, but the highest concentration tested was the limit concentration for this type of assay	None	Report no. 719/15-D6173, [redacted] 2002, IUCLID 8.5.4

A.3.8.2 In vivo

Table A-75: Summary table of in vivo genotoxicity studies

Method, duration of study, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. species and strain, sex, no per group, route, frequency of application, sampling times, duration of exposure)	Main effects, Observations (specify regarding dose and sampling time)	Remarks (e.g. major deviations)	Reference
Erythrocyte micronucleus test **OECD TG 474 (1997), EU B.12, JMAFF 59 Nohsan 4200 (1985),** **GLP, Reliability 1, Key study**	Dinotefuran, batch no. OFU-1207, purity >=99%. Concentrations 0 (vehicle, 0.5% aqueous carboxymethyl cellulose solution), 270, 540 and 1080 mg/kg/day on 2 consecutive days, 24 hours apart (total doses: 540, 1080 or 2160 mg/kg)	Mouse (BDF1 strain). Daily, gavage, for 2 days, 270 – 1080 mg/kg/day. Sampling times; 24 h after last dose, sampled from bone marrow	-ve No general toxicity observed in main study, but deaths occurred at 1800 mg/kg/day in a pilot study. An appropriate response was seen in the positive control group. Study not compliant with OECD 474 because only 1000 polychromatic erythrocytes/animal (the guideline recommends 2000/animal) were assessed for the presence of micronuclei.	Only 1000 polychromatic erythrocytes/animal were assessed for the presence of micronuclei, rather than the 2000 polychromatic erythrocytes/animal recommended in the test guideline.	Report no. 2498, [redacted] 1995, IUCLID no. 8.6.1

Erythrocyte micronucleus test **OECD TG 474 (2016), GLP, Reliability 1, Key study**	Dinotefuran, batch no. RD0518033, purity 99.21%. Single exposure concentrations 0 (vehicle, corn oil), 500, 1000 and 2000 mg/kg bw.	Mouse (Swiss albino mouse). Single exposure, gavage. 5 animals per sex per dose. 48 hour post exposure period.	-ve No deaths and no signs of general toxicity observed. There were no biologically relevant or statistically significant increases in the number of micronuclei detected in any treatment group when compared to the negative control. An appropriate response was seen in the positive control group	This study addressed the aneugenicity endpoint and demonstrated exposure in plasma.	Report no. 8721, [redacted] 2019, IUCLID no. 8.5.5

Table A-76: Summary table of human data on genotoxicity

No human data is available.

A.3.8.2.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Dinotefuran tested negative in a bacterial reverse mutation assay (Takeda 1996), an in vitro chromosome aberration assay ([redacted] 1996) and an in vitro mammalian cell gene mutation assay ([redacted] 2002). Each of these assays was conducted in compliance with the relevant OECD TG. Dinotefuran also tested negative in a non-standard bacterial DNA repair assay (B. subtilis). Dinotefuran tested negative in a bone marrow micronucleus test conducted in mice ([redacted] 1995). There was no evidence of general toxicity or a reduction of the PCE/NCE ratio. However, the dose levels were considered adequate because mortality was observed in a pilot study at 1800 mg/kg, relatively close to the highest level employed in the main study. This study was not compliant with the OECD TG (TG. 474, 1997) because only 1000 polychromatic erythrocytes/animal were assessed for the presence of micronuclei, rather than the 2000 polychromatic erythrocytes/animal recommended in the TG. Although a deficiency is identified (reduced statistical power), this study is considered acceptable as providing supporting information given the negative profile of dinotefuran in well conducted standard in vitro genotoxicity assays.
Dinotefuran tested negative in a second bone marrow micronucleus test conducted in mice ([redacted] 2019). There was no evidence of general toxicity or a reduction of the PCE/NCE ratio. The study contains no deficiencies and is compliant with the OECD TG (TG. 474, 2016). The study showed no test item related increase in bone marrow micronuclei up to the top dose of 2000 mg/kg bw in the mouse. The study demonstrated the presence of dinotefuran in plasma and therefore exposure of the bone marrow to the test material. Furthermore, this is supported by the available kinetic data in the rat. Overall, based on the negative results of this study, it can be concluded that dinotefuran is neither aneugenic nor clastogenic. These findings are consistent with the results of an earlier bone marrow micronucleus mouse study ([redacted], 1995) and other studies showing absence of a clastogenic effect. Additionally, this study ([redacted], 2019) addressed the aneugenicity endpoint.

A.3.8.2.2 Comparison with the CLP criteria

Dinotefuran tested negative in a bacterial reverse mutation assay, an in vitro mammalian cell gene mutation assay and in an in vitro chromosome aberration assay. Therefore, it can be concluded that dinotefuran is not genotoxic in vitro. Dinotefuran also tested negative in two in vivo bone marrow micronucleus tests in mice. Therefore, classification for germ cell mutagenicity is not justified, no classification is proposed.

A.3.8.2.3 Conclusion on classification and labelling for germ cell mutagenicity

Data available. Conclusive, not sufficient for classification.

A.3.8.2.4 Overall conclusion on genotoxicity related to risk assessment

Not applicable for the CLH report

A.3.9 Carcinogenicity

Table A-77: Summary table of carcinogenicity studies in animals

<table>
<tr><th>Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study</th><th>Species, Strain, Sex, No/Group</th><th>Test substance (including purity), Vehicle, Dose levels, Duration of exposure</th><th>NOAEL, LOAEL</th><th>Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects, for all dose levels)</th><th>Remarks (e.g. major deviations)</th><th>Reference</th></tr>
<tr><td>104-week combined chronic toxicity and carcinogenicity
Oral, dietary administration
OECD TG 453 (1981), EPA OPP 83-2 (1985), JMAFF 59 NohSan 4200 (1985)
GLP, Reliability 1, Key study</td><td>Rat, [redacted]:CD®(SD)BR (Sprague Dawley), M/F. 100 animals per sex per dose (control and high dose), 90 animals per sex per dose for other doses, 10 animals per sex per dose were sacrificed after 26, 52, 78 weeks</td><td>Dinotefuran batch no. 2200210, purity 98.9%
No vehicle, admixture to diet.
Dose levels 0, 60, 200, 2000, 20000 ppm
Intake 0, 3/4, 10/13, 100/127, 991/1332 mg/kg bw/day (M/F)
104 weeks exposure</td><td>NOAEL 20000 ppm equivalent to 991 and 1332 mg/kg bw/d, M/F respectively</td><td><u>Relevant to general toxicity:</u>
60 and 200 ppm: no adverse effects
20000 ppm: ↓ bodyweight gain (M 5.5 %, F 36 % at termination); ↓ food cons. (M&F up to 10 % weeks 1-77).
<u>Relevant to carcinogenicity:</u>
Terminal sacrifice and decedents from carcinogenicity groups
<table>
<tr><th>Finding</th><th colspan="5">Males: dose level (ppm)</th></tr>
<tr><th></th><th>0</th><th>60</th><th>200</th><th>2000</th><th>20000</th></tr>
<tr><td>Thyroid - No. examined</td><td>59</td><td>60</td><td>60</td><td>58</td><td>60</td></tr>
<tr><td>- C-cell adenoma(b)</td><td>7 11.9%)</td><td>10 17.2%)</td><td>10 17.5%)</td><td>12 21%)</td><td>15 (26%)</td></tr>
<tr><td>Historical control % range</td><td colspan="5">8.0 – 26.7 % [from 13 carcinogenicity studies, completed Jun 1998-April 2002]</td></tr>
<tr><th>Finding</th><th colspan="5">Females: dose level (ppm)</th></tr>
<tr><th></th><th>0</th><th>60</th><th>200</th><th>2000</th><th>20000</th></tr>
<tr><td>Thyroid - No. examined</td><td>58</td><td>59</td><td>53</td><td>56</td><td>58</td></tr>
</table></td><td>None</td><td>Report no. 6648-131 [redacted] 2000c, IUCLID no. 8.11</td></tr>
</table>

				- C-cell adenoma(b)	12 (20.6%)	9 (15.2%)	10 (18.8%)	4 (7.1%)	12 (20.6%)	
				Finding	**Males: dose level (ppm)**					
					0	**60**	**200**	**2000**	**20000**	
				Testes - no. examined	60	60	60	59	59	
				- benign interstitial cell tumour	2 (3%)	0 (0%)	2 (3%)	0 (0%)	5 (8.4%)	
				Historical control % range	0 - 4.6 %**					
					Females: dose level (ppm)					
					0	**60**	**200**	**2000**	**20000**	
				Mammary gland - no. examined	60	60	60	58	60	
				Adenoma (b)	11	11	7	9	9	
				- carcinoma (m)	10 (16.7%)	13 (21.7%)	13 (21.7%)	18 (31%)	17 (28%)	
				Historical control % range (carcinoma)	10-42.7 %**					
				* significantly different from controls, $p < 0.05$ b = benign m = malignant ** Historical control % ranges are based on vehicle control groups from 15 oral carcinogenicity studies in Sprague-Dawley rats conducted by the testing facility, completed December 1996 to April 2002 (the current study was completed June 1999), with group sizes of 60 to 105; test substance administration was either by gavage or via the diet.						

78-week carcinogenicity Oral, dietary administration OECD TG 451 (1981), EPA OPP 83-2 (1985), JMAFF 59 NohSan no. 4200 (1985) GLP, Reliability 1, Key study	Mouse, ([redacted]:CD-1®(ICR)BR VAF/Plus®), M/F. 70 animals per sex per dose, 10 animals per sex per dose were sacrificed after 52 weeks	Dinotefuran batch no. 2200210, purity 98.9% No vehicle, admixture to diet. Dose levels 0, 25, 250, 2500, 25000 ppm Intake 0, 0, 3/4, 34/45, 345/441, 3694/4728 mg/kg bw/day (M/F) 78 weeks exposure	NOEL 2500 ppm (equivalent to 345/441 mg/kg bw/d, M/F). All effects	<u>Relevant to general toxicity:</u> 25000 ppm only: ↓ bodyweight gain (M 18 %, F 25 % at termination), ↓ platelet counts at termination (M 20 %, F 17 %) <u>Relevant to carcinogenicity:</u> No treatment-related increases in tumour incidence observed	None	Report no. 6648-130 [redacted] 2000d,e IUCLID no. 8.11

Table A-78: Summary table of human carcinogenicity data

No human data is available.

Table A-79: Summary table of other relevant studies for carcinogenicity

No other studies are available.

A.3.9.1 Short summary and overall relevance of the provided information on carcinogenicity

The carcinogenic potential of dinotefuran has been well investigated in standard lifetime chronic/carcinogenicity dietary studies, conducted in rats and mice.

Rats
In a standard 104-week oral dietary chronic/carcinogenicity study in Sprague-Dawley rats, dietary levels 0, 60, 200, 2000 and 20000 ppm were administered ([redacted], 2000c). Survival was not affected by treatment.

Treatment related effects on bodyweight, bodyweight gain and food consumption

Week of study	Group mean body weight (g) of:									
	Males treated at (ppm):					Females treated at (ppm):				
	0	60	200	2000	20000	0	60	200	2000	20000
1	228	232	229	231	228	178	177	174	175	176
26	685	694	692	702	638*	344	352	362*	350	314*
50	794	802	815	822	722*	411	418	439*	418	347*
78	836	841	865	867	777*	482	490	529*	497	377*
105	758	792	808	800	729	553	608	565	545	417*
Weight gain (wks 1 - 104)	531	565	585	574	504	376	433	395	370	242*
Interval (weeks)	Group mean food consumption (g/week) of:									
	Males treated at (ppm):					Females treated at (ppm):				
	0	60	200	2000	20000	0	60	200	2000	20000
1 - 25	201.3	197.7	199.1	198.1	182.4[a]	141.9	210.8	139.6	138.0	128.9[a]
29 - 49	202.8	201.3	203.5	209.5	186.7[a]	152.7	151.5	156.2	153.7	143.3[a]
53 - 77	205.9	202.7	207.1	209.4	193.7[a]	164.4	166.3	165.6	168.3	148.0[a]
81 - 101	192.7	199.8	196.0	195.2	186.0	162.7	169.2	160.3	167.5	150.5

* $p < 0.05$;

[a] $p < 0.05$ for most weekly values

- Body weight: The body weight gains of both sexes were reduced by treatment at 20000ppm from week 2 but the effect was more severe in the females with overall (week 1 - 104) body weight gains reduced by 5.1 and 35.6% in males and females, respectively. The effect in males is considered not to be adverse. Body weight gain was unaffected by treatment at lower dose levels.
- Food consumption: The mean weekly food consumption of animals treated at 20000ppm was reduced by up to 10.0% during the first 77 weeks of treatment. Food consumption was not affected by treatment at dose levels up to 2000ppm.

Treatment related, non-adverse, non-neoplastic histopathological findings

Finding	Incidence in males treated at (ppm):				
	0	60	200	2000	20000
No. examined (kidneys)	100	90	89	89	100
- lymphohistiocytic infiltrate	42	51*	39	49*	65**
- tubular epithelial basophilia	42	47	37	51*	57*
- thickening of basement membrane	30	35	32	44**	44*
- pelvic mineralisation	5	5	4	7	27**
- chronic progressive nephropathy	35	26	36	24	14**
No. examined (thymus)	96	39	38	40	99
- lymphocytic depletion	5	3	3	3	13*
No. examined (prostate)	100	90	89	89	100
- chronic active inflammation	23	46**	53**	51**	36*
	Incidence in females treated at (ppm):				
	0	60	200	2000	20000
No. examined (kidneys)	100	90	89	90	100
- lymphohistiocytic infiltrate	43	43	35	41	40
- tubular epithelial basophilia	48	42	34	40	26**
- thickening of basement membrane	23	24	19	19	15
- pelvic mineralisation	42	42	42	44	47
- chronic progressive nephropathy	5	8	12*	8	0*
No. examined (thymus)	100	42	44	41	98
- lymphocytic depletion	9	4	2	2	11

* $p < 0.05$; ** $p < 0.01$

There were no treatment-related effects on the nature and incidence of adverse non-neoplastic histopathlogical findings at any dose level. However, males treated at 20000ppm showed higher incidences of the renal changes pelvic mineralisation, lymphohistiocytic infiltrate, tubular epithelial basophilia and thickening of the basement membrane. None of the renal changes is considered to be an adverse effect since they are either common findings in rats or can be correlated with the lower incidence of chronic progressive nephropathy in males at 20000ppm. Similarly, increased incidences of thymic lymphocyte depletion and prostatic chronic active inflammation in males at 20000ppm are considered not to be adverse effects since they occur commonly in the rat.

On the basis of a pair-feeding/palatability study and in the absence of other non-neoplastic effects, the NOAEL was re-defined on review as 20000 ppm.

Incidences of neoplastic findings at 20000 ppm higher than controls

Finding	Incidence in males treated at (ppm):				
	0	60	200	2000	20000
No. examined (thyroid)	99	89	90	88	100
- C-cell adenoma (b)	8	12	10	12	17*
- C-cell carcinoma (m)	1	0	0	0	0
- total (adenoma + carcinoma)	9	12	10	12	17
No. examined (testes)	100	89	90	89	99
- benign interstitial cell tumor	2	1	3	1	5
	Incidence in females treated at (ppm):				
	0	60	200	2000	20000
No. examined (thyroid)	100	90	90	89	100
- C-cell adenoma (b)	12	11	12	5	13
- C-cell carcinoma (m)	0	0	1	1	1
- total (adenoma + carcinoma)	12	11	13	6	14
No. examined (uterus)	100	90	90	90	100
- benign endometrial stromal polyps	1	0	3	3	6
No. examined (cervix)	100	40	43	40	100
- benign endometrial stromal polyps	1	1	1	1	1
No. examined (vagina)	100	89	90	90	100
- benign endometrial stromal polyps	0	0	1	1	0
Total (uterus, vagina and cervix)	2	1	5	5	7*
No. examined (mammary gland)	100	90	89	89	100
- adenoma (b)	11	11	7	9	9
- carcinoma (m)	13	15	17	18	22
- total (adenoma + carcinoma)	24	26	24	27	31

* $p < 0.05$; b benign; m malignant

This table presents neoplastic findings that require further discussion: animals treated at 20000 ppm showed slightly higher incidences of thyroid C-cell adenomas and benign testicular interstitial cell (Leydig cell) tumours in males, and mammary gland carcinomas in females.
Compared to controls; the incidence of thyroid C-cell adenoma in males was statistically significantly increased at the top dose only (26% at 20000 ppm and 11.9% in concurrent controls). In females, the incidence of C-cell adenoma in treated groups was comparable to controls. The background rate for this tumour type from the same testing facility is 8-26.7%. There were no changes in thyroid follicular cell tumour incidence.
The incidence of mammary gland carcinoma was increased in females at the top dose only (28% at 20000 ppm and 16.7% in concurrent controls). This change did not achieve statistical significance. The background rate for this tumour type, from the same testing facility is 10-42.7%. The incidence of mammary gland adenomas was not affected by treatment, at any dose level tested.
For the thyroid C-cell adenoma and mammary gland carcinoma; the observed incidences were within, or very close to, the laboratory historical control ranges for the same strain of rat, there was no evidence of pre-neoplastic lesions such as hypertrophy or hyperplasia and no evidence of mutagenicity. It can be concluded that the marginally higher incidences of thyroid C-cell adenoma and mammary gland carcinoma are incidental observations and not treatment-related. Therefore, thyroid C-cell adenoma and mammary gland carcinomas are not relevant for classification.
The incidence of interstitial cell adenoma (Leydig cell adenomas) was increased at the top dose only (8.4% at 20000 ppm compared to 3% in concurrent controls). This increase was outside the historical control range for the same testing facility (0-4.6%) but did not achieve statistical significance. There were no Leydig cell carcinomas.
Leydig cell adenomas arising via a non-genotoxic MoA usually occur against a background of Leydig

cell hyperplasia. In the rat carcinogenicity study; there was no evidence of Leydig cell hyperplasia in any interim sacrifice (weeks 26, 52 or 78), unscheduled sacrifice or terminal sacrifice group. The complete absence of this pre-neoplastic lesion reduces concern that the Leydig cell adenomas are treatment related. Furthermore, in the available repeated dose and reproductive toxicity studies, there were no changes indicative of an adverse effect on the testis or other reproductive organs/tissues. Providing some evidence that dinotefuran does not have any significant endocrine activity which could have caused the Leydig cell adenomas.
The slight increase in benign Leydig cell adenoma seen at the top dose in the rat carcinogenicity study is not considered to be treatment-related or biologically significant; as there was no dose response, a lack of statistical significance, no increase in Leydig cell hyperplasia and no evidence for endocrine activity. Overall, the increase in Leydig cell adenomas is not considered relevant for classification.

Mice
In a standard 78-week oral dietary carcinogenicity study in CD-1 mice, dietary levels 0, 25, 250, 2500 and 25000 ppm were administered ([redacted] 2000d,c). Survival was not affected by treatment. The only non-neoplastic effects were reduced bodyweight gains and reduced platelet counts at 25000 ppm.

Mean body weight gain of both sexes

Parameter	Males treated at (ppm):					Females treated at (ppm):				
	0	25	250	2500	25000	0	25	250	2500	25000
Mean BW gain (g)[a]	13.4	14.6	13.5	12.6	11.0*	13.9	14.8	13.4	13.6	10.4*

[a] Group mean body weight gain weeks 1 - 78;

[b] Group mean platelet count;

* $p < 0.05$

Platelets counts in both sexes

Parameter	Males treated at (ppm):					Females treated at (ppm):				
	0	25	250	2500	25000	0	25	250	2500	25000
Plt (103/µl)[b] - week 53	1125	1138	1241	1329	1147	1028	1139	988	1063	1035
Plt (103/µl)[b] - week 79	1405	1309	1545	1245	1125*	1038	1011	1021	966	857

There were no differences in the incidence of neoplastic findings in treated groups as compared to the controls.

Incidence of neoplastic lesions achieving the criteria for statistical analysis

Organ and lesion	Males treated at (ppm):					Females treated at (ppm):				
	0	25	250	2500	25000	0	25	250	2500	25000
No. examined	70	70	70	70	70	70	70	70	70	70
Lung:										
adenoma (b)	4	5	6	3	6	5	4	5	5	3
carcinoma (m)	3	0	0	1	0	0	0	0	1	0
total (b + m)	7	5	6	4	6	5	4	5	6	3
Liver:										
adenoma (b)	9	13	8	6	5	-	-	-	-	-
carcinoma (m)	4	3	1	1	2	-	-	-	-	-
total (b + m)	13	16	9	7	7	-	-	-	-	-
Multiple organs:										
haemangioma (b)	0	NE	NE	NE	1	1	NE	NE	NE	3
haemangiosarcoma	2	NE	NE	NE	0	1	NE	NE	NE	1
(m)	2	-	-	-	1	2	-	-	-	4
total (b + m)										
Multiple organs:										
stromal polyp (b)	-	-	-	-	-	3	NE	NE	NE	1
stromal sarcoma	-	-	-	-	-	2	NE	NE	NE	3
(m)	-	-	-	-	-	5	-	-	-	4
total (b + m)										
Multiple organs:										
leiomyoma (b)	-	-	-	-	-	1	NE	NE	NE	3
leiomyosarcoma	-	-	-	-	-	1	NE	NE	NE	2
(m)	-	-	-	-	-	2	-	-	-	5
total (b + m)										
Ovary:										
granulosa/theca cell tumour (b)	-	-	-	-	-	2	NE	NE	NE	1
granulosa/theca cell tumour (m)	-	-	-	-	-	1	NE	NE	NE	0
total (b + m)	-	-	-	-	-	3	-	-	-	1

NE = not evaluated;

b = benign;

m = malignant

Thus, it is concluded that dinotefuran is not carcinogenic in the mouse.

Table A-80: Compilation of some factors that may be taken into consideration in classification and labelling

See Above.

A.3.9.2 Comparison with the CLP criteria

There is no information on carcinogenic potential in humans; therefore, category 1A can be excluded. Dinotefuran tested negative in standard *in vitro* and *in vivo* mutagenicity studies, therefore there is no concern for tumour induction via a genotoxic MoA.
In rats, slightly higher incidences of benign Leydig cell tumours were observed at the top dose of 20000 ppm only. The slight increase in benign Leydig cell adenoma is not considered to be treatment-related or biologically significant; as there was no dose response, a lack of statistical significance, no

increase in Leydig cell hyperplasia and no evidence for endocrine activity.
There were no increases in tumour incidence in a standard lifetime study, conducted in mice at doses of up to 3694-4728 mg/kg bw/day via the diet. Overall, it is concluded that dinotefuran is not carcinogenic. No classification is proposed.

A.3.9.3 Conclusion on classification and labelling for carcinogenicity

Data available. Conclusive, not sufficient for classification.

A.3.9.4 Overall conclusion on carcinogenicity related to risk assessment

Not applicable for the CLH report

A.3.10 Reproductive toxicity

A.3.10.1 Sexual function and fertility

Table A-81: Summary table of animal studies on adverse effects on sexual function and fertility

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAELs, LOAELs (e.g. maternal/parental toxicity, effects on sexual function and fertility)	Results (for all dose levels, specify critical effects on sexual function and fertility for parental animals (and offspring if relevant), report e.g. incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
Oral, dietary	Rat, Wistar F0: 6/sex/group	0, 10000, 20000 ppm Intake 0, 700/779, 1340/1507 mg/kg bw/day (M/F)	NOEL (general toxicity) <10000 ppm NOEL (neonatal toxicity) <10000 ppm NOEL (reproduction toxicity) 10000 ppm	**General parental toxicity:** 10000 ppm: ↓ bodyweight gain (F, by 31 % wk 1-2); ↓ food cons. (F, up to 17 % wk 1-2) 20000 ppm: ↓ bodyweight gain (M, 61 % wk 1-2, F, 62 % wk 1-2); ↓ food cons. (M 17 %, wk 1, F, up to 22 % wk 1-2); ↑ incidence small thymus (F) **Neonatal:** 10000 ppm: ↓ pup bodyweights (25 % at weaning), ↓	Pilot Study	[redacted] 2001

				food cons. post weaning (up to 54 %) 20000 ppm: ↓ pup bodyweights (38 % at weaning), ↓ food cons. post weaning (up to 64 %) **Reproduction:** 10000 ppm: no adverse effects 20000 ppm: ↓ no. implantation sites (21 %); ↓ birth index (16 %)		
2-generation, oral dietary, OECD TG 416 (1999), OPPTS 870.3800 (1998), JMAFF 59 Nohsan 4200 (1985), GLP, reliability 1, Key study	Rat, Hanlbm: WIST (SPF), 25 animals per sex per group	Dinotefuran purity 98.9%, incorporated into diet, nominal doses 300, 1000, 3000, 10000 ppm, daily for 10 weeks prior to mating and through to weaning of F1 offspring, F1 generation offspring similarly treated.	NOEL (general toxicity) 3000 ppm, equivalent to 241 (M) and 267.9 (F) mg/kg bw/day NOEL (neonatal toxicity) 3000 ppm, equivalent to 241 (M) and 267.9 (F) mg/kg bw/day NOEL (reproduction toxicity) 10000 ppm, equivalent to 822 (M) and 907 (F) mg/kg bw/day	**General parental toxicity**: 300, 1000 ppm: no adverse effects 3000 ppm: very slight ↓ food cons. during lactation (F0&F1 F), not considered an adverse effect of treatment 10000 ppm: One death, possibly treatment related (F0 F); soft faeces during lactation (F0 F); ↓ bodyweight (F0&F1 M&F up to 8 % at end of dosing); transient ↓ food cons. early in dosing period (F0&F1 M, up to 16 %; F0&F1 F, up to 12 %); ↓	none	Report no. 775192 [redacted] (2002) IUCLID 8.10.2

				absolute spleen weight (F0 M, 10 % F0 F, 15 %) **Neonatal**: 300, 1000, 3000 ppm: no adverse effects 10000 ppm: ↓ pup bodyweights (F1&F2 M&F, by 12-15 % at weaning), ↓ relative spleen weight at weaning (F1&F2 M&F, 9-15 %) **Reproduction**: 300, 1000, 3000, 10000 ppm: no adverse effects		

Table A-82: Summary table of human data on adverse effects on sexual function and fertility

No human data is available.

Table A-83: Summary table of other relevant studies for sexual function and fertility

No other studies are available.

A.3.10.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In a pilot study for a rat 2-generation study, dietary dose levels 0, 10000 and 20000 ppm were administered ([redacted] 2001). Males and females were mated after a two week dosing period. Dosing continued during preganancy and lactation, and was terminated for selected F_1 animals two weeks after weaning. There were no treatment related F_0 mortalities or clinical signs. F_0 parental bodyweight gain and food consumption were reduced in a dose related manner at both 10000 and 20000 ppm. Treatment related necropsy findings were limited to the observation of small thymus in F_0 females. There were no effects on fertility or mating performance, although the numbers of implantation sites and live births was reduced at 20000 ppm. F_1 pup bodyweights during lactation and food consumption post weaning were reduced; pup viability was unaffected. A study NOAEL for general parental and neonatal toxicity could not be identified; the LOAEL for these endpoints is 10000 ppm. A study NOAEL for reproductive parameters is 1000 ppm. The parental intake at 10000 ppm is at least 700 and 779 mg/kg bw/day for males and females, respectively.

In a standard rat two-generation study, dietary dose levels 0, 300, 1000, 3000, 10000 ppm were administered ([redacted], 2002). One F0 high dose female died during the study on PND 21. Parental clinical signs of toxicity were limited to the observation of soft faeces during the lactation period in F0 females at 10000 ppm. For both sexes at 10000 ppm, F0 and F1 bodyweight gain was reduced, and there were transient reductions in food consumption at the start of the respective F0 and F1 dosing periods. Treatment related necropsy/pathology findings in the F0 and F1 parental generations were limited to reduced spleen weight. F0 and F1 fertility and mating performance, semen parameters and ovarian follicle counts were not affected by treatment. Sexual maturation of the F1, based on timings of preputial separation and vaginal opening, and F2 anogenital distance, were not affected.

A.3.10.1.2 Comparison with the CLP criteria

The potential adverse effects on sexual function and fertility have been investigated in a standard oral (dietary) rat 2-generation study and administration of dinotefuran did not cause specific adverse effects. Therefore, no classification for adverse effects on sexual function and fertility is proposed.

A.3.10.1.3 Overall conclusion on sexual function and fertility related to risk assessment

The potential adverse effects on sexual function and fertility have been investigated in a standard oral (dietary) rat 2-generation study and administration of dinotefuran did not cause specific adverse effects. Therefore, no risk assessment value is proposed.

Conclusion used in Risk Assessment – Effects on fertility

Value/conclusion	Not value for risk assessment
Justification for the value/conclusion	Not classified

A.3.10.2 Developmental toxicity

Table A-84: Summary table of animal studies on adverse effects on development

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAELs, LOAELs (e.g. maternal, teratogenicity, embryotoxicity, offspring, parental, reproductive toxicity)	Results, maternal/parental (e.g. corrected body weight gain, for all dose levels)	Results, developmental (e.g. pup survival, structural abnormalities, altered growth, functional deficiencies, incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
Studies in rats							
Developmental toxicity, oral gavage, OECD TG 414, GLP, reliability 1, Key study	Rat, [redacted]:CD(SD) IGS (SPF), 24 mated females per group	Dinotefuran purity 99.1%, 0.5% CMC vehicle, nominal doses 100, 300, 1000 mg/kg bw/d, daily exposure for gd 6-15, 5-day post-exposure period	NOAEL (maternal toxicity) 300 mg/kg bw/d NOAEL (developmental toxicity) 1000 mg/kg/d	Maternal: 100, 300 mg/kg bw/d: no adverse effects 1000 mg/kg bw/d: ↓ body wt gain (by 21 % gd 6-11), ↓ food consumption (~10 % gd 6-9), ↑ water consumption ~20 % gd 10-15)	Developmental: 100, 300, 1000 mg/kg bw/d: no adverse effects	The dosing period was shorter than required for the guideline. However, this is not considered to have compromised the validity of the study.	Report no. H-97163 [redacted] (1998b) IUCLID 8.10.1
Fertility and early embryonic development, oral gavage OECD Guidance 150 (level 4	Rat, Crj:CD(SD)IGS, 20 animals per sex per group	Dinotefuran purity 99.1%, nominal doses 100, 300, 1000 mg/kg bw/d, daily for 14 days prior	NOAEL (general toxicity) 1000 mg/kg bw/d NOAEL (reproductive function M/F) 1000 mg/kg	General parental toxicity: 300, mg/kg bw/d ↓ body wt gain (day 8, males),	Neonatal: 1000 mg/kg bw/d ↓in pre-implantation loss Reproduction: 100 mg/kg/d	none	Report no. MA02198 [redacted] (2003) IUCLID 8.10.1

study), JMOHW, 1997,2000, GLP, reliability 1, Key study		to mating until 1 day prior to necropsy for males, daily for 14 days prior to mating, during the 14 day mating period and until day 7 gestation for females.	bw/d NOAEL (early embryonic development) 1000 mg/kg bw/d		one female did not become pregnant		
Pre- and post-natal development, oral gavage, OECD Guidance 150 (level 4 study), JMOHW, 1997,2000, GLP, reliability 1, Key study	Rat, Crj:CD(SD)IGS, 24 females per group	Dinotefuran purity 99.1%, 0.5% CMC-Na vehicle, nominal doses 100, 300, 1000 mg/kg bw/d, daily exposure from Day 7 of gestation until Day 20 of lactation	NOAEL (general toxicity) 300 mg/kg bw/d NOAEL (F1 development) 300 mg/kg bw/d NOAEL (reproductive function) 1000 mg/kg bw/d	General toxicity: 1000 mg/kg bw/d ↓ bodywt gain Day 8-Day 20 gestation and ↓ fc Day 8-Day 15 gestation	F1 development: 1000 mg/kg bw/d ↓ bodywt gain birth to 70 days old Reproductive function: 100, 300, 1000 mg/kg bw/d: no adverse effects	none	Report no. MA02200 [redacted] (2004) IUCLID 8.10.1
Developmental neurotoxicity & immunotoxicity dose range-finding study, non-guideline, Oral dietary	Rat SD 10 mated F_0/sex/group	Dinotefuran (MTI 446) 0, 1000, 3000, 10000 ppm Intake (gestation) 0, 70, 212, 670 mg/kg bw/day	NOAEL 10000 ppm for maternal and developmental immunotoxicity, 670 mg/kg/day NOAEL 3000 ppm for neonatal toxicity, maternal intake 212 mg/kg bw/day	**Maternal toxicity:** 1000, 3000 ppm, 10000 ppm: no adverse effects **Immunotoxicity:** 1000, 3000 ppm, 10000 ppm: no adverse effects on innate and humoral components of immune system	**Neonatal general toxicity:** 1000, 3000 ppm: no adverse effects 10000 ppm: ↓ bodyweights from PND 13 to termination (by ~20 % on PND 21) **Developmental neurotoxicity:** not assessed		Report no. SRY00001 [redacted] 2009 IUCLID, 8.13.2-05

Developmental neurotoxicity, Oral, dietary OECD TG 426, OPPTS 870.6300, GLP Reliability 1, Key study	Rat, [redacted]:CD(SD), 25 mated females F0/sex/group	Dinotefuran purity 99.5%, no vehicle, nominal doses 0, 1000, 3000, 10000 ppm, (equivalent to 0, 79, 237, 784 mg/kg bw/day) daily exposure on Day 6 of gestation until Day 21 of lactation	NOAEL (maternal): 237 mg/kg bw/day NOAEL (neonatal toxicity and developmental neurotoxicity): 784 mg/kg bw/day	Maternal toxicity: 1000, 3000 ppm: no adverse effects 10000 ppm: ↓ bodyweight gain during gestation (11 % GD 6-20)	Neonatal general toxicity: 1000, 3000 ppm, 10000 ppm: no adverse effects Developmental neurotoxicity: 1000, 3000 ppm, 10000 ppm: no adverse effects	none	Report no. SRY00002 [redacted] (2010) IUCLID 8.13.2
Studies in rabbits							
Developmental toxicity, oral gavage, OECD TG 414, GLP, reliability 1, Key study	Rabbit, NSW, 22 mated females per group	Dinotefuran purity 99.1%, 0.5% CMC vehicle, nominal concentrations 52, 125, 300 mg/kg bw/d, daily exposure for gd 6-18, 10-day post-exposure period	NOEL (maternal toxicity) 52 mg/kg bw/d NOEL (developmental toxicity) 300 mg/kg bw/d	Maternal: 52 mg/kg bw/d: no adverse effects 125 mg/kg bw/d: ↓ bodywt gain (gd 6-11); macroscopic necropsy findings: pale brown discolouration of liver (8/22 animals), gray-white plaque in fundus of stomach (15/22) 300 mg/kg bw/day: clinical signs gd 6-14 (hypoactivity, prone position, panting, flushed nose & ears, tremors); ↓ bodywt gain (gd 6-18, 50 %); ↓ food consumption (gd 6-18, 23 %); ↓ water consumption (gd 13-15, ~25 %);	Developmental: 52, 125, 300 mg/kg bw /day: no adverse effects	The dosing period was shorter than required for the guideline. However, this is not considered to have compromised the validity of the study.	Report no. H-97166 [redacted] (1998e) IUCLID 8.10.1

				macroscopic necropsy findings: pale brown discolouration of liver (19/22), gray-white plaque in fundus of stomach (20/22), thickening of gastric mucosa (2/22)			
Developmental toxicity, oral gavage, OECD TG 414 (2001), OPPTS 870.3700 (1998), JMAFF 59 Nohsan 4200 (2000, 2011), GLP, reliability 1, Key study	Rabbit, Kbl:JW, 25 mated females per group	Dinotefuran purity 99.6%, 0.5% CMC vehicle, nominal concentrations 60, 175, 500 mg/kg bw/d, daily exposure for gd 6-27, 10-day post-exposure period	NOAEL (maternal toxicity) 175 mg/kg bw/d NOAEL (developmental toxicity) 500 mg/kg bw/d	Maternal: 60, 175 mg/kg bw/day: no adverse effects 500 mg/kg bw/day: one mortality (gd 27); clinical signs (tachypnoea gd 6 & 7), ↓ amount of faeces from gd 15; ↓ bodywt (from gd 6, by 7% gd 24), ↓ food consumption (22-54%)	Developmental: 60, 175, 500 mg/kg bw/day: no adverse effects	The dosing period was shorter than required for the guideline. However, this is not considered to have compromised the validity of the study.	Report no. SR12005 [redacted] (2013) IUCLID 8.10.1

Table A-85: Summary table of human data on adverse effects on development

No human data is available.

Table A-86: Summary table of other relevant studies for developmental toxicity

No other studies are available.

A.3.10.2.1 Short summary and overall relevance of the provided information on adverse effects on development

Rats

In a standard rat developmental toxicity study, gavage dose levels of 0 (0.5 % CMC vehicle), 100, 300 and 1000 mg/kg bw/day were administered ([redacted] 1998b). The dose levels were selected on the basis of the results of a pilot study in which slight maternal toxicity, but no developmental toxicity, was seen at 1000 mg/kg bw/day only, the highest dose level tested. In the main study, maternal toxicity was present only at 1000 mg/kg bw/day, observed as reduced bodyweight gain and food consumption during the early part of the dosing period and increased water consumption towards the end of the dosing period. Mean pre-implantation loss was noticeably higher at 1000 mg/kg/day than controls (24 % vs .9 %), but because implantation will have been completed by the commencement of dosing on gd 6 this was considered to be a chance finding and unrelated to dinotefuran treatment. No foetotoxicity/post-implantation loss, or skeletal or visceral malformations were observed at doses of up to 1,000 mg/kg bw/day. Overall it can be concluded that dinotefuran is not a developmental toxicant in rats.

In a study investigating the effects of dinotefuran on fertility and early embryonic development to implantation in rats, gavage dose levels of 0 (0.5% CMC-Na vehicle), 100, 300 and 1000 mg/kg bw/day were administered daily for 14 days ([redacted] 2003). There were no adverse effects on parental toxicity at any dose level; the decrease in body weight gain for males in the 300 mg/kg group was transient and not treatment related. There were no treatment-related effects on genital organ weights of males, the oestrous cycles or number of corpora lutea of females, the copulation index of males or female, or the fertility index. A statistically significant decrease was noted in the pre-implantation loss in the 1000 mg/kg bw group; this is due to the non-significant increase of the number of implantation at dose 1000 mg/kg bw compared with the control group. Therefore, this increase should not be considered as adverse. There were no further effects; it can thus be concluded that dinotefuran is not a developmental toxicant in rats.

In a study investigating the effects of dinotefuran on pre- and post-natal development, including maternal function, in rats, gavage dose levels of 0 (0.5% CMC-Na vehicle), 100, 300 and 1000 mg/kg bw/day were administered daily from Day 7 of gestation to Day 20 of lactation ([redacted] 2004). In dams (F0), suppressed body weight gain and decreased food consumption were noted in the 1000 mg/kg bw group as treatment-related effects. One dam in this group died during delivery, but the relationship between the death and treatment with the test article was unclear. Changes suggestive of treatment-related effects were not noted in the physical condition or gross pathology in any treated group. In addition, no treatment-related effects were noted on the reproductive functions of dams, such as maintenance of pregnancy, duration of gestation, delivery and nursing. In offspring (F1), suppressed body weight gain was noted in the 1000 mg/kg group, though the degree was slight. Changes suggestive of treatment-related effects were not noted in the viability, physical condition, physical development, behavioural development, sensory functions, emotionality,

spontaneous motility, learning ability, reproductive function or gross pathology in any treated group. In embryos (F2), no treatment-related effects were noted on the number of implantations or live embryos or pre- or post-implantation loss (%).

In a standard developmental neurotoxicity study, dietary dose levels 0, 1000, 3000 or 10000 ppm were administered ([redacted], 2010). The test diets were fed to groups of mated F0 females from GD6, through gestation and lactation, with exposure of the F1 generation offspring continuing until completion of the post-weaning developmental neurotoxicity evaluations (conducted PND 21-69). Developmental parameters assessed included preputial separation/vaginal opening, motor activity, acoustic startle inhibition response, learning and memory, neurohistopathology, brain weight and brain morphometry. Evidence of maternal toxicity was limited to the observation of reduced bodyweight gain during gestation (GD 6-21) at 10000 ppm only. For the F1 offspring, there was no evidence of general neonatal toxicity, because litter size, clinical condition, pup viability and bodyweights were comparable for all groups. There were no treatment related changes in the developmental neurotoxicity parameters.

Refer to section "Developmental neurotoxicity" for more details on developmental neurotoxicity and immunotoxicity study (Hoberman, 2009)

Rabbits

In the first standard rabbit developmental toxicity study, gavage dose levels of 0 (0.5 % CMC vehicle), 52, 125 and 300 mg/kg bw/day were administered ([redacted] 1998e). The dose levels were selected on the basis of the results of a pilot study in which marked maternal toxicity and abortions were observed at 1000 mg/kg bw/day. In the main study, marked maternal toxicity was present at 300 mg/kg/day, observed as reduced bodyweight gain, food consumption and water consumption and clinical signs from the first day of dosing, including hypoactivity, prone position, panting, flushed nose and ears, and tremors. The clinical signs had resolved by gd 14 and bodyweight gain from gd 19 was greater that controls. Less marked maternal toxicity was present at 125 mg/kg bw/day, observed as reduced bodyweight during the early part of the dosing period. Macroscopic necropsy findings of pale brown discolouration of liver and grey-white plaque in the fundus of stomach were noted in a number of mothers at 125 and 300 mg/kg bw/day; additionally, the gastric mucosa was thickened in two mothers at 300 mg/kg bw/day. However, these tissues were unremarkable on histological examination, and consequently the toxicological significance of the macroscopic necropsy findings is uncertain. No evidence of developmental toxicity or abortions was seen in the main study.

In a second standard rabbit developmental toxicity study, gavage dose levels of 0 (0.5 % CMC vehicle), 60, 175 and 500 mg/kg bw/day were administered ([redacted] 2013). The dose levels were selected on the basis of the results of a pilot study in which clinical signs of toxicity (tachypnoea, flushed appearance for up to 2.5 hours after dosing on first few days of dosing), reduced maternal bodyweight and reduced food consumption were observed at 600 and 1000 mg/kg bw/day. In the main study, maternal toxicity was present at 500 mg/kg bw/day, observed as clinical signs (tachypnoea) on gd 6 and 7, reduced bodyweights and reduced food consumption, and the death of one mother on gd 27 after a prolonged period of very low food consumption and bodyweight loss. There were no macroscopic necropsy changes in the maternal organs that were considered to be related to treatment. Three out of the 24 pregnant mothers at 500 mg/kg bw/day aborted, between gd 25 and 28, each after a prolonged period of very low food consumption; these abortions are considered to be treatment-related though likely to be secondary to the reduced maternal food consumption. At 175 mg/kg bw/day abortion occurred in 2/25 mothers, but these were regarded as not being related to dinotefuran treatment because abortion was also seen in 1/23 control mothers. There was no evidence of developmental toxicity; post implantation loss, litter size, foetal weights and sex ratios, and numbers of foetal malformations and variants were not affected by treatment.

A.3.10.2.2 Comparison with the CLP criteria

The developmental toxicity of dinotefuran has been investigated in standard oral (gavage) studies in

rats and rabbits. These studies show that dinotefuran does not have the capacity to cause specific adverse effects on development and is not a developmental toxicant.

A.3.10.2.3 Overall conclusion on effects on development related to risk assessment

Not applicable for the CLH report

A.3.10.3 Effects on or via lactation

Table A-87: Summary table of animal studies on adverse effects on or via lactation

No animal data is available.

Table A-88: Summary table of human data on adverse effects on or via lactation

No human data is available.

Table A-89: Summary table of other relevant studies for adverse effects on or via lactation

No other studies are available.

A.3.10.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

In the two-generation study, the neonates, F1 and F2 bodyweights during lactation were reduced by 12-15% at 10000 ppm. At this dose level, general toxicity was observed in the dams; including one death (for which a treatment related aetiology could not be dismissed), soft faeces during lactation (F0 F1); decreased bodyweight (up to 8 % at the end of dosing), decreased food consumption and decreased absolute spleen weight. Given the high dose level and clinical signs of toxicity in dams, it is considered that classification for lactational effects is not required.

A.3.10.3.2 Comparison with the CLP criteria

There is no evidence that dinotefuran caused a specific adverse effect on pups via lactation, therefore classification for lactational effects is not proposed.

A.3.10.3.3 Overall conclusion on effects on or via lactation related to risk assessment

Not applicable for the CLH report

A.3.10.4 Conclusion on classification and labelling for reproductive toxicity

Dinotefuran is not a reprotoxicant base on the extensive database.

A.3.10.5 Overall conclusion on reproductive toxicity related to risk assessment

Not applicable for the CLH report

A.3.11 Aspiration hazard

According to CLP regulation, section 3.10.1.6.2a, Aspiration Hazard is intended to apply to liquid substances and mixtures only. Since Dinotefuran is a solid, further consideration of this endpoint is therefore not required.

Table A-90: Summary table of evidence for aspiration hazard

No data is available.

A.3.11.1 Short summary and overall relevance of the provided information on aspiration hazard

- Aspiration hazard Hazard class not applicable (e.g. physical state or chemical structure)

A.3.11.2 Comparison with the CLP criteria

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A.3.11.3 Conclusion on classification and labelling for aspiration hazard

- *Aspiration hazard Hazard class not applicable (e.g. physical state or chemical structure)*

A.3.12 Neurotoxicity

Table A-91: Summary table of animal studies on neurotoxicity

Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAEL, LOAEL	Results	Remarks (e.g. major deviations)	Reference
Acute neurotoxicity, 14 days exposure, oral dietary, OECD TG 424, OPPTS 870.6200, GLP, Reliability 1, Key study	Rat, [redacted]:CD®(SD) IGS BR, males/females, 10/sex/group	Dinotefuran, 98.9%, 0.5% CMC vehicle, single administration of 0, 325, 750, 1500 mg/kg bw/d	NOAEL (both sexes) >1500 mg/kg	Males and females at 1500 mg/kg bw had statistically significantly lower motor activity on day 1, transient and not other correlating changes therefore not adverse nor treatment related.	None	Report no. 6648-147 [redacted] (2001a) IUCLID 8.13.2
Subchronic neurotoxicity, 13-weeks exposure, oral dietary, OECD TG 424 (1998), OPPTS 870.6200 (1998), GLP, Reliability 1, Key study	Rat, [redacted]:CD®(SD) IGS BR, males/females, 10/sex/group	Dinotefuran, 98.9%, no vehicle, daily administration of 0, 500, 5000, 50000 ppm	NOAEL for all effects 5000 ppm (equivalent to 327 (M) and 400 (F) mg/kg bw/day) NOEL for neurotoxicity effects 50000 ppm (equivalent to 3413 (M) and 3806 (F) mg/kg bw/d)	Reduction in body weight gain and food consumption observed at 50000 ppm. Absence of neurobehavioural and neuropathological effects at 50000 ppm	None	Report no. 6648-148 [redacted] (2001b) IUCLID 8.13.2
Developmental neurotoxicity & immunotoxicity dose range-finding study,	Rat SD 10 mated F_0/sex/group	Dinotefuran (MTI 446) 0, 1000, 3000, 10000 ppm Intake	NOAEL 10000 ppm for maternal and developmental immunotoxicity,	**Maternal toxicity:** 1000, 3000 ppm, 10000 ppm: no adverse effects		Report no. SRY00001 [redacted] 2009 IUCLID, 8.13.2-05

non-guideline, Oral dietary		(gestation) 0, 70, 212, 670 mg/kg bw/day	670 mg/kg/day NOAEL 3000 ppm for neonatal toxicity, maternal intake 212 mg/kg bw/day	**Neonatal general toxicity:** 1000, 3000 ppm: no adverse effects 10000 ppm: ↓ bodyweights from PND 13 to termination (by ~20 % on PND 21) **Developmental neurotoxicity:** not assessed **Immunotoxicity:** 1000, 3000 ppm, 10000 ppm: no adverse effects on innate and humoral components of immune system		
Developmental neurotoxicity, Oral, dietary OECD TG 426, OPPTS 870.6300, GLP Reliability 1, Key study	Rat, [redacted]:CD(SD), 25 mated females F0/sex/group	Dinotefuran purity 99.5%, no vehicle, nominal doses 0, 1000, 3000, 10000 ppm, (equivalent to 0, 79, 237, 784 mg/kg bw/day) daily exposure on Day 6 of gestation until Day 21 of lactation	NOAEL (maternal): 237 mg/kg bw/day NOAEL (neonatal toxicity and developmental neurotoxicity): 784 mg/kg bw/day	Maternal toxicity: 1000, 3000 ppm: no adverse effects 10000 ppm: ↓ bodyweight gain during gestation (11 % GD 6-20) Neonatal general toxicity: 1000, 3000 ppm, 10000 ppm: no adverse effects Developmental neurotoxicity: 1000, 3000 ppm, 10000 ppm: no adverse effects	None	Report no. SRY00002 [redacted] (2010) IUCLID 8.13.2

Table A-92: Summary table of human data on neurotoxicity

No human data is available.

A.3.12.1 Short summary and overall relevance of the provided information on neurotoxicity

Acute and subchronic neurotoxicity

In a standard acute oral neurotoxicity study in Sprague-Dawley rats, a single gavage dose of 0 (0.5 % CMC vehicle only), 325, 750 or 1500 mg/kg bw was administered ([redacted], 2001a). The only treatment related change reported was a reduction in motor activity score at the highest dose level in the assessments conducted 3 hours after dosing. Based on this observation, a study NOAEL of 750 mg/kg bw is identified. However, this transient minor change is considered to be a manifestation of general toxicity, and because no neuropathological changes were detected it can be concluded that dinotefuran is not acutely neurotoxic.

In a standard 13 week oral dietary neurotoxicity study in Sprague-Dawley rats, dietary levels of 0, 500, 5000 and 50000 ppm were administered ([redacted], 2001b). The only treatment related changes reported were, at 50000 ppm only, reduced bodyweight gain and food consumption in both sexes and a reduction in motor activity score in females at the assessments conducted during week 2. Based on these observations, a study NOAEL of 5000 ppm (intake 327 mg/kg bw/day for males and 400 mg/kg bw/day for females) is identified. These changes are considered to be manifestations of general toxicity and because no neuropathological changes were detected. Therefore it can be concluded that dinotefuran is not neurotoxic.

Developmental neurotoxicty

In a dose range-finding study for main developmental neurotoxicity and immunotoxicity investigations, groups of 10 mated females were exposed to dietary levels of 0, 1000, 3000 or 10000 ppm from GD 6 through to the termination of selected F_1 generation pups on post weaning days 36-49 (Hoberman, 2009). Two F_1 pups/sex/Litter were selected for each of the two immunological assays, an antibody-forming cell (AFC) assay and splenocyte phenotyping with a natural killer (NK) cell assay. The following parameters were evaluated: viability, clinical observations, body weights, behaviour, food consumption, spleen weights, immunological evaluations (spleen IgM AFC response, spleen cell phenotyping, NK cell activity) and necropsy observations. There was no evidence of maternal toxicity. However, in the F_1 offspring, bodyweights were reduced at the highest dose level from PND 13 to termination. No adverse effects on innate and humoral components of the immune system of the F_1 pups were observed.

In a standard developmental neurotoxicity study, dietary dose levels 0, 1000, 3000 or 10000 ppm were administered ([redacted], 2010). The test diets were fed to groups of mated F_0 females from GD6, through gestation and lactation, with exposure of the F_1 generation offspring continuing until completion of the post-weaning developmental neurotoxicity evaluations (conducted PND 21-69). Developmental parameters assessed included preputial separation/vaginal opening, motor activity, acoustic startle inhibition response, learning and memory, neurohistopathology, brain weight and brain morphometry. Evidence of maternal toxicity was limited to the observation of reduced bodyweight gain during gestation (GD 6-21) at 10000 ppm only. For the F_1 offspring, there was no evidence of general neonatal toxicity, because litter size, clinical condition, pup viability and bodyweights were comparable for all groups. There were no treatment related changes in the developmental neurotoxicity parameters. Thus, the study NOAELs are 3000 ppm (intake during gestation 237 mg/kg bw/day) and for maternal toxicity and 10000 ppm (maternal intake during gestation 784 mg/kg bw/day) for general neonatal and developmental neurotoxicity.

A.3.12.2 Comparison with the CLP criteria

Dinotefuran is not a neuro toxicant base on the extensive database.

A.3.12.3 Conclusion on neurotoxicity related to risk assessment

Not applicable for the CLH report

A.3.13 Immunotoxicity

Table A-93: Summary table of in vitro immunotoxicity studies

No in vitro data is available.

Table A-94: Summary table of animal studies on immunotoxicity

Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAEL, LOAEL	Results	Remarks (e.g. major deviations)	Reference
Immuntoxicity, 28 days exposure, oral dietary, OPPTS 870.7800, GLP, Reliability 1, Key study	Rat, [redacted]:CD® (SD), males/females, 10/sex/dose (control and treatment) 8/sex/dose (positive control)	Dinotefuran, 97.9%, no vehicle, 0, 2240, 5600, 14000 ppm	NOAEL for all effects 5600 ppm (equivalent to 425 (M) and 430 (F) mg/kg bw/d) NOEL immunotoxicity 14000 ppm (equivalent to 992 (M) and 1018 (F) mg/kg bw/d)	There was no immuno-toxicologically relevant effect of dinotefuran on the humoral T-lymphocyte-dependent response against antigen on sheep red blood cells. There were no statistically significant differences in the number of cells/spleen, PFC/10^6 viable	None	Report no. MCW0018 [redacted] (2011) And amended report [redacted] (2012) IUCLID 8.13.4

				cells or PFC/spleen, when compared to the control, for all the treatment groups. The magnitude of the effect on body weight in males demonstrated that 14000 ppm was the maximum tolerated dose for this study type and duration.		
Immuntoxicity, 28 days exposure, oral dietary, OPPTS 870.7800, GLP, Reliability 1, Key study	Mouse, [redacted]:CD1 (ICR), males/females, 10/sex/dose (control and treatment) 8/sex/dose (positive control)	Dinotefuran, 97.9%, no vehicle, 0, 1120, 2800, 7000 ppm	NOAEL for all effects 7000 ppm (equivalent to 1053 (M) and 1438 (F) mg/kg bw/d) NOEL for immunotoxicity 7000 ppm (equivalent to 1053 (M) and 1438 (F) mg/kg bw/d)	Based on no effect in the PFC assay at the highest dose level employed. Dinotefuran was well tolerated at the highest dose level employed.	None	Report no. MCW0019 [redacted] (2011) IUCLID 8.13.4

Table A-95: Summary table of human data on immunotoxicity

No human data is available.

A.3.13.1 Short summary and overall relevance of the provided information on immunotoxicity

In a standard immunotoxicity study in rats, dietary dose levels 0, 2240, 5600, 14000 ppm were administered for 28 days ([redacted], 2012). Following immunisation by intravenous injection of sheep red blood cells (SRBC), the spleen of each animal was retained at termination and used as the source of splenocytes for conducting a plaque forming cell (PFC) assay using a modification of the Jerne PFC assay. General toxicity was evident at 14000 ppm, observed as reduced bodyweight gain and food consumption. There were no significant differences in the number of cells/spleen, PFC/10^6 viable cells or PFC/spleen in the PFC assay in the treated groups, demonstrating that dinotefuran has no effect on the humoral T-lymphocyte-dependent response against antigen on SRBC. Study NOAELs of 5600 ppm (intake 425 mg/kg bw/day in males and 430 mg/kg bw/day in females) for general toxicity and 14000 ppm (the highest dose level tested, intake 992 mg/kg bw/day in males and 1018 mg/kg bw/day in females) for immunotoxicity are identified.

A similar immunotoxicity study was conducted in mice, using dietary dose levels of 0, 1120, 2800 and 7000 ppm ([redacted], 2011). There was no evidence of general toxicity and there were no effects on the humoral T-lymphocyte-dependent response against antigen on SRBC in the dinotefuran groups. A study NOAEL of 7000 ppm (the highest dose level tested, intake 1053 mg/kg bw/day in males and 1438 mg/kg bw/day in females) for general toxicity and immunotoxicity are identified.

Additionally, a pilot investigation into developmental immunotoxicity was conducted using 10 male and 10 female F1 progeny/group per immunological endpoint as part of a rat oral (dietary) study summarised in Section 3.9 ([redacted], 2009). No adverse effects on innate and humoral components of the immune system of F_1 pups were reported.

A.3.13.2 Comparison with the CLP criteria

Dinotefuran is not an immuno-toxicant base on the extensive database.

A.3.13.3 Conclusion on immunotoxicity related to risk assessment

Not applicable for the CLH report

A.3.14 Endocrine disruption

Not applicable for the CLH report

Table A-96: Summary table of in vitro studies on endocrine disruption

Not applicable for the CLH report

Table A-97: Summary table of animal data on endocrine disruption

Not applicable for the CLH report

Table A-98: Summary table of human data on endocrine disruption

Not applicable for the CLH report

Table A-99: Summary table of other evidence on endocrine disruption

Not applicable for the CLH report

A.3.15 Further Human data

Please refer to the confidential annex (table 96).

Table A-100: Summary table of further human data

See confidential annex

A.3.16 Other data

Table A-101: Summary table of other data

Type of data/report, Reliability, Key/supportive study	Test substance (including purity), Vehicle	Relevant information about the study	Main effects, Observations	Reference
Pair-feeding/ palatability investigative study No OECD Guideline, GLP, Reliability 1, Key study	Dinotefuran, 98.86%, Pair matched phase 20000 and 50000 ppm; palatability phase 4000 and 20000 ppm	Rat, Crl:CD®(SD) IGS BR, males/females, 10/sex/group Controls group-matched and ad libitum controls included.	Effects on weight gain at 20000 and 50000 ppm attributable to unpalatability of treated diet.	Report no. MCW0059 [redacted], 2015a IUCLID 8.13.6 Amendment 1, [redacted], 2015b

SUMMARY OF PAIR-FEEDING/ PALATABILITY INVESTIGATIVE STUDY IN RAT

This study was performed to investigate if reduced food consumption and body weight gain, reported in previous toxicity studies performed on dinotefuran were due to unpalatability of the test diets and/or to non-specific toxicity. Moreover, the use of a group-matched feeding design also enabled the delineation of alterations in food consumption and body weight gain which may have been due to a combination of both reduced diet palatability and non-specific toxicity. For this purpose, groups of individually-caged rats treated with dinotefuran were group-matched with groups of untreated animals fed an amount of control diet equal to the group mean food consumption (less dinotefuran content) of the matched treated group on the previous day. The study was also designed to investigate if a preference existed for rats to consume untreated diet, or diets containing dinotefuran, and in this phase of the study the animals were fed *ad libitum* and were given two feed-pots, one containing control diet and the other containing treated diet), with the position of the feed pots within the cage being switched daily.

In the group-feeding phase of the study, the incorporation of dinotefuran in the diet at concentrations of 20000 or 50000 ppm produced an immediate (from Day 1) decrease in the food consumption of both sexes which persisted throughout the four-week treatment period. The effect on Day 1 was very marked as consumption was reduced by 40 and 50% (males and females respectively) at 20000 ppm and by 80 and 68% (males and females respectively) at 50000 ppm. The overall pattern of food consumption in dinotefuran-treated animals comprised a marked decrease in Week 1, followed by a progressive increase in consumption during the subsequent three weeks. Nevertheless, the overall food consumption at both 20000 and 50000 ppm remained significantly lower than the *ad libitum*-fed control group.

Since reduced food consumption occurred from the start of treatment, the etiology of the effect may be inferred from a consideration of the food consumption and ingested dose data for Day 1 of the study because a concentration-dependency would strongly suggest a diet palatability issue rather than non-specific toxicity. Males treated at 20000 ppm ingested a higher dose on Day 1 (1434 mg/kg bw) than the males treated at 50000 ppm (1195 mg/kg bw), but the effect on food consumption was much greater at 50000 ppm than at 20000 ppm. In females the effect was less clear because the dose ingested at 50000 ppm (1750 mg/kg bw) was slightly higher than the dose ingested at 20000 ppm (1078 mg/kg bw). Nevertheless, these data strongly suggest reduced palatability as the cause of the observed reduction in food consumption. Moreover, as food consumption, and therefore ingested dose, increased progressively during the study, reduced food consumption cannot be attributed to a nonspecific toxic effect on food consumption, the magnitude of which would be expected to increase with increasing dose. Therefore, the extent of the effect on food consumption was clearly concentration-dependent and strongly suggestive of an effect mediated exclusively by diet unpalatability.
There was a clear preference for untreated diet in the palatability groups (where the animals were given free choice), which demonstrated persistent and almost complete rejection of the diet containing 20000 ppm dinotefuran, and a less marked and more transient rejection of diet containing 4000 ppm. These data support further the contention that diets containing dinotefuran at 4000 ppm or more are unpalatable to rats. These data, together with the food consumption data from the group-matched phase, indicate that the degree of unpalatability is concentration-dependent in the range 4000 – 50000 ppm.

In the group-matched phase, body weight change in the groups treated with 20000 or 50000 ppm dinotefuran, and their group-matched controls, reflected the observed pattern of food consumption (*viz*. an immediate and marked reduction in weight gain, or frank body weight loss, followed by increasing body weight gain as the study progressed). Nevertheless, overall body weight gain at both 20000 and 50000 ppm, and their group-matched controls, remained significantly lower than the *ad libitum*-fed control group. In both sexes, at both diet concentrations, body weight gains of the dinotefuran-treated groups were similar, or superior, to the weight gains of their group-matched controls. Therefore, there was no evidence to support a non-specific toxicity etiology, and it can be inferred with a high degree of confidence that reduced body weight gain in dinotefuran-treated groups was due entirely to reduced food consumption.

A.4 Environmental effects assessment

A.4.1 Fate and distribution in the environment

A.4.1.1 Degradation

A.4.1.1.1 Abiotic degradation

Hydrolysis

Table A-102: Summary table- Hydrolysis

Method, Guideline, GLP status, Reliability, Key/supportive study	pH	Temp. [°C]	Initial TS concentration, C0[g/l]	Half-life, DT50 [d]	Coefficient of correlation, r2	Reference
OECD TG 111 EU C.7 (EEC) GLP Reliability 1 Key study	4	50	1.85	n.c.	n.a.	[redacted] (1998) IUCLID no. 10.1.1.1.a
	7		1.91	n.c.	n.a.	
	9		2.05	n.c.	n.a.	
	11 *		2.10	45	not given	
	13 *		2.05	4.2	not given	

n.a. = not applicable; n.c. = not calculated as no significant degradation reported in study. Less than 10 % hydrolysis observed after 5 days, equivalent to an environmental half-life of greater that 1 year at each pH value investigated.
* pH 11 and pH 13 are not environmentally relevant, however included in the study as additional pH.

The hydrolytic stability of Dinotefuran (with reported purity of 99.5 %) at nominal concentration of 2 $g.L^{-1}$ was studied using sterile phosphate and acetate buffer solutions at pH 4 (3.99), 7 (7.00) and 9 (9.03) plus glycine / sodium chloride buffer solutions at pH 11 (11.04) and 13 (12.99). These were maintained at 50°C in the dark in accordance with OECD Guideline 111 and Method C7 of Commission Directive 92/69/EEC ([redacted], 1998) and in accordance with the principles of GLP.

After approximately 7 d (170 h), the hydrolytic degradation was found to be 1.1% at pH 4, 3.7% at pH 7 and 10.2% at pH 9. However, at pH 11, only 15.2% of dinotefuran remained after 120 h and, at pH 13, only 2.0% remained after 24 h. Under extreme alkaline conditions, dinotefuran was found to undergo degradation to form UF.

Conclusion

As there was <11% hydrolysis observed following 7 d incubation in buffer solutions of pH 4, 7 and 9 at 50°C, Dinotefuran is considered to be hydrolytically stable and therefore no additional testing is considered necessary. Based upon results obtained at elevated temperature (50°C), the hydrolytic half-life (DT_{50}) for the compound can be considered to be in excess of 1 year when converted to average EU outdoor temperature (12°C).

Although significant hydrolysis was evident under extreme alkaline conditions, this has not been considered relevant due to the high pH values which were tested. Whilst levels of breakdown product, UF, were not quantified in the study as it focussed specifically on measuring dinotefuran, it is stated that UF was the "expected major hydrolysate". A DT_{50} value for a.s. normalised to 12°C was calculated as 39.2 d (pH 11) and 3.66 d (pH 13) so if products containing dinotefuran were to be exposed to alkaline cleaning solutions, any discharges to drains would quickly reduce in pH by dilution with wastewater and so significant formation of UF (metabolite) is unlikely to occur.

Hydrolysis is therefore not expected to be a major degradation pathway for this compound in the environment.

Phototransformation in water

Table A-103: Summary table- Photolysis in water

Method, Guideline, GLP status, Reliability, Key/supportive study	Initial molar TS concentration	Total recovery of test substance [% of appl. AS]	Photolysis rate constant (kcp)	Direct photolysis sunlight rate constant (kpE)	Reaction quantum yield (φcE)	Half-life (t1/2E)	Reference
OPPTS 835.2210 Directives 95/36/EEC and 94/37/EEC SETAC (1995) GLP Reliability 1 Key study	1:1 mixture of G- and F-label Dinotefuran, 0.720 mg/L	95.5 – 105.0	0.7391 d^{-1}	-	1.57E-04	0.9 days	[redacted] (2002e) IUCLID no. 10.1.1.1.b

Photolysis of dinotefuran in water was investigated in a study ([redacted], 2002e) performed in line with Directive 95/36/EEC, Directive 94/37/EEC, SETAC guidance plus US-EPA OPPTS 835.2210 guidelines and in accordance with the principles of GLP.

Sterile aqueous solutions of 0.72 mg l^{-1} of ^{14}C-labelled Dinotefuran (achieved by mixing equal aliquots of guanidine labelled and furanyl labelled compound) were prepared and buffered to pH 7. Samples were then irradiated continuously for 13.8 d at a controlled temperature between 23–24°C using a xenon arc lamp and all light with a wavelength of <290 nm was filtered out. Samples were assayed at 0, 0.1, 0.2, 0.4, 0.9, 1.8, 4.9, 6.9, 11.0 and 13.8 d for radiochemical balance and degradation pattern. Dark controls were run under the same conditions but only assayed at 0, 6.9 and 13.8 d.

In this study, total recovery of test samples was reported as 95.5–105.0% AR whilst values of 101.8–103.8 % AR were obtained for dark controls. From an initial mean measured concentration of 0.725 $mg.L^{-1}$, dinotefuran degraded rapidly such that only 0.016 $mg.L^{-1}$ was considered to remain after 6.9 d, giving rise to an experimental half-life of 0.9 d (21.6 h) following first order kinetics. Under non-irradiated control conditions, the test compound was shown to be stable based upon results from radio-chromatography as >97 % of AR was recovered as dinotefuran at each sampling point.

Photolytic degradation led to formation of up to 18 photoproducts, although only 6 were characterised by co-chromatography with reference compounds: DN (maximum of 7.4% AR at 11.0 d), UF (maximum of 10.6 % AR at 13.8 d), MG (maximum of 10.2% AR at 1.8 d), BCDN (maximum of 16.1% AR at 1.8 d) plus combined DN-2-OH & DN-3-OH (maximum of 28.1% AR at 13.8 d). One transformation product, coded as M2, could not be identified although maximum levels reached 16.6% AR at 11 d but, based upon chromatographic behaviour, was considered to be a multi-component fraction (with individual levels of components all <10%). Many unknown metabolites (specifically M6, M7, M8, M9, M10, M11, M12, M16 and M18) were present at maximum levels ≤3.9% of AR and could not be detected at several sampling points so were considered as minor. The remaining unknown metabolites (M3, M4 and M5) all reached maximum levels between 6.46-9.1% AR during the study which were below the level considered to identify them as "major". Only those metabolites with levels >10% AR and predicted breakdown products (such as DN) were characterised.

The quantum yield of direct photodegradation of dinotefuran at 23-24°C in pure water was then used to estimate its environmental half-life in natural waters by means of the GC-Solar simulation model. Depending upon season, theoretical half-lives were considered to range between 1.70–4.34 d (30°N), 1.80–7.76 d (40°N) and 1.97–18.60 d (50°N). Conditions in the GC-Solar program assumed pure water close to the surface (0-5 mm) of the water body, 10° of longitude, terrestrial atmosphere

type with typical ephemerides and ozone values.

Conclusion

Photolytic breakdown of dinotefuran gave rise to 18 photoproducts with the major metabolites (present at $\geq$10 %) being UF, MG, DN-2-OH & DN-3-OH, BCDN plus an unidentified mixture of at least two components coded as M2. Although an experimental degradation DT_{50} of 0.9 d was derived from first order kinetic modelling of study results, this was derived from continuous exposure to light.

Results of the photolysis study with dinotefuran indicate that direct photodegradation in water could contribute to the overall elimination of the compound in the aquatic compartment. However, it must be noted that incident solar radiation will vary between different locations and at different times of the year. Furthermore, where natural surface waters are turbid, aqueous photolysis reactions would only likely occur very close to the surface of a water body and, in general, partitioning to water and sediment might act as a contributing factor to removal from the water phase. Therefore, it is difficult to accurately predict the influence of photolysis in such systems on an EU-wide basis. In Northern European scenarios similar to UK conditions, it is likely that photolysis will only have a relatively minor impact on dissipation (turbidity reducing light transmission and energy thus limiting photolytic potential). However, where water bodies are considered to be slow moving (e.g. ponds and lakes), they could potentially be less turbid than rivers / streams so photolysis could be more relevant. The metabolites that were considered major (i.e. >10 % formation) were noted to be formed at levels that only just exceeded 10% under test conditions that are designed to maximise their formation (e.g. small optically dilute sterile aqueous solutions under constant irradiation). Taking into account the additional factors highlighted above and the fact that the indoor use pattern proposed for the representative product will not result in any direct exposure to surface waters, the UK CA considers that the formation of aqueous photolytic metabolites does not need to be considered as part of the EU environmental exposure assessment. However, this route of degradation should be considered on a case-by-case basis by individual Member States depending upon local conditions, especially if use patterns were to be extended / changed and could potentially lead to direct exposure of surface water

Estimated photo-oxidation in air

Table A-104: Summary table- Photo-oxidation in air

Model	Light protection (yes/no)	Estimated daily (24h) OH concentration [OH/cm³]	Overall OH rate constant [cm³/molecule ec]	Half-life [hr]	Reference
Estimation (Atkinson) **US-EPA AOPWIN, version 1.70 (1995)**	-	-	160.596 E-12	0.067 d (12 h day; 1.5E6) 0.033 d (24 h day; 1.5E6)	[redacted] (2000)
Estimation (Atkinson) **US-EPA AOPWIN, version 1.92 (2010)**	-	-	156.0666 E-12	0.10 d or 2.4 h (24-h day; 5.0E5)	QSAR output92 IUCLID no. 10.3

The half-life of Dinotefuran in air due to indirect photodegradation, i.e. oxidation with photochemically produced hydroxyl radicals, was calculated using the software programme AOPWIN, v1.70, 1995 by US-EPA based upon QSAR methods developed by Dr. Roger Atkinson and co-workers. AOPWIN requires only a chemical structure to make these predictions, with structures entered into AOPWIN by SMILES (Simplified Molecular Input Line Entry System) notations.

Guidance provided to support this particular model recommends use of 12h atmospheric hydroxyl radical concentrations (1.5 x 10^6 OH^- molecules cm^{-3}) during sunlight hours to take account of airborne pollution. As a consequence, the half-life of Dinotefuran in the troposphere was calculated to be 0.033 d based upon a degradation rate of 160.596 x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} ([redacted], 2000).

However, the UK CA had undertaken additional calculations to revise half-life using average 24-h OH^- radical concentrations (5 x 10^5 molecules cm^{-3}) reportedly to account for relatively unpolluted air in the EU, as outlined within section 2.3.6.3 of the former TGD for risk assessment, based upon the formula that:

$$T_{½} = \frac{\ln 2}{[K_{OH} \bullet [OH\ rad]}$$

where K_{OH} is estimated hydroxyl radical reaction rate, predicted as 156.0666 x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} when modelled using the latest Version 1.92 of AOPWIN and SMILES notations for a.s. of [C1(CCOC1)CNC(=NN(=O)(=O))NC] and [C(NC)(=NN(=O)(=O))NCC1(CCOC1)]

When taking account of criteria specified within the TGD, revised results presented in Table A-108 indicate that estimated atmospheric half-life of dinotefuran was found to be 0.1 d.

Conclusion

The estimated half-life for dinotefuran in air was found to be 0.1 d (or 2.4 h), indicating that after evaporation or exposure to the air, the substance is rapidly degraded in the atmosphere and the transport over longer distances or accumulation in air is negligible.

A.4.1.1.2 Biotic degradation, initial studies

Biodegradability (ready/inherent)

Table A-105: Summary table - biodegradation studies (ready/inherent)

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Test parameter	Inoculum			Additional substrate	Test sub-stance concentr	Degradation		Remarks [positive control]	Reference
			Type	Concentration	Adaptation			Incubation period	Degree [%]		
OECD TG 301F EU C.4-D GLP Reliability 1 Key study	Yes	BOD	Aerobic activated sludge	1.5 g/L dry matter (final conc. 29 g/L)	Yes*	Sodium benzoate	103	28 days	0	10-day window criteria not passed	[redacted] (2012b) IUCLID no. 10.1.1.2

[1] Test on inherent or ready biodegradability according to OECD criteria

* The solid material of sludge is reported as being centrifuged, re-suspended (3 times) in test water and aerated overnight

Dinotefuran (of 99.4% purity) was investigated for its ready biodegradability in a GLP compliant study ([redacted], 2012b) comparable to OECD Guideline 301 F (1992; "Manometric Respirometry Test") and Commission Regulation 440/2008/EC : Method C.4-D. It was performed using an initial mean concentration of 103 mg a.s. L^{-1} for 28 days under aerobic conditions in the dark. Incubation was carried out at 21-22°C with bacteria collected from activated sludge of a wastewater plant treating predominantly domestic sewage (Rossdorf in Germany) and pH was reported to vary from 6.8–7.6 over the test period. The reference control was performed with 100 mg.L^{-1} of sodium benzoate. Degradation was followed by determination of oxygen uptake (consumption of oxygen (BOD)). Mean biodegradation of dinotefuran over 28 days was determined as 0%.

Conclusion

Based on the results of a Manometric Respiratory Test (OECD 301 F), Dinotefuran can be classified as "not readily biodegradable" according

to the definitions given by the OECD guidelines for assessing ready biodegradability. An inherent biodegradation study was not performed but a more realistic water/sediment degradation study (outlined in Section 4.1.1.2.2) has been provided.

A.4.1.1.3 Rate and route of degradation including identification of metabolites and degradation products

A.4.1.1.3.1 Biological sewage treatment

Not applicable for the CLH report

Aerobic biodegradation

Table A-106: Summary table - STP aerobic biodegradation

Not applicable for the CLH report

Anaerobic biodegradation

Table A-107: Summary table - STP anaerobic biodegradation

Not applicable for the CLH report

STP simulation test

Table A-108: Summary table - STP simulation test

Not applicable for the CLH report

A.4.1.1.3.2 Biodegradation in freshwater

Aerobic aquatic degradation

Table A-109: Summary table - Freshwater aerobic biodegradation

Data waiving.

The representative biocidal product is not intended for direct emission to water. Therefore, provision of this study is not required.

Estimation of dinotefuran's degradation in water can be extracted from the water/sediment degradation test if required.

Water/sediment degradation test

Table A-110: Summary table - fresh water/sediment degradation

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Exposure	Test system		Test substance concentration (mg/L)	Incubation period (days)	Degradation Total system (DT_{50}, days)*	Remarks	Reference
			Water	Sediment					
AEROBIC									
EPA 162-4, SETAC Guideline 8.2, Commission Directive 95/36/EC of 14 July 1995 Equivalent to OECD TG 308 GLP Reliability 1 Key study	Yes	20±1°C, in the dark, aerobic	River (Mumpf, Switzerland)	River (Mumpf, Switzerland)	0.0507	320	56.7	Metabolite DN reached a maximum of 23.1% AR in total river system	[redacted] (2000l) IUCLID no. 10.1.3
			Pond (Judenweiher, Switzerland)	Pond (Judenweiher, Switzerland)	0.0507		44.5	Metabolite DN reached a maximum of 32.6% in total pond system	
OPPTS 835.4300, OPPTS 835.4400, equivalent to OECD TG 308, GLP Reliability 1 Key study	Yes	20±2°C, in the dark, aerobic	Lake (Calwich Abbey, UK)	Lake (Calwich Abbey, UK)	0.204	100	24.2	Metabolite DN reached max. occurrence of 69.6% AR	[redacted] (2011c) IUCLID no. 10.1.3
			Lake (Swiss Lake, UK)	Lake (Swiss Lake, UK)	0.199		64.0	Metabolite DN reached max. occurrence of 47.4% AR	
OECD TG 308, OPPTS 835.4300, GLP Reliability 1 Key study	Yes	20-25°C, in natural light, aerobic	Lake (Calwich Abbey, UK)	Lake (Calwich Abbey, UK)	0.0692	14	2.19	Unknown polar metabolite reached max. occurrence of 15.8% AR	[redacted] (2020a) IUCLID no. 10.1.3
			Lake (Emperor Lake)	Lake (Emperor Lake, UK)	0.0618		3.07	Unknown polar metabolite reached max. occurrence of	

								12.3% AR	
ANAEROBIC									
OECD TG 308, OPPTS 835.4300, OPPTS 835.4400, equivalent to OECD 308, GLP Reliability 1 Key study	Yes	20±2°C, in the dark, anaerobic	Lake (Calwich Abbey, UK)	Lake (Calwich Abbey, UK)	0.204	100	26.0	Metabolite DN reached max. occurrence of 74.4% AR	[redacted] (2011c) IUCLID no. 10.1.3
			Lake (Swiss Lake, UK)	Lake (Swiss Lake, UK)	0.199		48.3	Metabolite DN reached max. occurrence of 66.3% AR	
1 Test according to/equivalent to OECD criteria *** Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12° C.**									

Summary table - metabolite DN formed in fresh water/sediment aerobic degradation of the dinotefuran study

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Exposure	Test system		Test substance concentration (mg/L)	Incubation period (days)	Degradation Total system (DT_{50}, days)*	Remarks	Reference
			Water	Sediment					
AEROBIC									
EPA 162-4, SETAC Guideline 8.2, Commission Directive 95/36/EC of 14 July 1995 Equivalent to OECD TG 308 GLP Reliability 1 Key study	Yes	20±1°C, in the dark, aerobic	River (Mumpf, Switzerland)	River (Mumpf, Switzerland)	0.0507	320	114		[redacted] (2000l) IUCLID no. 10.1.3
			Pond (Judenweiher, Switzerland)	Pond (Judenweiher, Switzerland)	0.0507		80		

OPPTS 835.4300, OPPTS 835.4400, equivalent to OECD TG 308, GLP Reliability 1 Key study	Yes	20±2°C, in the dark, aerobic	Lake (Calwich Abbey, UK)	Lake (Calwich Abbey, UK)	0.204	100	n.c.	DT_{50} cannot be derived due to insufficient number of data points	[redacted] (2011c) IUCLID no. 10.1.3
			Lake (Swiss Lake, UK)	Lake (Swiss Lake, UK)	0.199		n.c.	DT_{50} cannot be derived due to insufficient number of data points	
1 Test according to/equivalent to OECD criteria *** Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12° C.**									

n.c. = not calculated.

Due to the absence of ready biodegradability and potential for limited indirect exposure of surface waters, the fate of Dinotefuran in water/sediment systems was investigated under laboratory conditions.

The applicant provided three degradation tests in the water-sediment system : two studies under dark laboratory conditions at 20°C and one study under outdoor natural light, at 20-25°C. Moreover one study was also performed under dark anaerobic laboratory conditions at 20°C. The degradation of the metabolite DN was also studies in the two studies under dark laboratory conditions.

In the study of [redacted] (2000l), aerobic degradation of ^{14}C-labelled Dinotefuran was investigated in pond and river systems. Samples of each sediment and its associated surface water at an approximate ratio of 1:3 (taken from River Rhine near Mumpf in Switzerland and a freshwater pond near Judenweiher in Switzerland) were treated with [^{14}C]-dinotefuran at a rate of 0.05 $mg.L^{-1}$ which was applied to the surface of the water phase. Treated samples were incubated in the dark under aerobic conditions at a temperature of 20±1°C for 320 days, with volatile radioactivity trapped in NaOH traps (for $^{14}CO_2$) and ethylene glycol (for organic volatiles).
Total recoveries of radioactivity (mass balance) were generally 96.6 ± 3.7% of AR (applied radioactivity) for the pond system (ranging between 90.9–102.2% AR) and 95.2±5.9% of AR for the river system (ranging between 80.6–101.3% AR). However, it should be noted the recovery in the river system exceeded 90% AR at every sampling point up to and including 258 d (90.1–101.3%) and only dropped to 80.6% at study completion (320 d) so has not been considered to reduce overall reliability of the study.
Levels of radioactivity associated with the surface water samples quickly declined as the incubation progressed, accounting for 48.8% AR in the river system and 23.4% AR in the pond system after 56 d. Over the same period (56 d), radioactivity extracted from freshwater sediment had increased to 24.7% AR in the river system and 36.8% AR in the pond system. At study completion, only 8.3 % AR was detected in the water phase of the river system whilst only 2.6% AR remained in the water phase of the pond system. Non-extractable residues increased steadily and significantly in both systems over the duration of incubation (320 d), with 62.9% AR in the pond system and 28.2% AR in the river system at study termination. Significant levels of mineralisation was observed in both systems, reaching maximum levels of 19.9% AR as $^{14}CO_2$ (pond system) on day 258 and 34.9% AR as $^{14}CO_2$ (river system) on day 320. Other organic volatiles could not be detected.
In terms of the test material, ^{14}C-dinotefuran was shown to degrade in aerobic aquatic systems, with "total system" degradation (DT_{50}) half-lives of 56.7 d (river) and 44.5 d (pond) determined by first order kinetic modelling at 20°C. As the study demonstrated significant

relocation of test material to the sediment phase, dissipation half-lives at 20°C for dinotefuran of 49.2 d (river) and 23.0 d (pond) from the water phase were also derived by first order kinetic modelling. When normalised to 12°C, dissipation DT_{50} values would be equivalent to 93.3 d (river) and 43.6 d (pond).

Although up to 6 degradation products were detected (including UF, MNG and NG at <4.0 % AR), only one main transformation product was characterised – DN. There is evidence to show that this major metabolite underwent further degradation in both systems as levels of DN reached a maximum of 23.1% AR after 180 d (river system) and a maximum of 32.6% AR after 103 d (pond system) before falling to 9.0% AR and 7.8% AR respectively by study completion.

Based upon the study results, it is evident that emissions of dinotefuran reaching surface waters will first dissipate from the water phase to the sediment phase and then undergo steady degradation in both river and pond systems, predominantly to DN. Although degradation would not likely be rapid, significant levels of mineralisation can be predicted thus supporting removal from the aquatic compartment.

Table 4.4 Aquatic degradation of Dinotefuran and major metabolite DN at 20°C ([redacted], 2000l)

Water-Sediment system	Component	Compound	DT_{50} (d)	DT_{90} (d)
River (Rhine near Mumpf)	Surface Water (dissipation)	Dinotefuran	49.2	163.3
	Total System (degradation)	Dinotefuran (individual) Dinotefuran (sequential)	56.7 59.0	188.5 n.c.
	Total System (degradation)	DN (individual) DN (sequential)	114 105	378.0 n.c.
Pond (near Judenweiher)	Surface Water (dissipation)	Dinotefuran	23.0	76.3
	Total System (degradation)	Dinotefuran (individual) Dinotefuran (sequential)	44.5 46.6	147.8 n.c.
	Total System (degradation)	DN (individual) DN (sequential)	80.0 86.8	267.0 n.c.

n.c. – not calculated

DT_{50} values predicted by the Applicant in **Table 4.4** have been derived from several kinetic models (including one seeking "best fit to data") and all half-lives were calculated individually (i.e. parent and metabolite degradation were not considered sequentially). As a consequence, the UK CA as RMS for the first inclusion had has considered it necessary to run additional sequential "parent and metabolite" models using SFO kinetics at 20°C and has determined similar but not identical half-lives than those reported in the study. Therefore, it is considered more relevant to use sequential degradation DT_{50} values in risk assessment. Appropriate total river system DT_{50} values at 20°C for

dinotefuran and DN would therefore be 59.0 d and 105 d respectively whilst appropriate DT_{50} values for total pond system at 20°C would be 46.6 d (dinotefuran) and 86.8 d (DN).

The total system degradation DT_{50} values calculated by UK CA for each substance at 20°C and then normalise to 12°C (average EU outdoor temperature), are 112 days (k value: 0.0062 d^{-1}) for river system and 88.3 days (k value: 0.0079 d^{-1}) for pond system for the active substance Dinotefuran and 199d for river system and 165 days for pond system for its metabolite DN, respectively.

In the study of [redacted] (2011c), the aerobic and anaerobic degradation of ^{14}C-labelled Dinotefuran was investigated in the two water-sediment systems Swiss Lake and Calwich Abbey Lake. Samples of each sediment and its associated surface water at an approximate ratio of 1:3, taken from Swiss Lake and Calwich Abbey Lake. The sediment from Swiss Lake was a sand with a slightly acidic pH and low organic carbon while that from Calwich Abbey Lake was a slightly basic silt loam with a higher organic carbon content. Samples were treated with [^{14}C]-dinotefuran at a rate of 0.2 $mg.L^{-1}$ which was applied to the surface of the water phase. Treated samples were incubated were incubated under aerobic or anaerobic conditions at 20±2°C in darkness for periods of up to 100 days, with volatile radioactivity trapped in KOH traps with phenolphthalein (for $^{14}CO_2$) and ethylene digol (for organic volatiles).

For the aerobic experiment, total recoveries of radioactivity (mass balances) were 94.4-100.8% AR for both aquatic sediments and radiolabels. Total radioactivity declined in water with time, representing means of 16.3% AR and 29.9% AR after 100 days in Calwich Abbey Lake and Swiss Lake samples, respectively. There were corresponding increases with time in sediment radioactivity (58.3 -77.5% at day 100). Non-extractable residues in the sediment accounted for means of 9.2% AR for Calwich Abbey Lake and 3.2% AR for Swiss Lake after 100 days. Volatile radioactivity, all associated with $^{14}CO_2$, represented 3.1% AR after 100 days in the Calwich Abbey Lake samples and 7.5% AR after 100 days in the Swiss Lake samples.

For the anaerobic experiment, total recoveries of radioactivity (mass balances) were 91.2-99.4% AR for both aquatic sediments and radiolabels. Total radioactivity declined in water with time, representing means of 15.7% AR and 24.5% AR after 100 days in Calwich Abbey Lake and Swiss Lake samples, respectively. There were corresponding increases with time in sediment radioactivity (69.9 - 79.3% at day 100). Non-extractable residues in the sediment accounted for means of 10.4% AR for Calwich Abbey Lake and 5.8% AR for Swiss Lake after 100 days. Volatile radioactivity, all associated with $^{14}CO_2$, represented approximately 1 % AR after 100 days in both sediments.
Chromatographic profiles were qualitatively similar between radiolabels and aquatic sediments. A significant metabolite in both the aerobic and anaerobic experiments was DN, formed by loss of the 2-nitro group. This degradation product accounted for up to 74.4% AR in the total system. A number of minor degradation products were found, each accounting for 9.6% AR in any system.
DT_{50} and DT_{90} values (in days) for the decline of dinotefuran from the water, sediment and total aquatic sediment system are shown in **Table 4.5** below.

Table 4.5 Aquatic degradation of dinotefuran and major metabolite DN at 20°C ([redacted], 2011c)

Water-Sediment system	Component	DT_{50} (d)	DT_{90} (d)

Aerobic experiment			
Calwich Abbey	Surface Water	18.8	62.3
	Sediment	14.6	48.6
	Total System	24.2	80.3
Swiss lake	Surface Water	47.1	156
	Sediment	128	425
	Total System	64.0	213
Anaerobic experiment			
Calwich Abbey	Surface Water	19.8	65.9
	Sediment	36.4	121
	Total System	26.0	86.5
Swiss lake	Surface Water	36.6	122
	Sediment	32.1	107
	Total System	48.3	160

In the study of [redacted] (2020a), the aerobic degradation of ^{14}C-labelled Dinotefuran was investigated in two natural water-sediment systems outdoors under natural sunlight. The sediments and overlying natural waters were collected from Calwich Abbey, Staffordshire, UK and Emperor Lake, Chatsworth, Derbyshire, UK.

Samples of each sediment and its associated surface water at an approximate ratio of 1:3 to 1:3.5 (with a sediment layer of 2.0 cm) were treated with [^{14}C]-dinotefuran at a rate of 69.2 µg a.i./L for Calwich Abbey samples and 61.8 µg a.i./L for Emperor Lake samples, respectively, applied to the surface of the water phase. Treated samples were incubated outdoor under natural sunlight aerobic conditions at a temperature of 20-25°C for 14 days, with volatile radioactivity trapped in NaOH traps (for $^{14}CO_2$) and ethylene glycol (for organic volatiles). Samples were analysed immediately following test item application and after the following periods of aerobic incubation: 3, 6, 18, 24 hours, 3, 7 and 14 days.

Total recoveries of radioactivity (mass balance) were 95.0 ± 6.0% of AR (ranging between 90.4–106.9% AR) for Calwich Abbey test system and 100.4 ± 5.4 % of AR (ranging between 90.9–110.8% AR) for Emperor Lake test system.

Dinotefuran degraded rapidly in both test systems during the incubation period. It accounted for a mean of 1.2% AR in the total Calwich Abbey test system and 12.1% AR in the total Emperor Lake test system, by 14 DAT. Only low levels of dinotefuran were observed in sediment extracts, reaching a maximum of 3.4% AR at 0.125 DAT and 1.6% AR at 7 DAT for Calwich Abbey and Emperor Lake, respectively.

A significant level of radioactivity was attributed to polar material for both test systems. This reached a maximum level of 53.3% AR in Calwich Abbey Day 14 Replicate 2 and 35.7% AR in Emperor Lake Day 7 Replicate 1 for the total test system. A structure was postulated for a radiolabelled component (component A).

The degradation rate (DT_{50} and DT_{90}) of dinotefuran was determined using non-linear regression and a single first order kinetic model (SFO, CAKE, Version 3.3). The degradation rates are summarised in **Table 4.6** below:

Table 4.6 Aquatic degradation of dinotefuran and major metabolite DN at 20°C ([redacted], 2020a)

Water-Sediment system	Component	DT_{50} (d)	DT_{90} (d)
Calwich Abbey	Surface Water	2.15	7.14
	Total System	2.19	7.27
Emperor Lake	Surface Water	2.88	9.58
	Total System	3.07	10.2

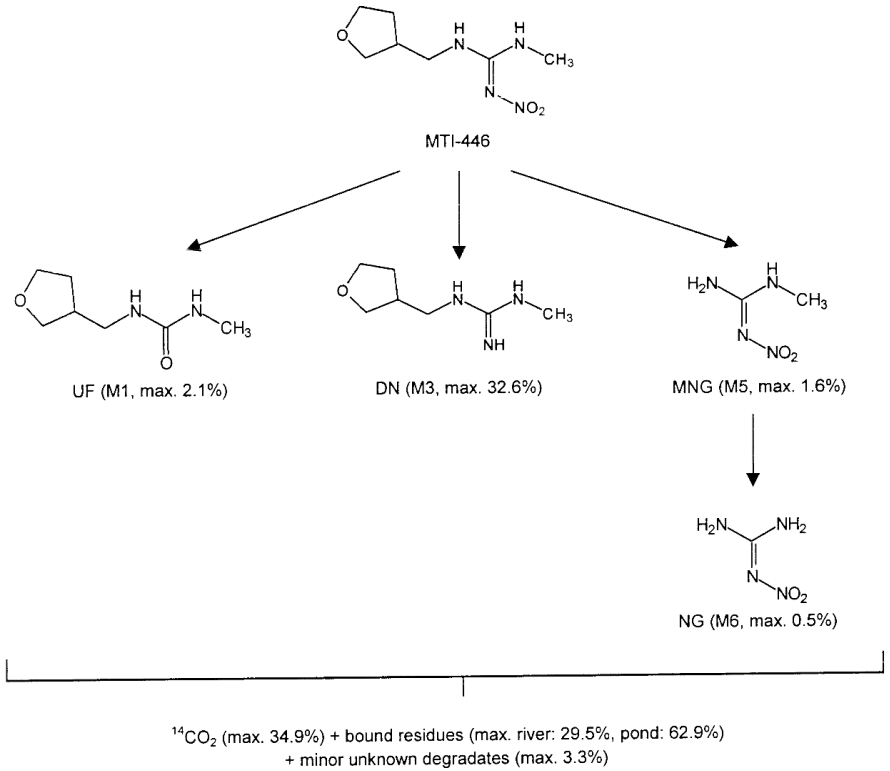

Figure A-4-1 Proposed metabolic pathway for dinotefuran in both aquatic systems (based on [redacted], 2000l)

Conclusion

The study of [redacted] (2011c) has been re-evaluated by eCA NL in the frame of a product authorization. The degradation kinetics were recalculated using Computer Assisted Kinetic Evaluation (CAKE version 3.3) software and following the guidance : OECD 308, RIVM manual, OPPTS 835 3100 and OPPTS 835 3180. This re-evaluation has been the subject of a discussion during ENV WG-V-2019 to determine whether Dinotefuran meet the (very) persistence criteria. The WG agreed with the DT_{50} calculations performed by the eCA.

The study of [redacted] (2020b) presents a re-evaluation of the water sediment degradation kinetics studies conducted with Dinotefuran (i.e. of ([redacted], 2000l, [redacted], 2011c and [redacted], 2020a) in order to estimate degradation half-lives (DT_{50}) for ^{14}C-Dinotefuran using Computer Assisted Kinetic Evaluation (CAKE version 3.3) software and following the FOCUS Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies (2006). The choice of the selected model took into consideration the visual assessment (good, acceptable, poor), estimation of the χ^2 (the best-fit model should be <15) and t-test (i.e. 5% significance level) to assess significance of the degradation parameters.

In the study conducted under aerobic conditions by [redacted] (2000l) and in the study conducted under aerobic and anaerobic conditions by [redacted] (2011c), degradation of the parent compound and the formation and decline of metabolite DN were considered simultaneously, since DN was observed at 10 % of applied radioactivity (%AR) and therefore considered as a major metabolite. With respect to the sediment phase, due to its physico-chemical properties (i.e. high water solubility and low sorption corresponding respectively to >39 g/L and 25.4 L/kg) dinotefuran is not expected to sorb to the sediment. Due to these properties, residues in sediment should be interpreted as dinotefuran in solution of the interstitial water present in the sediment phase and not as dinotefuran directly sorbed to the sediment phase particles. Therefore, no calculation of DT_{50} in the sediment compartment was performed as it was not expected to be reliable. The kinetic simulation of [redacted] (2020a), considered simple degradation of the parent to sink for the whole system and water phase.

The DT_{50} were normalised to reference temperature conditions of 12°C, following equation 28 of the GBPR (2017). In the studies from [redacted] (2011c) and [redacted] (2000l) the experimental temperature corresponded to 20 °C, whereas in the study from [redacted], (2020a) temperatures corresponded to 21.9°C and 22.9°C for Emperor Lake and Calwich Abbey Lake, respectively. Temperature-normalised DT_{50} values for the aerobic and anaerobic degradation in studies are reported in **Table 4-7**.

The whole system DT50 of dinotefuran is available from >3 systems. Therefore according to the GBPR (2017), a geometric mean of 36.2 days is proposed by the Applicant. However taking into account the calculation agreed at ENV WG-V-2019, a geometric mean of 37.6 days is proposed to be used for risk assessment of the parent compound in the water-sediment compartment. For classification purposes, it was agreed at ENV WG-V-2019 the most stringent result should be used according to REACH R11 criteria. Consequently it is appropriate to use of the value of 145.40 days (Swiss lake, normalised to 12°C).

Table 4.7 Aquatic degradation of Dinotefuran under aerobic and anaerobic conditions after normalisation to reference temperature of 12°C

Aerobic conditions				
Water-Sediment system	**Phase**	**DT_{50} (d) ([redacted], 2020b)**	**Normalised DT_{50} (d) ([redacted], 2020b)**	**Normalised DT_{50} (d)**
River ([redacted], 2000l)	Surface Water	50.8	96.3	-
Pond ([redacted], 2000l)	Surface Water	50.8	96.3	-
Calwich Lake ([redacted], 2011c)	Surface Water	20.1	38	42.98[1]
Swiss Lake ([redacted], 2011c)	Surface Water	50.4	95.5	107.80[1]
Calwich Abbey Lake ([redacted], 2020a)	Surface Water	2.15	5.14	-
Calwich Abbey Lake ([redacted], 2020a)	Surface Water	2.88	6.36	-
River ([redacted], 2000l)	Total System	59.1	112	112
Pond ([redacted], 2000l)	Total System	46.5	88.2	88.2
Calwich Lake ([redacted], 2011c)	Total System	26.1	49.4	55.81[1]
Swiss Lake ([redacted], 2011c)	Total System	68	129	145.4[1]
Calwich Abbey Lake ([redacted], 2020a)	Total System	2.19	5.24	5.24
Calwich Abbey Lake ([redacted], 2020a)	Total System	3.07	6.78	6.78
GEOMETRIC MEAN	**WHOLE SYSTEM**	**-**	**36.2**	**37.6**

Anaerobic conditions			
Water-Sediment system	**Phase**	**DT_{50} (d) ([redacted], 2020b)**	**Normalised DT_{50} (d) ([redacted], 2020b)**
Calwich Lake ([redacted], 2011c)	Surface Water	21.0	39.8
	Total System	27.5	52.2
Swiss Lake ([redacted], 2011c)	Surface Water	38.7	73.4
	Total System	52.4	99.4

[1] Values calculated by eCA NL and agreed at ENV WG-V-2019

Information on the metabolite DN is available from the studies conducted in the dark ([redacted] 2000l and [redacted] 2011c). The study conducted by [redacted] (2011c) does not allow for the selection of a reliable DT_{50}, considering that towards the end of the study, the concentration of the metabolite DN increases and a decline phase is not clearly observed during the whole incubation time (100 days). Nevertheless, in the study conducted by ([redacted], 2000l), a decline phase is observed after 100 days, until the end of the study (i.e. 320 days of incubation). Therefore, the assessment of the decline phase for the metabolite DN, requires an incubation period longer than 100 days in order to observe the decline phase required to calculate a reliable and realistic DT50. Consequently, only the DT_{50} values derived from [redacted] (2000l) should be taken into account.

Under exclusively anaerobic conditions, metabolite DN is formed as the major metabolite both in a soil degradation study ([redacted], 2003b) and in a water/sediment study ([redacted], 2011c); therefore, DN is expected to be formed mainly under anaerobic conditions. In the studies conducted under aerobic conditions by [redacted] (2000l) and [redacted] (2011c), DN is observed in concentrations which consider this metabolite to be a major metabolite in aerobic systems. However, in aerobic studies, the sediment layers immediately below the superficial layer are expected to be anaerobic because the oxygen pumped to the water/sediment system stays only in the superficial layer of the sediment. Therefore, degradation in aerobic systems also includes anaerobic processes, which are responsible for the formation of DN in aerobic studies. Diffusion processes are subsequently involved in the distribution of DN also in the water layer. Hence, a risk assessment for DN in the water and sediment compartment under aerobic conditions should not be performed.

A.4.1.1.3.3 Biodegradation in seawater

Seawater degradation study

Table A-111: Summary table - Seawater aerobic biodegradation

No data is available.

Seawater/sediment degradation study

Table A-112: Summary table - seawater/sediment biodegradation

Data waiving.

If a substance is to be used or released in marine environments in considerable amounts (e.g. it is known to be repeatedly used or continuously released in marine environments), then a seawater biodegradation test according to OECD Test Guideline 306 (Biodegradability in Seawater) will be required. The representative biocidal product is not intended for use where release in the marine environment would occur. Therefore, provision of this study is not required. For CLH purposed, the information provided in the fresh water section is considered enough to lead to a classification.

A.4.1.1.3.4 Higher tier degradation studies in water or sediment

Data waiving.

As a refinement for risk assessment, higher tier studies may be required. Based upon the use of the representative biocidal product, higher tier studies for refinement of risk assessment are not required.

A.4.1.1.3.5 Biodegradation during manure storage

Table A-113: Summary table - Biodegradation during manure storage

Not applicable for the CLH report

A.4.1.1.3.6 Biotic degradation in soil

A.4.1.1.3.6.1 Laboratory soil degradation studies

Aerobic biodegradation

Table A-114: Summary table - Aerobic biodegradation in soil- laboratory study

Method, Guideline, GLP status, Reliability, Key	Test type[1]	Exposure	Test system				Test substance conc. (mg a.s./ kg dsw)	Incubation period (days)	Degradation DT_{50} (days)*	Remarks	Reference
			Soil origin	Soil type	pH	OC %					
Commission Directive 95/36/EC of 14 July 1995, SETAC 1995 Part 1, OECD Aerobic/anaerobic transformation in soil (draft, August 2000) GLP Reliability 1 Key study	Yes	20±2°C, in the dark	Gartenacker, Switzerland	Silt loam	7.2	1.8	0.3	120	10.2	Metabolite MNG and NG were formed as major degradation products MNG reached a maximum of 15.6% AR at 20°C. NG accounted a maximum of 5.4% AR.	[redacted] (2003b), IUCLID no. 10.2.1
		10±2°C, in the dark							21.1		
SETAC 1995 Part 1, 1.1 Aerobic degradation, GLP Reliability 1 Key study	Yes	20±2ºC, in the dark	Ringenwald, Germany	Sand	6.25	1.19	0.4	28# and 49&	16.4#	Dinotefuran mineralised to $^{14}CO_2$ ranging from 36.2% to 70.2% AR for eleven soils. The rate of degradation of dinotefuran in soils was faster than rate of mineralisation	[redacted] (2001e), IUCLID no. 10.2.1
			Stolpe, Germany	Sandy loam	6.14	1.22			13.9#		
			Zwingenber, Germany	Loam	7.39	1.27			15.5#		
			Karolinenhof Germany	Loamy sand	7.11	2.18			10.7#		
			Otzberg, Germany	Silt loam	7.31	1.46			9.4#		
			Borstel, Germany	Loamy sand	5.60	1.77			23.0&		
			Velten, Germany	Sand	4.22	1.42			65.5&		
			Walluf, Germany	Silt loam	7.20	1.60			26.1&		
			Rossdorf, Germany	Loam	7.35	0.68			22.3&		

			Phoeben, Germany	Sand	6.81	0.77			20.8[&]		
			Mechthildshausen, Germany	Loam	7.27	1.22			16.7[&]		

[1] Test according to/equivalent to OECD criteria
*** Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12°C.**
[#]Samples extracted on 28 day
[&] Samples extracted on 28 day and additionally on 49 day of incubation

Summary table - Metabolite MNG formed in aerobic biodegradation in soil of the active substance- laboratory study

Method, Guideline, GLP status, Reliability, Key	Test type[1]	Exposure	Test system				Test substance conc. (mg a.s./ kg dsw)	Incubation period (days)	Degradation DT_{50} (days)*	Remarks	Reference
			Soil origin	Soil type	pH	OC %					
Commission Directive 95/36/EC of 14 July 1995, SETAC 1995 Part 1, OECD Aerobic/anaerobic transformation in soil (draft, August 2000) GLP Reliability 1 Key study	Yes	20±2°C, in the dark	Gartenacker, Switzerland	Silt loam	7.2	1.8	0.3	120	87.7		[redacted] (2003b), IUCLID no. 10.2.1
		10±2°C, in the dark							Not calculated		

[1] Test according to OECD criteria
*** Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12°C.**

Due to the restricted use pattern of the reference product – Dinotefuran 2% bait – with professional indoor application of gel bait to areas not prone to frequent wet cleaning for the control of cockroaches, the Applicant does not consider that data investigating the aerobic degradation of dinotefuran in soil should be required.

However, for completeness, an aerobic degradation study in one European soil at two different temperatures was provided. In the study by [redacted] (2003b), the route and rate of aerobic degradation of ^{14}C-labelled dinotefuran (achieved by mixing equal aliquots of guanidine labelled and furanyl labelled compound) in a single soil (silt loam) was investigated in the laboratory performed in line with Directive 95/36/EEC : Annex II – 7.1.1.2, SETAC : Part 1 guidance plus draft OECD guidelines and in accordance with the principles of GLP. Soil samples were treated with 0.31 mg.kg^{-1} dwt of radio-labelled a.s. and were then incubated aerobically in the dark at both 10±2°C and 20±2°C for 120 days. Immediately after application (day 0) and 3, 7, 10, 14, 21, 28, 62 and 120 d, one sample of each system (10°C and 20°C) was taken for quantification by LSC and analysis by HPLC or TLC. In addition, duplicate samples were analysed on days 0 and 28 from the 20°C test system.

Table 4.8 Characteristics of test soil (aerobic degradation study)

Characteristic	Test soil
Origin	Gartenacker, Switzerland
Soil classification (USDA)	Silt loam
Clay [%]	10.3
Silt [%]	52.3
Sand [%]	37.4
pH (0.01M $CaCl_2$)	7.2
Organic carbon [g / 100 g soil]	1.8
CEC [meq / 100 g soil]	13.1
Maximum WHC at pF1 (g / 100 g wet soil)	67.5
40 % MWC (g / 100 g wet soil)	27.0

^{14}C-dinotefuran was shown to degrade quickly in aerated soil, with half-lives of 10.2 days (20°C) and 21.1 days (10°C) determined by first order kinetic modelling. Total recoveries of radioactivity (mass balance) were generally 93.5±1.8% of AR for the 20°C test system (ranging between 91.0–95.9% AR) and 93.5±2.4% of AR for the 10°C test system (ranging between 90.1–95.9% AR). Mineralisation to $^{14}CO_2$ was high at both temperatures, reaching maximum levels of 52.1% (20ºC) and 43.7% (10ºC) of AR by study completion (120 days). Bound residues in soil increased steadily during the study until they reached 25.7% AR (20°C test system) and 19.9% AR (10°C test system) at termination on day 120.

Although up to 9 degradation products were detected, only two main transformation products were characterised – MNG and NG (all others namely UF, FNG and 5 unidentified compounds were detected at $\leq$1% in both test systems). Only MNG can be considered as a major metabolite with levels >10% AR reported during the study but NG (reported levels <6%) has also been monitored as it is considered to be a degradation product of MNG. There is evidence to show that neither of these metabolites of dinotefuran accumulated in either soil system but likely underwent further degradation. Levels of MNG reached a maximum of 15.6% AR after 28 days (20°C test system) and a maximum of 16.0% AR after 62 days (10°C test system), falling to 7.3% AR and 14.9% AR respectively by study completion. NG only reached a maximum of 5.2% AR on day 62 in the 20°C test system and a maximum of 5.4% AR on day 120 in the 10°C test system.

A new aerobic degradation study on 12 German soils, incubated at 20°C, was submitted in the frame

of the renewal of the approval. In the study by [redacted] (2001e), the route and rate of aerobic degradation of 14C-labelled Dinotefuran (achieved by mixing equal aliquots of guanidine labelled and furanyl labelled compound) was measured.

The kinetic of both studies was re-evaluated by [redacted] (2020b) and [redacted] (2020c), leading to a Dinotefuran geometric mean DT_{50} of 32.4 days at 12°C (n=13). However some discrepancies were noted between the DT_{50} values reported in the report of [redacted] (2020b) and the report of [redacted] (2001e).

Therefore, the soil aerobic biodegradation was recalculated taking into account the half-lives values of the original report of [redacted] (2001e). The DT_{50} were normalised to reference temperature conditions of 12°C, following equation 28 of the GBPR (2017). Temperature-normalised DT_{50} values are reported in **Table 4-8**.

The DT_{50} of Dinotefuran being available from 12 soil, a geometric mean of 32.4 days was derived according to the GBPR (2017), for risk assessment. For classification purposes, it was reminded at ENV WG-V-2019 the most stringent result should be used according to REACH R11 criteria. Consequently it is appropriate to use of the value of 190.9 days (Stolpe, Germany, normalised to 12°C).

Table 4.9 Soil degradation of Dinotefuran under aerobic conditions after normalisation to reference temperature of 12°C

Aerobic conditions						
Soil	**Incubation temperature (°C)**	**Compound**	**DT_{50} (d) ([redacted], 2020b)**	**Normalised DT_{50} (d) ([redacted], 2020b)**	**DT_{50} (d) (original study)**	**Normalised DT_{50} (d) (original study)**
Gartenacker, Switzerland [redacted] (2003b)	20	Dinotefuran	9.79	18.6	10.2	19.3
Gartenacker, Switzerland [redacted] (2003b)	10	Dinotefuran	75.1	142	75.1	142.4
Ringenwald, Germany [redacted] (2001e)	20	Dinotefuran	20.3	17.3	21.1	18.0
Stolpe, Germany [redacted] (2001e)	20	Dinotefuran	224	191	224	190.9
Zwingenber, Germany [redacted] (2001e)	20	Dinotefuran	15.3	29	16.4	31.1
Karolinenhof Germany [redacted] (2001e)	20	Dinotefuran	11.4	21.6	13.9	26.4
Otzberg, Germany [redacted] (2001e)	20	Dinotefuran	13.3	25.2	15.5	29.4
Borstel, Germany [redacted] (2001e)	20	Dinotefuran	10.8	20.5	10.7	20.3
Velten, Germany [redacted] (2001e)	20	Dinotefuran	9.5	18	9.4	17.8
Walluf, Germany [redacted] (2001e)	20	Dinotefuran	21.5	40.8	23	43.6
Rossdorf, Germany [redacted] (2001e)	20	Dinotefuran	65.3	124	65.5	124.2
Phoeben, Germany [redacted] (2001e)	20	Dinotefuran	26.1	49.5	26.1	49.5
Mechthildshausen, Germany	20	Dinotefuran	22.3	42.3	22.3	42.3

[redacted] (2001e)						
GEOMETRIC MEAN				31.0		**32.4**

Conclusion

Based upon the results of the two degradation studies in soil, it is evident that Dinotefuran will quickly degrade in soil under aerobic conditions, with a calculated geometric mean half-life (DT_{50}) of 32.4 days, normalized to 12°C. In addition, geometric mean DT_{90} values of 107.6 days (normalised to 12°C) was determined by first order kinetic modelling. Half-life modelling of the major metabolite MNG could only be performed using data obtained in the 20°C test system, giving rise a predicted DT_{50} of 87.7 days using first order kinetics.

When parent and metabolite are sequentially modelled together using SFO kinetics at 20°C, the UK CA as RMS for the first inclusion of the active had determined slightly faster half-lives than those reported in the study, with DT_{50} values 72.4 d (MNG). Therefore, as this value represent more appropriate determination of degradation half-lives, it is proposed to use these sequential DT_{50} values derived at 20°C and then normalise to 12°C (average EU outdoor temperature) for risk assessment purposes. As a consequence, corrected DT_{50} value in line with equation 28 of the of the GBPR (2017) would be 137 days (MNG).

Taking account of results obtained in this aerobic degradation study, the Applicant has proposed a route for metabolism of dinotefuran (coded as MTI-446) in the (aerobic) soil compartment.

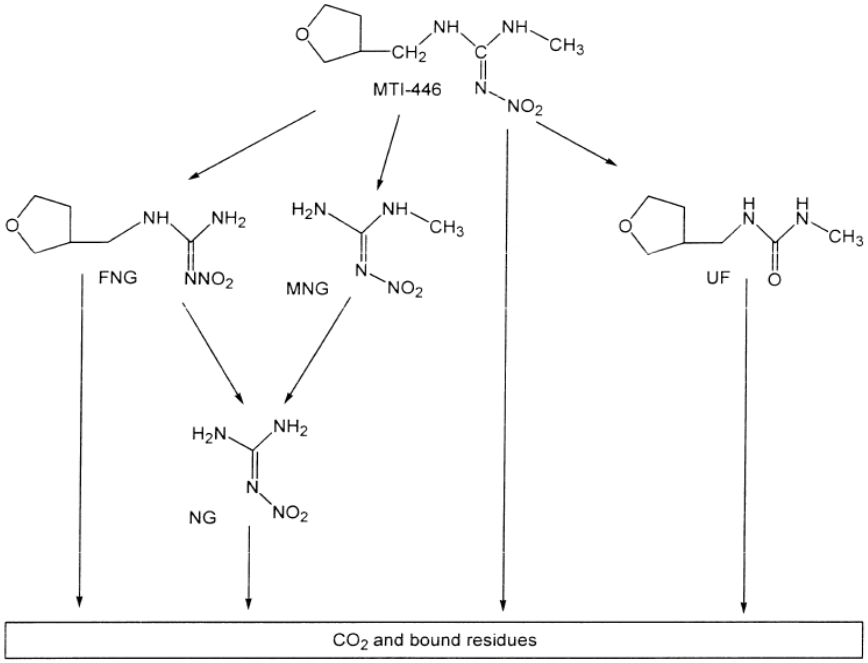

Figure A-4-2 Proposed metabolic pathway for dinotefuran in soil (under aerobic conditions)

Anaerobic biodegradation

Table A-115: Summary table - Anaerobic biodegradation in soil- laboratory study

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Exposure	Test system				Test substance concentr.	Incubation period	Degradation DT50	Remarks	Reference
			Soil origin	Soil type	pH	OC %					
Commission Directive 95/36/EC of 14 July 1995, SETAC 1995 Part 1-2 Anaerobic degradation, EPA 162-2 (1982), JMAFF 12 Nohsan 8147, GLP, Reliability 1, Key study	Yes	20±2°C, in the dark	Gartenacker, Switzerland	Silt loam	7.22	1.78	0.31	120	Water phase: 22.0 Total system: 77.0	Metabolite DN reached a max. of 33.1% in total system, additional 8.7% extracted by harsh extractions. Metabolite UF reached a max. of 7.7% in total system	[redacted] (2003c). IUCLID no. 10.2.1

[1] ***Test according to OECD criteria***
* Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12°C.

Due to the restricted use pattern of the reference product – Dinotefuran 2 % bait – with professional indoor application of gel bait to areas not prone to frequent wet cleaning for the control of cockroaches, the Applicant does not consider that data investigating the anaerobic degradation of dinotefuran in soil should be required.

However, for completeness, an anaerobic degradation study in one European soil at 20°C was provided. In the study by [redacted] (2003c), the route and rate of anaerobic degradation of ^{14}C-labelled dinotefuran (achieved by mixing equal aliquots of guanidine labelled and furanyl labelled compound) in a single soil (silt loam) was investigated in the laboratory performed in line with Directive 95/36/EEC : Annex II – 7.1.1.2, SETAC : Part 1 guidance plus US-EPA N-162-2 guidelines and in accordance with the principles of GLP. Soil samples were treated with 0.31 mg.kg^{-1} dwt of radio-labelled a.s. and stored anaerobically (by flooding with water followed by incubation under a stream of nitrogen) in the dark at 20±2°C for 120 d. Immediately after application (day 0) and 3, 7, 14, 28, 59 and 120 d, one sample was taken for quantification by LSC and analysis by HPLC or TLC (duplicate samples were only analysed on days 0 and 120).

Table 4.10 Characteristics of test soil (anaerobic degradation study)

Characteristic	Test soil
Origin	Gartenacker, Switzerland
Soil classification (USDA)	Silt loam
Clay [%]	10.3
Silt [%]	52.3
Sand [%]	37.4
pH (0.01M $CaCl_2$)	7.22
Organic carbon [g / 100 g soil]	1.78
CEC [meq / 100 g soil]	13.11
Maximum WHC at pF1 (g / 100 g wet soil)	67.5

Although the same Swiss sample (with identical batch number) was used in the aerobic and anaerobic soil degradation studies, slight variations in characteristics were noted in respective test reports

^{14}C-dinotefuran was shown to degrade slowly under anaerobic conditions in soil, with a half-life for total system of 77.0 d (and DT_{90} of 256 d) at 20°C determined by first order kinetic modelling. Total recoveries of radioactivity (mass balance) were 96.0±2.5% of AR (ranging between 92.1–98.4% AR). Only limited mineralisation to $^{14}CO_2$ could be detected, reaching a maximum level of only 4.2% of AR by study completion (120 d). Bound residues in soil increased steadily during the study until they reached a maximum of 10.7% AR on day 59 and then dropped to 9.1% AR at termination on day 120.

The Applicant did investigate anaerobic degradation specifically within the water phase and predicted a DT_{50} of 22.0 d and DT_{90} of 183 d based upon biphasic modelling. However, this is not a true reflection of anaerobic degradation as it is clear from study results that dinotefuran dissipates from the water phase into the soil (solid) phase. Although a "water phase" DT_{50} of 22.0 d has been determined, the total system still contains 82.2% of applied dinotefuran at 28 d. As a result, these values have been disregarded for risk assessment purposes.

Although several minor degradation products were detected, only two main transformation products were characterised – DN and UF. Levels of both major metabolites increased over the study, with DN reaching a maximum of 33.1% AR after 120 d and UF reaching a maximum of 7.7% AR after 120 d. Harsh extraction of soil samples at 120 days gave rise to total DN levels of 41.8% AR at study completion.

It should be noted that whilst significant levels of DN were detected in the anaerobic soil degradation study when negligible amounts were detected in the aerobic degradation study (0.2% DN was detected only after harsh extraction of soil sample at 120 days in the 20°C test system), formation may not be as a result of unique reactions occurring under anaerobic conditions. Levels of DN are comparable to those observed in the aerobic water-sediment degradation study (see 4.1.1.2.2) but, whilst soil samples in the anaerobic degradation study were flooded with water prior to incubation under nitrogen, dinotefuran was not added until anaerobic conditions were established. It has been suggested that in water-sediment studies, the overlying water is aerated but in a manner to avoid disturbance to the sediment layer and so only the sediment surface may be considered as aerobic. If underlying sediment can therefore be considered anaerobic, then DN would most likely form in anoxic conditions and not be considered as a significant aerobic degradate.

Conclusion

Based upon the study results, it is evident that dinotefuran will slowly degrade in soil under anaerobic conditions, with an estimated "total system" half-life (DT_{50}) of 77.0 d plus DT_{90} of 256 d at 20°C using

first order kinetic modelling. Half-life modelling of its major metabolites, DN and UF, could not be performed due to a lack of reported degradation. For risk assessment purposes, it is proposed to use the "total system" DT_{50} value presented in the study summary for dinotefuran at 20°C and normalise to 12°C (average EU outdoor temperature). Therefore, the corrected DT_{50} value in line with equation 25 of the TGD would be 146 d (for dinotefuran).

Based upon results obtained in the anaerobic degradation study, the Applicant has proposed a route for metabolism of dinotefuran (coded as MTI-446) in the (anaerobic) soil compartment.

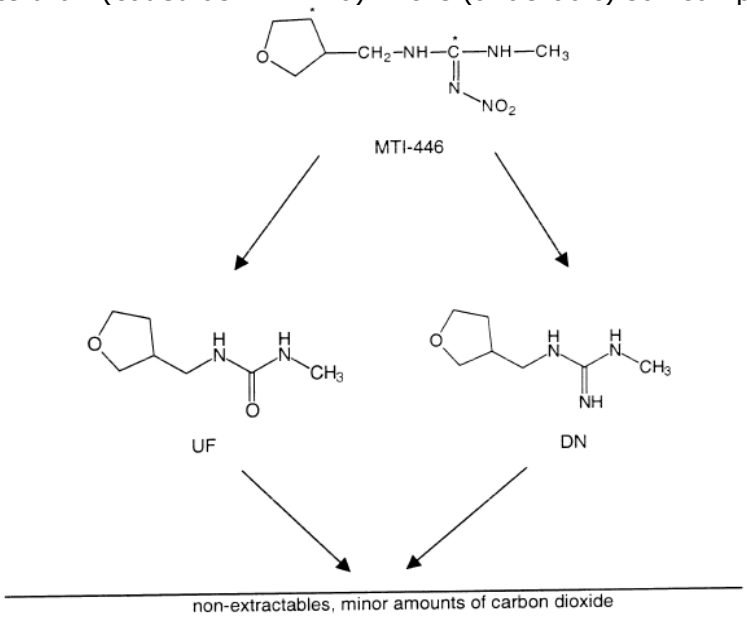

Figure A-4-3 Proposed metabolic pathway for dinotefuran in soil (under anaerobic conditions)

Photodegradation on soil

Table : Summary table – Photodegradation on soil- laboratory study

Method, Guideline, GLP status, Reliability, supportive study	Exposure	Test system				Test substance concentr.	Incubation period	Degradation (DT_{50}, days)*	Remarks	Reference
		Soil origin	Soil type	pH	OC %					
EPA 161-3, SETAC 1995, Section 2.0, GLP Reliability 1 Supportive study	20±1°C, 12 h light/ 12 h dark	Ohio, USA	Loamy sand	6.9	1.1	0.56	32	46	Minor metabolites were detected at levels of 3.4%AR or less.	[redacted] (2001g), IUCLID no. 10.2.1
*** Values are the same as those provided in the study reports; prior to kinetics re-evaluation and normalisation to 12° C.**										

A.4.1.1.3.6.2 Higher tier degradation studies in soil

Field dissipation studies (field studies, two soil types)

Table A-116: Summary table - Field dissipation

Data waiving.
As a refinement, higher tier field studies (soil and/or water-sediment compartment) may be required to identify secondary ecological effects when a habitat such as a water body, wetland, forest or field is treated. The representative biocidal product is not intended to treat natural habitats. Therefore, provision of this study is not required.

A.4.1.1.3.7 Short summary and overall relevance of the provided information on degradation and conclusion on rapid degradation for classification and labelling purposes

The abiotic degradation of dinotefuran studies include hydrolysis, photolysis in water and on soil as well as photo-oxidation in air. Dinotefuran was found to be hydrolytically stable at environmentally relevant pH (4 to 9). The active substance underwent rapid photolysis in water under artificial light with a DT_{50} of 0.9 days under the experimental conditions. According to laboratory and literature data, photolysis in water may be a major and rapid pathway for the disappearance of dinotefuran from the aquatic environment. The photo-oxidation of Dinotefuran in air was calculated to be rapid, with a DT_{50} of 2.4 h predicted by the software program AOPWIN.

Dinotefuran failed to pass the 10 days window criteria in ready-biodegradability test. However, it underwent significant biodegradation in aerobic water-sediment studies: the degradation was investigated in four water-sediment systems under dark laboratory conditions at 20°C and two systems under outdoor natural light representing more realistic conditions (Table 69). Under anaerobic conditions, Dinotefuran degraded with a DT_{50} ranging between 26.0 days (Calwich Abbey) and 48.3 days (Swiss Lake) at 20°C. A total system geometric mean DT_{50} of 37.6 days (normalised to 12°C) was derived from the DT_{50} values available for six aerobic water-sediment systems. The geometric mean DT_{50} will be used for the risk assessment. For classification purposes, the most stringent result should be used according to REACH R11 criteria. Consequently it is appropriate to use of the value of 145.40 days (Swiss lake, normalised to 12°C).

DN is the major metabolite in all dark water-sediment degradation studies : it reached a maximum level of 69.9% AR under aerobic conditions and a maximum of 74.4% AR in the anaerobic conditions in the lake system (Calwich Abbey). In the degradation study under aerobic and sunlight conditions, an unknown metabolite (component A), which was not observed in the studies conducted in the dark, reached a maximum of 15.8% AR in the Calwich Abbey Lake water phase while metabolite DN was not found.

Degradation of dinotefuran in soil was performed in 12 soils under aerobic conditions in the laboratory. Dinotefuran degraded in soil to form MNG as a major metabolite. The normalised geometric mean DT_{50} of 32.4 days at 12 °C, derived from 12 soils, will be used for risk assessment while the most stringent half-life of 190.9 days (Stolpe, Germany, normalised to 12°C) should be used for classification according to REACH R11 criteria.

It is noted that the photolysis on soil was slower than the degradation by microorganisms, with an estimated DT_{50} of 46 days. Moreover under anaerobic conditions, Dinotefuran degraded to form the major metabolite DN reaching a maximum of 33.1% in total system.

According to the above results Dinotefuran is **not** considered **rapidly degradable** in natural environment

A.4.1.2 Distribution

A.4.1.2.1 Adsorption onto/desorption from soils

Table A-117: Summary table - Adsorption/desorption

Method, Guideline, GLP status, Reliability, Key/supportive study	Soil	Adsorbed AS [%]**	Ka	KaOC	Kd, KdOC, Ka/Kd	R^2	1/n	Remarks	Reference
OECD TG 106 (2000), Commission Directive 95/36/EC, EPA 163-1 (1989), Annex Revision 3 by FAO (draft 1993), GLP, Reliability 1, Key study	Soil 1: (Speyer 2.2, Germany)	13.1%#	0.119	6	1.429; 66; 0.083	0.9841	0.847	Adsorption-desorption isotherms were determined in an advanced test on five soils at five concentrations covering two orders of magnitude. The soil/solution ratio was 1:1 and an equilibrium time of 48 hours was used. According to McCall Classification, dinotefuran was found to have very high mobility in soils.	[redacted] (2001e). IUCLID no. 10.1.2
	Soil 2: Senozan, France	20.1%#	0.215	22	1.778; 178; 0.121	0.9947	0.877		
	Soil 3: North Dakota, USA	63.1%	1.009	42	9.524; 397; 0.106	0.9976	0.847		
	Soil 4: North Dakota, USA	47.2%	0.713	45	3.405; 213; 0.209	0.9983	0.877		
	Soil 5: Minnesota, USA	61.6%	1.221	42	8.680; 299; 0.141	0.9978	0.892		

Ka = Adsorption coefficient
KaOC = Adsorption coefficient based on organic carbon content
Kd = Desorption coefficient
KdOC = Desorption coefficient based on organic carbon content
Ka/ Kd = Adsorption / Desorption distribution coefficient
** % of applied amount adsorbed after 48 hours in screening test
# % of applied amount adsorbed after 48 hours in preliminary test

Table A-118: Summary table - Adsorption/desorption metabolite/ degradant/ transformation- or reaction product

Adsorption / desorption of dinotefuran in soil was investigated by means of a preliminary, screening and advanced study performed to OECD Guideline 106, Commission Directive 95/36/EC plus US-EPA OPP Guideline N-163-1 and in accordance with the principles of GLP ([redacted], 2001e).

In the preliminary study, aqueous test solutions of guanidine side chain ^{14}C-labelled dinotefuran were prepared in 0.01M $CaCl_2$ at a concentration of 0.259 mg mL^{-1} and applied to 20 g, 4 g and 1 g samples of two different soil types (loamy sand and silt loam). Samples were then incubated on a shaker at 20°C in the dark, with aliquots removed and analysed after 2, 4, 24 and 48 h (by LSC at all sampling

points and HPLC only at 48 h) to study adsorption behaviour of the test compound.

In the screening study, aqueous test solutions of guanidine side chain ^{14}C-labelled dinotefuran were prepared in 0.01M $CaCl_2$ at a concentration of either 0.463 mg.L^{-1} or 0.519 mg.mL^{-1} and applied to 10 g samples of six different soil types (loamy sand, silt loam, loam, sandy loam, clay loam and sand). Samples were then incubated on a shaker at 20°C in the dark, with aliquots removed and analysed after 2, 4, 24 and 48 h (by LSC at all sampling points and HPLC only at 48 h) to determine adsorption and distribution coefficients kd and KOC. Values were found to range between 9.0 L.kg^{-1} (loamy sand)–71.0 L.kg^{-1} (loam), giving rise to an arithmetic mean KOC of 41.5 L.kg^{-1} (n=6) in the screening study.

In the advanced study, aqueous test solutions of guanidine side chain ^{14}C-labelled dinotefuran were prepared in 0.01M $CaCl_2$ at five concentrations (0.964, 0.243, 0.049, 0.024 and 0.010 mg l-1) and applied to 10 g samples of five different soil types (loamy sand, silt loam, loam, sandy loam and clay loam). Samples were then incubated on a shaker at 20 °C in the dark, with aliquots removed and analysed after 2, 4, 24 and 48 h (by LSC at all sampling points and HPLC only at 48 h) to determine adsorption isotherms and analysis after 4, 24 and 47 h for desorption isotherms.

During each phase of the study (preliminary, screening and advanced), the test material ^{14}C-dinotefuran was shown to be stable in both aqueous solution and soil/solution mixture, with mass balance indicating no loss of radioactivity. Based upon test results presented in Table 4.13, sorption appeared to correlate reasonably well with soil organic carbon content.

Conclusion

Based on the results from the advanced study, dinotefuran has the potential for high mobility in a variety of soil types as K_{OC} values in the five soil types ranged from 6.0–45.0 L.kg^{-1} (with an arithmetic mean K_{OC} of 31.4 L.kg^{-1} where n = 5). This mean value compares favourably with the mean value derived in the screening study (K_{OC} of 41.5 L.kg^{-1} where n=6).

It is proposed to use the geometric mean Ka_{OC} of 25.4 L.kg^{-1} derived from the advanced study for risk assessment purposes under PT 18, in accordance with the BPR Guidance, Vol IV, Parts B+C, Version 2.0, October 2017).

A.4.1.2.2 Higher tier soil adsorption studies

No higher tier soil adsorption studies were performed for dinotefuran.

A.4.1.2.3 Volatilisation

Regarding volatilisation, please see Part A, section 1.3 Physical and chemical properties of the active substance.

A.4.1.3 Bioaccumulation

Measured aquatic bioconcentration

Table A-119: Summary table - Measured aquatic bioconcentration

Data waiving.
The experimental determination may not need to be carried out if it can be demonstrated on the basis of physicochemical properties (e.g. log K_{OW} <3) or other evidence that the substance has a low potential for bioconcentration. The aquatic bioconcentration factor has been estimated as the log K_{OW} of Dinotefuran is -0.549. Therefore, provision of this study is not required.

Estimated aquatic bioconcentration

Table A-120: Summary table - Estimated aquatic bioconcentration

Basis for estimation	Log Kow (measured)	Estimated BCF for fish (freshwater)	Estimated BCF for fish eating bird/predator	Remarks	Reference
BCF for fish is derived from the phys-chem properties of dinotefuran	--0.549at 25 ºC ([redacted], 2000a)	0.014 ([redacted] 1982)[1];			IUCLID 9.1.7
		0.068 ([redacted]., 1979)[2]			

[1] [redacted], 1982. Correlation of bioconcentration factors. Env. Sci.Technol. 16: 274 – 278
[2] [redacted] 1979, Measuring and estimating the bioconcentration factor of chemicals on fish. J.Fish.Res. Board Can. 36: 1040-1048

Dinotefuran is highly soluble in water with a solubility of 39.83 g/L ([redacted], 2000a) and does not dissociate over the environmentally significant pH range. Dinotefuran has a partition coefficient n-octanol/water log K_{OW} = -0.549at 25ºC (K_{OW} = 0.283). The requirement for measured bioconcentration studies in aquatic organisms is triggered when the log K_{OW} is > 3 (whereas it is log Kow>4 for classification purpose). Since the log K_{OW} for dinotefuran is -0.549, there is no risk of bioconcentration in fish and no requirement to measure experimentally directly.

Therefore no studies were submitted to address the bioconcentration potential of dinotefuran in the aquatic compartment on the basis that bioconcentration testing with aquatic organisms is unnecessary as the log K_{ow} is -0.549at pH 7 (and 25°C). The lack of potential for bioconcentration can be further supported using the available QSAR equation developed by Veith *et al*., (1979), according to the BPR guidance, Vol IV, Part A, Version 1.2, May 2018 and the equation 93 of BPR Guidance, Vol IV, Parts B+C, Version 2.0, October 2017):

Log BCF_{fish} = (0.85 * log K_{ow}) - 0.70 = - 1.166

Although the model is considered most appropriate for substances with log K_{ow} values between 2–6, the BCF_{fish} value for dinotefuran of only 0.068 is indicative that this substance would not trigger a concern for bioconcentration or bioaccumulation. Furthermore, the Applicant has submitted additional BCF modelling performed to the Mackay BCF regression model (Mackay, 1982) which indicates a potential bioaccumulation factor of only 0.014.

Considering the potential persistency of the major metabolite DN in aquatic systems based upon reported (normalised) DT_{50} values of 165–199 d from water-sediment studies, some assessment of aquatic bioaccumulation should also be performed. Although no partition coefficient data are currently available, US-EPA EPISuite v4.11 (KOWWIN) predicts a log K_{ow} value for DN of -0.18 using a SMILES notation of N=C(NC)NCC1CCOC1. This converts to a log BCF_{fish} of -0.853 and BCF_{fish} value of 0.14, indicating that this aquatic metabolite would not trigger a concern for bioconcentration or bioaccumulation.

Measured terrestrial bioconcentration

Not applicable for the CLH report

Table A-121: Summary table - Measured terrestrial bioconcentration

Not applicable for the CLH report

Estimated terrestrial bioconcentration

Not applicable for the CLH report

Table A-122: Summary table - Estimated terrestrial bioconcentration

Not applicable for the CLH report

A.4.1.3.1 Short summary and overall relevance of the provided information on bioaccumulation and conclusion on bioaccumulation potential for classification and labelling purposes

The log K_{OW} of dinotefuran is -0.549at 25ºC and the estimated BCF value for fish. As the log K_{OW} of dinotefuran is <4, dinotefuran has a very low potential for bioaccumulation and consequently thus not meet the classification criteria for bioaccumulation.

A.4.1.4 Monitoring data

Not monitoring data is available

A.4.2 Effects on environmental organisms

A.4.2.1 Atmosphere

Not applicable for the CLH report

A.4.2.2 Toxicity to sewage treatment plant (STP) microorganisms

Inhibition of microbial activity (aquatic)

Table A-123: Summary table - Inhibition of microbial activity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species/ Inoculum	Endpoint	Exposure		Results			Reference
			Design	Duration	NOEC	EC10	EC50	
Respiration inhibition test OECD TG 209 (2010) GLP Reliability: 1 Key study	Activated sludge microorganisms	Respiration rate	3 concentrations	3 h	1000 mg/L (nominal)	-	>1000 mg/L (nominal)	[redacted], 2012a IUCLID 9.1.5

An activated sludge respiration inhibition test was performed with dinotefuran technical (99.4%) to investigate the effects on microbial activity. The study was performed in accordance with the OECD Guideline 209 (2010).

A range-finding test was performed which also served as a limit test with test item concentrations of 10, 100 and 1000 mg/L. The test parameters examined were total inhibition, inhibition of the heterotrophic organisms and inhibition of nitrifying bacteria.

The study was well conducted and both the NOEC of 1000 mg/L and the 3 h EC_{50} value of >1000 mg/L are considered reliable and appropriate for use in risk assessment.

A.4.2.3 Aquatic compartment

A.4.2.3.1 Freshwater compartment

Acute/short-term toxicity (freshwater)

Table A-124: Summary table – acute/short-term aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results	Remarks	Reference
				Design	Duration	$LC/EC_{50}/ErC_{50}$		
Fish								
Acute toxicity OPPTS 850.1075 EEC C.1 OECD TG 203 (1992) GLP Reliability: 1 Key study	Rainbow trout (*Oncorhyncus mykiss*)	Mortality Sublethal effects	dinotefuran (97.26%)	Limit test	96 h	> 100 mg/L (nominal)		[redacted], 1999 1st amendment Author, 2000 IUCLID 9.1.1
Acute toxicity OPPTS 850.1075 EEC C.1 OECD TG 203 (1992) GLP Reliability: 1 Supportive study	Sheepshead minnow (*Cyprinodon variegatus*)	Mortality Sublethal effects	dinotefuran (99.2%)	Limit test	96 h	> 109 mg/L (mean measured)		[redacted], 2001a IUCLID 9.1.1
Acute toxicity OPPTS 850.1075 EEC C.1 OECD TG 203 (1992) GLP Reliability: 1 Supportive study	Bluegill sunfish (*Lepomis macrochirus*)	Mortality Sublethal effects	dinotefuran (97.26%)	Limit test	96 h	> 100 mg/L (nominal)		[redacted], 2000a 1st amendment [redacted], 2000a IUCLID 9.1.1

Acute toxicity **OPPTS 850.1075** **EEC C.1** **OECD TG 203 (1992)** **GLP** **Reliability: 1** **Supportive study**	common carp (*Cyprinus carpio*)	Mortality Sublethal effects	dinotefuran (97.26%)	Limit test	96 h	> 100 mg/L (nominal)		[redacted], 2000b IUCLID 9.1.1
Acute toxicity **OPPTS 850.1075** **EEC C.1** **OECD TG 203 (1992)** **GLP** **Reliability: 2** **Key study**	Rainbow trout (*Oncorhyncus mykiss*)	Mortality Sublethal effects	DN phosphate (99.95%)	Extended limit test, 3 concentrations	96 h	> 100 mg/L (nominal)		[redacted], 2002a IUCLID 9.1.1
Acute toxicity **OPPTS 850.1075** **EEC C.1** **OECD TG 203 (1992)** **GLP** **Reliability: 2-3** **Supportive study**	Bluegill sunfish (*Lepomis macrochirus*)	Mortality Sublethal effects	DN phosphate (n.r.)	Extended limit test, 3 concentrations	96 h	> 100 mg/L (nominal)		[redacted], 2002b IUCLID 9.1.1
Invertebrates								
Acute toxicity **OPPTS 850.1010** **EEC C.2** **OECD TG 202 (1984)** **GLP** **Reliability: 1** **Key study**	*Daphnia magna*	Immobilisation	dinotefuran (97.26%)	Limit test	48 h	> 1000 mg/L (nominal)		[redacted], 2000b, 1st amendment Author, 2000b IUCLID 9.1.2
Acute toxicity **OPPTS 850.1010** **EEC C.2** **OECD TG 202 (1992)** **GLP** **Reliability: 1** **Key study**	*Daphnia magna*	Immobilisation	DN phosphate (99.5%)	Extended limit test, 3 concentrations	48 h	>100 mg/L (nominal)		[redacted], 2001b IUCLID 9.1.2

Algae (growth inhibition)								
Acute toxicity **OECD TG 201(1984)** **EEC C.3 (1992)** **OPPTS 850.5400** **GLP** **Reliability: 1** **Key study**	*Pseudokirchneriella subcapitata*	Growth inhibition	dinotefuran (97.26%)	Dose response, 3 concentrations	96 h	>100 mg/L (nominal)		[redacted], 2000d 1st and 2nd amendment Author, 2000 IUCLID 9.1.3
Acute toxicity **OECD TG 201(1984)** **OPPTS 850.5400** **GLP** **Reliability: 2** **Key study**	*Selenastrum capricornutum*	Growth inhibition	DN phosphate (99.5%)	Dose response, 3 concentrations	96 h	>100 mg/L (nominal)		[redacted], 2002c IUCLID 9.1.3
Other aquatic plants								
Acute toxicity **OPPTS 850.4400** **OECD TG 221 (draft 2000)** **GLP** **Reliability: 1** **Key study**	*Lemna gibba*	Growth inhibition	dinotefuran (99.2%)	dose response	7 d	>110 mg/L (nominal)		[redacted], 2002d IUCLID 9.1.10

Description of the available acute toxicity studies

Acute (short-term) toxicity to fish - Dinotefuran

Four studies were performed in different species to investigate the acute toxicity of dinotefuran (as MTI-446) to fish : bluegill sunfish (*Lepomis macrochirus*), common carp (*Cyprinus carpia*), sheepshead minnow (*Cyprinodon variegatus*) and rainbow trout (*Oncorhynchus mykiss*). Endpoints (LC_{50}) for these studies were >100, >100, >109 and >100 mg/L respectively. Since only one acute fish study is required by the Technical Guidance Document, a Robust Study Summary was only submitted for the rainbow trout and the results presented here. The rainbow trout is the species most commonly used in ecotoxicity tests and is known to be a suitable and sensitive representative species.

An acute 96-hour static study (limit test) was performed to determine the toxicity of dinotefuran (MTI-446) to rainbow trout (*Oncorhynchus mykiss*). The study was performed in accordance with the following guidelines: US EPA OPPTS 850.1075, Commission Directive 92/69/EEC (C.1) and OECD Guideline No.203.
The LC_{50} (>100 mg/L) of dinotefuran to rainbow trout was determined directly from the raw data as there was no mortality or any sign of

toxicity in the test item group. The results from additional studies (based in either nominal or measured values) support this endpoint with similar LC_{50} values reported for freshwater and marine species (100 – 109 mg/L). Indeed, no mortality or any sign of toxicity were reported at the test concentrations.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the acute toxicity to fish. Therefore, the 96-hour LC_{50} of 100 mg/L is considered suitable for use in the risk assessment.

Acute (short-term) toxicity to fish - DN phosphate

Two acute 96-hour semi-static studies (extended limit test) were performed to determine the toxicity of DN Phosphate to rainbow trout (*Oncorhynchus mykiss*) and bluegill sunfish (*Lepomis macrochirus*).

An acute 96-hour static study (limit test) was performed to determine the toxicity of DN Phosphate to rainbow trout (*Oncorhynchus mykiss*). The study was performed in accordance with the following guidelines: US EPA OPPTS 850.1075 and OECD Guideline No.203.
The concentration of the test item in the control and the highest dose used (100 mg/L) was measured at 0, 24, 72 and 96 h (prior to any medium change) and the endpoints determined using the nominal concentration. The LC_{50} (>100 mg/L) of DN Phosphate to rainbow trout was determined directly from the raw data as there was no mortality or any sign of toxicity in the test item group. The results from an additional study in bluegill sunfish support this endpoint with an identical LC_{50} value reported (based on nominal values). Indeed, no mortality or any sign of toxicity were reported at the test concentrations.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the acute toxicity to fish. Therefore, the 96-hour LC_{50} of 100 mg/L is considered suitable for use in the risk assessment.

Acute (short-term) toxicity to aquatic invertebrates – Dinotefuran

A static 48-hour limit test was performed to assess the acute toxicity of dinotefuran (MTI-446) to *Daphnia magna*. The study was performed in accordance with the following guidelines: OECD Guideline No.202 (Part 1), Directive 92/69/EEC (Part C.2) and US EPA OPPTS 850.1010.

The test was performed at a nominal concentration of 1000 mg/L. The concentration of the test item was measured at the beginning and end of the test and found to be within acceptable limits. Immobility was the endpoint assessed.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study could be used to address the toxicity of dinotefuran to aquatic invertebrates. The 48-hour EC_{50} of >1000 mg/L is considered suitable for use in risk assessment. No mortality was recorded in the test item group. However, an additional acute study performed with the saltwater mysid (*Mysidopsis bahia*) demonstrated far greater sensitivity to dinotefuran (LC_{50} 0.79 mg/L) as does the chironomid acute study (see Section 4.2.1.3.1) with an LC_{50} of 72.1 µg/L. Consequently, given the apparent insensitivity of daphnids and the intended use of the product, it is believed that the sensitivity of these alternative species should be considered when performing the risk assessment.

Acute (short-term) toxicity to aquatic invertebrates – DN phosphate

A static 48-hour extended limit test was performed to assess the toxicity of DN Phosphate to *Daphnia magna*. The study was performed in accordance with the following guidelines: OECD Guideline No.202 (Part 1), Directive 92/69/EEC (Part C.2) and US EPA OPPTS 850.1010.

The test was performed at nominal concentrations of 1, 10 and 100 mg/L. Concentrations of test item were measured at the beginning and end of the test in the highest dose group used. The endpoint was determined using the nominal concentrations.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the toxicity of DN Phosphate to aquatic invertebrates. The 48-hour EC_{50} of >100 mg/L is considered suitable for use in risk assessment. No mortality was recorded at test concentrations.

Acute (short-term) toxicity to algae – Dinotefuran

A 96 h static algal growth inhibition study was performed to determine the effect of dinotefuran (MTI-446) on the growth of *Pseudokirchneriella subcapitata*. The study was performed in accordance with the following guidelines : US EPA OPPTS 850.5400, OECD Guideline No.201 1984 and Directive 92/69/EEC (C.3).

The test was performed at nominal concentrations of 6.25, 12.5, 25, 50, and 100 mg/L. Concentration of the test item was measured at the highest dose level prior to test initiation and after 96 hours.
Test parameters examined were biomass and growth rate with samples taken at 24, 48, 72 and 96 hours to determine cell density.

This study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the acute toxicity to algae. The 96 h E_rC_{50} was considered to be 100 mg/L and is appropriate for use in risk assessment. No significant effect on growth rate or biomass was recorded at test concentrations ($p < 0.05$).

Acute (short-term) toxicity to algae – DN phosphate

A 96 h static algal growth inhibition study (extended limit test) was performed to determine the effect of DN Phosphate on the growth of *Selenastrum capricornutum* (now known as *Pseudokirchneriella subcapitata*). The study was performed in accordance with the following guidelines: US EPA OPPTS 850.5400 and OECD Guideline No.201 (1984).

The test was performed at nominal concentrations of 1, 10 and 100 mg/L. Concentrations of the test item were determined the highest dose concentration and the control at 0 and 96 hours.
Test parameters examined were cell concentrations and growth rate. Samples were taken at 24, 48, 72 and 96 hours to determine cell densities.

This study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the acute toxicity to algae. The 96 h E_rC_{50} was considered to be 100 mg/L and is appropriate for use in risk assessment. No significant effect on growth rate or biomass was recorded at test concentrations ($p < 0.05$).

Acute (short-term) toxicity to other aquatic plants – Dinotefuran

A semi-static, 7 day growth inhibition test was conducted to investigate the effect of dinotefuran (MTI-446) on the aquatic higher plant *Lemna gibba*. The study was performed in accordance with OPPTS 850.4400 and under the consideration of OECD TG 221 (draft October 2000).

The test was performed at nominal concentrations of 11, 20, 35, 62 and 110 mg/L. Samples for analysis of test item concentration were taken on days 0, 2, 4 and 7. Only the samples for the highest dose concentration (and the control) were analysed since all other concentrations were < the 7-day NOEC.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the toxicity to aquatic higher plants. The 7-day NOEC was found to be 110 mg/L and is considered to be suitable for use in risk assessment. No significant effect on growth rate or biomass was recorded at test concentrations ($p < 0.05$).

Chronic/long-term toxicity (freshwater)

Table A-125: Summary table - chronic/long-term aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results	Remarks	Reference
				Design	Duration	LOEC/NOEC/EC_{10}		
Fish								
Early life stage (ELS) **OECD TG 210** **OPPTS 850.1400** **GLP** **Reliability 2** **Key study**	Rainbow trout (*Onchorhynchus mykiss*)	Development, growth, survival	Dinotefuran (98.9%)	Limit test	94 d	Overall NOEC 10.1 mg/L (mean measured)		[redacted] 2001d IUCLID 9.1.6.1
Invertebrates								
Chronic toxicity **OPPTS 850.1300** **OECD TG 211** **GLP** **Reliability 1** **Key study**	*Daphnia magna*	Survival Reproduction Growth	Dinotefuran (97.26%)	Dose - response, 5 concentrations	21 d	Overall NOEC 100 mg/L (nominal)		[redacted] 2000e IUCLID 9.1.6.2
Algae								
Please refer to Acute/short-term toxicity (freshwater) above								

Description of the available chronic toxicity studies

Chronic toxicity to fish - Dinotefuran

An early-life stage toxicity study (limit test) was performed to determine the chronic toxicity of dinotefuran (MTI-446) to the rainbow trout (*Oncorhynchus mykiss*). The study was performed in accordance with the following guidelines : OECD Guideline No.210 and US EPA OPPTS 850.1400.

The concentration of the test item in the control and only dose level used (10 mg/L) was measured on days 0, 6, 13, 20, 27, 31, 35, 41, 48, 52, 55, 62, 69, 76, 84, and 94. Measured values were outside the acceptable ranges for part of the exposure period; however, the geometric mean measured dose over the exposure period was calculated to be 10.1 mg/L.
The biological endpoints measured during the study were: egg development, hatching, larvae survival, time to swim up, survival and development of juvenile fish. Fish length and weight were determined at the end of the exposure phase.

The results for 10.1 mg/L (mean measured) were similar for all responses assessed with no parameter being more sensitive than any other. Values were nearly identical to control values, consequently the NOEC was determined directly from the raw data.

The study was well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the chronic toxicity to fish. The 94 d NOEC for dinotefuran to rainbow trout was considered by the RMS to be 10.1 mg/L (mean measured). This value is considered to be acceptable for use in risk assessment.

Chronic toxicity to aquatic invertebrates - Dinotefuran

A 21-day semi-static dose response test was performed to assess the chronic toxicity to *Daphnia magna*. The study was performed in accordance with the following guidelines : OECD No.211 and OPPTS 850.1300.

The test was performed at nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg/L. Analysis of test item concentration was carried out at 100 mg/L. Test parameters examined included survival, reproduction and growth.

The NOEC was determined to be 10.0 mg/L (no significant differences compared to the control according to a Williams-test, one-sided smaller, p = 0.05)

The study was well conducted using an appropriate species and it is considered that the endpoint could be used to address the chronic toxicity of dinotefuran to aquatic invertebrates. However, an additional chronic toxicity study was performed using the saltwater mysid (*Mysidopsis bahia*) that demonstrated increased sensitivity (NOEC 0.089 mg/L). Given the apparent insensitivity of daphnids to the product it is considered that studies using other aquatic species may be more relevant to use in the risk assessment (such as the chronic chironomid test using spiked water). Information on endpoints for other neonicotinoids (e.g. imidacloprid, clothianidin) that demonstrate the relative insensitivity of daphnids is available in the EFSA conclusions/Review Reports [1].

Chronic toxicity to algae or other aquatic plants

Please refer to the studies detailed in the section Acute/short-term toxicity (freshwater) above.

[1] EFSA conclusions/Review Reports that can be accessed via
http://www.efsa.europa.eu/en/publications/efsajournal.htm#Conclusion and
https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=search.as.

A.4.2.3.2 Sediment compartment (freshwater)

Acute/short-term toxicity (freshwater sediment)

Table A-126: Summary table - acute/short-term toxicity to sediment dwelling organisms

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results	Remarks	Reference
				Design	Duration	LC/EC50		
Acute toxicity **Based on OECD TG 202** **EEC C.2** **GLP** **Reliability 1** **Key study**	*Chironomus riparius*	Mortality	Dinotefuran (97.26%)	Dose response, 6 concentrations	48 h	72.1 µg/L (nominal)		[redacted], 2000f IUCLID 9.1.9

The acute toxicity of dinotefuran (MTI-446) to sediment dwelling aquatic invertebrates was investigated with a 48-hour study using *Chironomus riparius*. Since no actual guidelines exist for this type of test the test item administration was based on OECD TG 202 and Directive 92/69/EEC, C2 and the species and age were based on the proposal for a BBA guideline, 1995 "Effect of plant protection products on the development of sediment-dwelling larvae of *Chironomus riparius* in a water sediment system" and the OECD 219, draft document February 2000, adopted 13 April 2004. It must be noted that the test system did not contain any sediment : test organisms were only exposed through the water column.

First instar larvae were exposed to the test item at concentrations of 2.2, 4.6, 10, 22, 46 and 100 µg/L in water and observed after 24 and 48 hours. Survival and symptoms of toxicity were monitored. Test item concentrations were monitored at 0 and 48 hours.

The LC_{50} was determined to be 72.1 µg/L and the NOEC was determined to be 22 µg/L (directly determined from raw data).

As the study was conducted according to the OECD TG 219 document (now adopted), it is considered that this study has been well conducted. The study also demonstrates that chironomids are more sensitive to dinotefuran than other aquatic invertebrates (such as daphnids) and given that this study was performed without sediment it would be appropriate to use the result in risk assessment for aquatic species.

Chronic/long-term toxicity (freshwater sediment)

Table A-127: Summary table - chronic/long-term toxicity to sediment dwelling organisms

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results	Remarks	Reference
				Design	Duration	LOEC/NOEC/EC10		
Chronic toxicity OECD TG 219 (draft 2001) BBA-Guideline (draft 1995) GLP Reliability 1 Key study	*Chironomus riparius*	Larval development	Dinotefuran (97.26%)	Dose response, 5 concentrations	27 d	NOEC : 2.54 µg/L	Effects based on the geometric mean of the lowest initial recoveries of dinotefuran (72% and 56%) of NOEC at nominal concentration, i.e. geomean of 0.72 x 4 µg/L and 0.56 x 4 µg/L	[redacted], 2003a IUCLID 9.1.9
Chronic toxicity OECD TG 218 (draft 2001) GLP Reliability 1 Key study	*Chironomus riparius*	Larval development	DN phosphate (97.27%)	Dose response, 5 concentrations	27 d	NOEC : 5.0 mg/kg dry sediment	Effects based on initial sediment concentrations	[redacted], 2007 IUCLID 9.1.9

Chronic toxicity (freshwater sediment) – Dinotefuran

A 27-day chronic test was performed with dinotefuran (MTI-446) to assess the toxicity to *Chironomus riparius* in a sediment-water system using spiked water. The guideline followed was the OECD TG 219 (draft February 2001, adopted 13 April 2004).

The test item was added to the water column to give nominal concentrations of 2, 4, 8, 16 and 32 µg/L. Concentrations of the test item in the water column, pore water and sediment were measured on days 0, 7 and 27 at 8 and 32 µg/L. Endpoints included the emergence ratio and development time and rate.

The overall NOEC was determined to be 4 µg/L (nominal) by the applicant, based on a Williams-test (α = 0.05, one-sided smaller) and the EC_{50} for emergence was determined to be 14.5 µg/L (nominal).

The study was well conducted and performed using a suitable species. However, the NOEC and EC_{50} were determined using nominal concentrations as opposed to measured concentrations after one hour as recommended by the guideline. Given that this study provides useful data on a sensitive species it was considered that, rather than reject the data, it would be appropriate to calculate the NOEC based on analysed concentrations: lowest percentage of test item present in analysed concentrations at the start and end of the test (72 and 56 % respectively) multiplied by the nominal NOEC and the geomean taken of the two resulting values. This results in a value of 2.54 µg/L. This revised NOEC is considered acceptable for use in risk assessment and suitable for classification and labelling of the active substance, as already discussed during the first approval of Dinotefuran. Indeed the test item was added to the water column, before naturally partitioning to sediment. The test system therefore represents a realistic exposure of test organisms through water, especially as concentrations of Dinotefuran measured in the water column at the end of the test still represented 56 to 61% of the nominal concentrations.

Chronic toxicity (freshwater sediment) – DN phosphate

A 27-day chronic test was performed with DN Phosphate to assess the toxicity to *Chironomus riparius* in a water-sediment system using spiked sediment. The guideline followed was the OECD 218 (draft February 2001).

The test item was added to the sediment 7 days prior to introduction of the larvae. Nominal concentrations of 0.32, 0.63, 1.25, 2.5, 5.0 mg/kg dry sediment were used. Concentrations of the test item in the water column, pore water and sediment were measured on days 0, 7 and 27 at 1.25 and 5.0 mg/kg. Endpoints included the emergence ratio and development time and rate.

The overall NOEC was determined to be 5 mg/kg dwt, based on a Dunnett's test (α= 0.05, one-sided smaller) and the EC_{50} for emergence and development were both determined to be > 5 mg/kg dwt. The study was well conducted and performed using a suitable species. It is considered that the endpoint from this study can be used to assess the chronic toxicity of DN Phosphate to sediment dwelling invertebrates. The NOEC 5 mg/kg is suitable for use in risk assessment.

A.4.2.3.3 Marine compartment

Acute/short-term toxicity (seawater)

Table A-128: Summary table - acute/short-term aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results		Reference
				Design	Duration	NOEC	LC/EC50	
Acute toxicity **OPPTS 850.1035** **EPA Subdivision E, Series 72-3** **GLP** **Reliability: 2** **Key study**	Saltwater mysid (*Americamysis bahia*)	Mortality	Dinotefuran (99.2%)	Dose-response, 6 concentrations	96 h	0.49 mg/L (mean measured)	0.79 mg/L (mean measured)	[redacted], 2001e IUCLID 9.1.2

A flow-through 96-hour toxicity test was performed to assess the toxicity of dinotefuran (MTI-446) to the saltwater mysid *Americamysis bahia*. The study was performed in accordance with the guideline US EPA OPPTS 850.1035.

The test was performed at nominal concentrations of 0.063, 0.13, 0.25, 0.5, 1.0 and 2.0 mg/L. Concentrations of test item were measured at t = 0h, 48h and 96h in each dose group. The endpoints were determined using the mean measured concentrations.

The overall NOEC was determined to be 0.49 mg/L (directly from raw data) and the LC_{50} was determined to be 0.79 mg/L.

The study was quite well conducted using an appropriate species and it is considered that the endpoint from this study can be used to address the toxicity dinotefuran to seawater invertebrates. The 96-hour EC_{50} of 0.79 mg/L is considered suitable for use in classification.

This study, which was part of the data package submitted for the first PT18 Assessment Report (17 June 2014), is provided for the completion of the CLH report.

Chronic/long-term toxicity (seawater)

Table A-129: Summary table - chronic aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results	Remarks	Reference
				Design	Duration	NOEC		
Chronic toxicity OPPTS 850.1350 GLP Reliability: 2-3 Key study	Saltwater mysid (*Americamysis bahia*)	Survival Reproduction Growth	Dinotefuran (97.9%)	5 concentrations dose response	35 d	89 µg/L (mean measured)		[redacted], 2011b IUCLID 9.1.9

A 35-day chronic test was performed with dinotefuran to assess the toxicity to the saltwater mysid *Americamysis bahia* in flow-through conditions. The guideline followed was the OPPTS 850.1350 (1996).

The test was performed at nominal concentrations of 0.044, 0.088, 0.18, 0.35 and 0.70 mg/L. Endpoints included the survival of parent, the number of young produced by female and their sex ratio as well as the total body length and dry weight of parents and offspring.

The overall NOEC was determined to be 89 µg/L based on a statistically significant decreases in reproduction (Dunnett's test, $p \leq 0.05$).

The study was quite well conducted and performed using a suitable species and it is considered that the endpoint from this study can be used to address the toxicity dinotefuran to seawater invertebrates. The NOEC of 89 µg/L is considered suitable for use in classification.

This study, which was part of the data package submitted for the first PT18 Assessment Report (17 June 2014), is provided for the completion of the CLH report.

A.4.2.3.4 Seawater sediment compartment

Acute/short-term toxicity (seawater sediment)

Table A-130: Summary table - acute/short-term toxicity to sea sediment dwelling organisms

Not applicable

Chronic/long-term toxicity (sea sediment)

Table A-131: Summary table - long-term/ chronic toxicity to sea sediment dwelling organisms

Data waiving.
Information is required when there is a likelihood that the sea sediment compartment will become exposed to the active substance. It is not likely that the sea sediment compartment will become exposed from the use of dinotefuran. Therefore, provision of this study is not required.

A.4.2.3.5 Higher tier studies on aquatic organisms

No higher tier studies on aquatic organisms are available or required.

A.4.2.4 Terrestrial compartment

Not applicable for the CLH report

Toxicity to terrestrial organisms, acute/short-term tests

Table A-132: Summary table – acute/short-term terrestrial toxicity

Not applicable for the CLH report

Toxicity to terrestrial organisms, chronic/long-term tests

Table A-133: Summary table – chronic/long-term terrestrial toxicity

Not applicable for the CLH report

A.4.2.5 Groundwater

Not applicable for the CLH report

A.4.2.6 Birds and mammals

Not applicable for the CLH report

Table A-134: Summary table – toxicity to birds and mammals

Not applicable for the CLH report

A.4.2.7 Primary and secondary poisoning

Not applicable for the CLH report

Primary poisoning

Table A-135: Summary table – Primary poisoning

Not applicable for the CLH report

Secondary poisoning

Table A-136: Summary table – Secondary poisoning

Not applicable for the CLH report

A.4.3 Endocrine disruption

Not applicable for the CLH report

Table A-137: Summary table of ecotoxicological data on endocrine disruption

Not applicable for the CLH report

A.4.4 Derivation of PNECs

Not applicable for the CLH report

A.4.5 Overall summary of acute and chronic aquatic toxicity data and Comparison with the CLP criteria

A.4.5.1 Acute aquatic hazard

Table A-138: Summary of key information on acute/ short-term aquatic toxicity relevant for aquatic acute classification

Method	Species	Test material	Results	Remarks	Reference
Fish					
Acute toxicity	Rainbow trout	Dinotefuran	LC_{50} > 100 mg/L	Same endpoint for the	[redacted], 1999

OPPTS 850.1075 EEC C.1 OECD TG 203 (1992) GLP Reliability: 1 Key study	(*Oncorhyncus mykiss*)		(nominal)	metabolite DN phosphate.	1st amendment [redacted], 2000 IUCLID 9.1.1
Invertebrates					
Acute toxicity OPPTS 850.1035 EPA Subdivision E, Series 72-3 GLP Reliability: 2 Key study	Saltwater mysid (*Americamysis bahia*)	Dinotefuran	LC_{50} = 0.79 mg/L (mean measured)	Endpoint for the metabolite DN phosphate with *D. magna* much higher (LC_{50} > 100 mg/L).	[redacted], 2001f IUCLID 9.1.2
Algae					
Acute toxicity OECD TG 201(1984) EEC C.3 (1992) OPPTS 850.5400 GLP Reliability: 1 Key study	*Pseudokirchneriella subcapitata*	Dinotefuran	ErC_{50} > 100 mg/L (nominal)	Same endpoint for the metabolite DN phosphate.	[redacted], 2000d 1st and 2nd amendment [redacted], 2000d IUCLID 9.1.3
Other aquatic plants					
Acute toxicity OPPTS 850.4400 OECD TG 221 (draft 2000) GLP Reliability: 1 Key study	*Lemna gibba*	Dinotefuran	NOEC > 110 mg/L (nominal)		[redacted], 2002d IUCLID 9.1.10
Other					
Acute toxicity Based on OECD TG 202 EEC C.2 GLP Reliability 1 Key study	***Chironomus riparius***	**Dinotefuran**	**LC_{50} = 72.1 µg/L (nominal)**	**Study relevant for aquatic species as performed without sediment**	**[redacted], 2000f IUCLID 9.1.9**

The Applicant has submitted a new study with the saltwater mysid *Americamysis bahia* for classification purpose (LC_{50} = 0.79 mg/L). However

according to the available data, the most sensitive acute endpoint is that derived for the *Chironomus riparius* 48h study (LC_{50} = 0.0721 mg/L). In the first PT18 Assessment Report (17 June 2014), it was agreed that the chronic test with the same species is considered to be relevant for aquatic species as it has been performed without sediments. The acute toxicity study with *Chironomus riparius* was also performed without sediment, making this test relevant for classification of the aquatic species. Moreover using the endpoint derived from *Americamysis* study would result in an underestimation of the true toxicity of Dinotefuran as this species shows a ten times lower sensitivity to the active substance than *Chironomus.*
The trigger of ≤ 1 mg/L given in the Table 4.10 in Annex I of the Guidance on the Application of the CLP Criteria (Version 4.1, 2015) being exceeded, Dinotefuran can thus be considered to have fulfilled the criterion for category **Aquatic Acute 1 (H400: Very toxic to aquatic life)**. The relevant associated **M-factor is 10** according to Table 4.1.3 for CLP guidance.

A.4.5.2 Long-term aquatic hazard (including information on bioaccumulation and degradation)

Table A-139: Summary of key information on chronic/ long-term aquatic toxicity relevant for aquatic chronic classification

Method	Species	Test material	Results	Remarks	Reference
Fish					
Early life stage (ELS) **OECD TG 210** **OPPTS 850.1400** **GLP** **Reliability 2** **Key study**	Rainbow trout (*Onchorhynchus mykiss*)	Dinotefuran	NOEC = 10.1 mg/L (mean measured)		[redacted], 2001c IUCLID 9.1.6.1
Invertebrates					
Chronic toxicity **OPPTS 850.1350** **GLP** **Reliability: 2-3** **Key study**	Saltwater mysid (*Americamysis bahia*)	Dinotefuran	NOEC = 89 µg/L (mean measured)		[redacted], 2011b IUCLID 9.1.9
Other					

Chronic toxicity OECD TG 219 (draft 2001) BBA-Guideline (draft 1995) GLP Reliability 1 Key study	***Chironomus riparius***	**Dinotefuran**	**NOEC = 2.54 µg/L (initial)**	**Endpoint for the metabolite DN phosphate much higher (NOEC = 5.0 mg/kg dwt).**	**[redacted], 2003a IUCLID 9.1.9**

Dinotefuran has a low potential for bioaccumulation in aquatic organisms as its predicted log Kow value is -0.549, which is below the trigger of log Kow ≥3. Its major metabolites DN (aquatic compartment) has predicted log Kow values of -0.18 and is also not expected to bioaccumulate. Confirmatory QSAR modelling give rise to predicted BCF values for fish of 0.068 (EUSES 2.1.2), which is <0.1 and, therefore, the bioaccumulation criterion is not fulfilled.

Dinotefuran is not biodegradable according to OECD 301F ready-biodegradability test (0% degradation after 28d; 22°C). Three equivalent aerobic water-sediment studies were performed to investigate biodegradation in more realistic conditions : two studies under dark laboratory conditions at 20°C and one study under outdoor natural light, at 20-25°C. Moreover one water-sediment study was also performed under dark anaerobic laboratory conditions at 20°C.
However as it was discussed during ENV WG-V-2019, the worst-case $DegT_{50}$ should be used to determine whether the P-criterion is met according to the BPR guidance, which refers to the REACH R11 criteria. Indeed the REACH guidance states: "*For the same environmental compartment, when four or less results are available, the most stringent result should be used with respect to the PBT assessment*."
Hence, it was concluded that the whole system $DegT_{50}$ is used to determine the persistence trigger of both water and sediment. Using the DT_{50} values of each compartment for the (v)P criterion would result in an overestimation of the true degradation.
Hence, the highest whole system $DegT_{50}$ to be considered is **145.4 days**. This would indicate vP for the water compartment and P for the sediment (criteria: P in water when DT50 > 40 d; vP in water when DT50 > 60 d; P in sediment when DT50 > 120 d; vP in sediment when DT50 > 180 d).

The Applicant has submitted a new study with the saltwater mysid *Americamysis bahia* for classification purpose (NOEC = 0.089 mg/L). However according to the available data, the most sensitive chronic endpoint is that derived for the *Chironomus riparius* 27-day study (NOEC = 0.00254 mg/L). In the first PT18 Assessment Report (17 June 2014), it was agreed that this test is considered to be relevant for aquatic species as it has been performed without sediments. Moreover using the endpoint derived from *Americamysis* study would result in an underestimation of the true toxicity of Dinotefuran as this species shows a thirty-five times lower sensitivity to the active substance than *Chironomus.*
The substance is considered non-rapidly degradable and the trigger of ≤ 0.1 mg/L given in the Table 4.10 in Annex I of the CLP Guidance being exceeded, Dinotefuran can thus be considered to have fulfilled the criterion for category **Aquatic Chronic 1 (H410: Very toxic to aquatic life with long lasting effects)**. The relevant associated **M-factor is 10** according to Table 4.1.3 for CLP guidance.

A.4.5.3 Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria

Aquatic acute classification according to CLP criteria

The lowest LC_{50} value is 0.0721 mg/L, which is below the trigger value of 1 mg/L. Dinotefuran therefore fulfils the criteria for classification as Aquatic Acute 1 (H400). As the lowest LC_{50} value is between 0.01 and 0.1, this leads to an M-factor 10.

Aquatic chronic classification according to CLP criteria

Dinotefuran is not rapidly degradable and chronic data are available for all trophic levels. The lowest NOEC is 0.00254 mg/L, which is below the trigger value of 0.1 mg/L. Dinotefuran therefore fulfils the criteria for classification as Aquatic Chronic 1 (H410). As the lowest NOEC value is between 0.001 and 0.01, this leads to an M-factor 10.

A.5 Assessment of additional hazards

A.5.1 Hazardous to the ozone layer

Data waiving	
Information requirement	There is no requirement under the BPR to provide information on hazards to the ozone layer.
Justification	The overall OH rate constant of dinotefuran is 156.066E-12 cm³ per molecule s^{-1} which equals a 24-hour day half-life of 0.1 day. Moreover there is no absorption bands in the atmospheric window, and no Cl, F, N or S functional group in the molecule No hazard to the ozone layer is thus expected.

A.5.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

A.5.1.2 Dinotefuran is not listed in Annex I to Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009. Moreover on the basis of the structure and on the physico-chemical properties of the active substances (absence of absorption bands in the atmospheric window, short atmospheric lifetime, absence of Cl, F, N or S functional group in the molecule), Dinotefuran is not expected to present a potential danger to the structure and /or functioning of the stratospheric ozone layer. **Comparison with the CLP criteria**

Dinotefuran is not expected to present a potential danger to the structure and /or functioning of the stratospheric ozone layer.

Conclusion on classification and labelling for hazardous to the ozone layer

Dinotefuran does not present a potential danger to the structure and /or functioning of the stratospheric ozone layer.

A.6 Additional Labelling

No additional labelling under the CLP Regulation is proposed.

A.7 Assessment of exclusion criteria, substitution criteria and POP

Not applicable for the CLH report

A.7.1 Exclusion criteria

A.7.1.1 Assessment of CMR properties

Not applicable for the CLH report

A.7.1.2 Assessment of endocrine disrupting properties

Not applicable for the CLH report

A.7.1.3 PBT Assessment (following Annex XIII to Regulation (EC) No 1907/2006)

Not applicable for the CLH report

A.7.2 Substitution criteria

Not applicable for the CLH report

A.7.3 Assessment of long-range environmental transportation and impact on environmental compartments

Not applicable for the CLH report

D. Appendices

Appendix I: List of endpoints

Not applicable for the CLH report.

Appendix II: Human exposure calculations

Not applicable for the CLH report.

Appendix III: Environmental emission (and exposure) calculations

Not applicable for the CLH report.

Appendix IV: List of terms and abbreviations

See document.

Appendix V: Overall reference list (including data owner and confidentiality claim)

Physical-Chemical properties part:

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[2] (Yes/No)	Applicability	
							CAR/RAR	CLH
[redacted]	2001		Determination of the explosive properties MTI-446 according to EC Council Directive 92/69/EEC, Part. A.14, RCC Ltd., report no. 780197, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2006		Dinotefuran technical description of starting materials and manufacturing process; Dinotefuran	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y

[2] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process. For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

			technical discussion of formation of impurities, NA Contract Laboratories, no report no., non-GLP, unpublished					
[redacted]	2013 (a)		Analysis of 10 Nitrosamines in six batches of dinotefuran technical. AgChem Product Development, Ricerca Biosciences, LLC. Report no. 030901-1, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2013 (b)		Analysis of 10 Nitrosamines in six batches of dinotefuran technical. AgChem Product Development, Ricerca Biosciences, LLC. Report no. 030901-1, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2005		Analysis of active ingredient and impurities in dinotefuran technical, Japan Analytical Chemistry Consultants Co., Ltd., report no. GT0504, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]		2012	Expert statement. Dinotefuran: calculation of Henry's Law Constant, LKC Switzerland Ltd., report no. 11-LKC-04, non-GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2002		Independent laboratory validation of methods for the	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y

			analysis of MTI-446 and its metabolite MNG in soil, Wildlife International, Ltd., report no. 236C-106, GLP, unpublished					
[redacted]		2000a	MTI-446 Product chemistry, Ricerca, LLC, report no. 011098-1, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]		2000b	Report amendment: MTI-446 Product chemistry, Ricerca, LLC, report no. 011098-1-1, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	1999a		Physical state of dinotefuran (MTI-446), Mitsui Chemicals, Inc. Life Science Laboratory, no report no., non-GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	1999b		Colour of dinotefuran (MTI-446), Mitsui Chemicals, Inc. Life Science Laboratory, no report no., non-GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	1999c		Odour of dinotefuran (MTI-446), Mitsui Chemicals, Inc. Life Science Laboratory, no report no., non-GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	1996		MTI-446: Determination of the physico-chemical properties, Huntington Life Sciences, report no.	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y

			MTO097/980159, GLP, unpublished					
[redacted]	1998 & 2000		MTI-446 : Determination of hydrolysis as a function of pH, Huntingdon Life Sciences, , report no. 95/MTO098/1216 (MRID 45640101). (GLP, unpublished) & Report amendment 1 : Determination of hydrolysis as a function of pH, Huntingdon Life Sciences, , report no. 95/MTO098/1216. (Unpublished)	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2001 a		Determination of the flammability of MTI-446, RCC Ltd., report no. 780175, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2000		Determination of the relative self-ignition temperature of MTI-446, RCC Ltd., report no. 780186, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2001 c		Determination of the surface tension of an aqueous solution of MTI-446, RCC Ltd., report no. 780208, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2001 b		Determination of the oxidizing properties (solids) of MTI-446, RCC Ltd., report no. 780210, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2003		Determination of the storage stability and corrosion	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y

			stability of MTI-446 technical material (shelf life at room temperature), RCC Ltd., report no. 828865, GLP, unpublished					
[redacted]	2001		Validation of the residue analytical method for MTI-446 in soil, RCC Ltd., report no. 739923, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2012		Determination of optical rotation of dinotefuran Omuto Analysis Dept. Mitsui Chemical Analysis & Consulting Service Inc., report no. M112010042 non-GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2020a		Content analysis of dinotefuran technical CERI Japan, report no. 86393 GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y
[redacted]	2020b		Validation of analytical methods for dinotefuran technical, CERI Japan, report no. 86392 GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Yes	Y	Y

Human Health part:

Data protection from the first approval *- 01/06/2015 - 31/11/2024*

Not confidential (as per article 66):

Confidential (as per article 66) :

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	1996	A.3.8.1.	MTI-446: Microbial reverse mutation assay, Chromosome [redacted], report no. CRC3133, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1999	A.3.8.1.	A DNA repair assay of Bacillus subtilison MTI-446, [redacted], October 2, 1996, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1996	A.3.8.1.	MTI-446: In vitro mammalian cytogenetics test, Chromosome [redacted], report no. CRC0076, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002	A.3.8.1.	MTI-446 technical material: mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre fluctuation technique, [redacted], report no. 719/15-D6173, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	1997 a	A.3.2.1. A.3.2.4.	Acute oral toxicity study of MTI-446 in rats, [redacted], report no. CHW 6648-118, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 b	A.3.2.1. A.3.2.4.	Acute oral toxicity study of MTI-446 in mice [redacted], report no. CHW 6648-119, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000	A.3.2.1.	First amendment to report - Acute oral toxicity study of MTI-446 in mice [redacted], report no. CHW 6648-119, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 c	A.3.2.2. A.3.2.4.	Acute dermal toxicity study of MTI-446 in rats [redacted], report no. CHW 6648-120, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1999	A.3.2.3. A.3.2.4.	MTI-446: Acute inhalation (nose only) toxicity study in the rat, [redacted], report no. 1300/3-D6154, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 a	A.3.2.3. A.3.2.4.	First amendment to report - MTI-446: Acute inhalation (nose only) toxicity study in the rat, [redacted], report no. 1300/3-D6154, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 b	A.3.2.3. A.3.2.4.	Second amendment to report - MTI-446: Acute inhalation (nose	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			only) toxicity study in the rat, [redacted], report no. 1300/3-D6154, GLP, unpublished					
[redacted]	1998 a	A.3.3.	Primary dermal irritation study of MTI-446 in rabbits, [redacted], report no. [redacted] 6648-121, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1998 b	A.3.4.	Primary eye irritation study of MTI-446 in rabbits, [redacted], report no. [redacted] 6648-122, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 d	A.3.5.	Dermal sensitization study of MTI-446 in guinea pigs - maximisation test, [redacted], report no. [redacted] 6648-123, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2011	A.3.13.	Dinotefuran: 4-week dietary immunotoxicity study in the CD rat, [redacted], report no. MCW0018, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2012	A.3.13.	Amended Report - Dinotefuran: 4-week dietary immunotoxicity study in the CD rat, [redacted], report no. MCW0018, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2011	A.3.13.	Dinotefuran: 4-week dietary immunotoxicity study in the CD-1 mouse, [redacted], report no. MCW0019, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 a	A.3.1	Metabolism of [14C]-MTI-446 in rats, [redacted], report no. [redacted] 6648-136, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 b	A.3.1	First amendment to report –	Y	Mitsui Chemical	Y	Y	Y

			Metabolism of [14C]-MTI-446 in rats, [redacted], report no. [redacted] 6648-136, GLP, unpublished		s Agro, Inc.			
[redacted]	2001	A.3.1	Second amendment to report – Metabolism of [14C]-MTI-446 in rats, [redacted] report no. 6648-136, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 c	A.3.1	Absorption, distribution, metabolism and excretion of [G-14C]-MTI-446 following administration of a single oral dose to neonatal rats, [redacted] report no. 6648-141, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 d	A.3.1	First amendment to report - Absorption, distribution, metabolism and excretion of [G-14C]-MTI-446 following administration of a single oral dose to neonatal rats, [redacted], report no. [redacted] 6648-141, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2006 b	A.3.1	Dermal absorption of [14C]MTI-446 formulated as aqueous solution in the rat (in vivo), [redacted], report no. A25975, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 a	A.3.7.1.	4-week dietary toxicity study with MTI-446 in rats, [redacted], report no. CHW 6648-125, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 b	A.3.7.1.	4-week dietary toxicity study	Y	Mitsui Chemical	Y	Y	Y

			with MTI-446 in mice, [redacted], Report No. CHW 6648-124, GLP, unpublished		s Agro, Inc.			
[redacted]	2001 b	A.3.7.1.	28-day dermal toxicity study with MTI-446 in rat, [redacted], report no. 6648-149, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002	A.3.7.1.	MTI-446: 28-day inhalation (nose only) toxicity study in the rat, [redacted], report no. 719/16, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 c	A.3.7.2.	13-week dietary toxicity study with MTI-446 in rats, [redacted], report no. CHW 6648-127, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 a	A.3.7.2.	First amendment to report - 13-week dietary toxicity study with MTI-446 in rats, [redacted], report no. CHW 6648-127, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1997 d	A.3.7.2.	13-week dietary toxicity study with MTI-446 in mice, [redacted], report no. CHW 6648-126, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 b	A.3.7.2.	First amendment to report: - 13-week dietary toxicity study with MTI-446 in mice, [redacted], report no. CHW 6648-126, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1999 a	A.3.7.2.	13-week dietary toxicity study with MTI-446 in dogs, [redacted], report no. [redacted] 6648-128 GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1999 b	A.3.7.2.	First amendment to report - 13-week dietary toxicity study	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			with MTI-446 in dogs, [redacted], report no. [redacted] 6648-128 GLP, unpublished					
[redacted]	1999 c	A.3.7.3.	52-week dietary chronic toxicity study with MTI-446 in dogs, [redacted] report no. 6648-129, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2005	A.3.7.4	Historical control data for 52-week dog studies, no laboratory name, MRID No. 4563972, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1995	A.3.8.2.	Micronucleus test of EXP-316 with mice, [redacted], report no. 2498, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 c	A.3.7.3. A.3.9.	104-week dietary combined chronic toxicity and carcinogenicity study with MTI-446 in rats, [redacted], report no. [redacted] 6648-131, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 d	A.3.7.3. A.3.9.	78-week dietary carcinogenicity study with MTI-446 in mice, [redacted]., report no. 6648-130, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 e	A.3.7.3. A.3.9.	First amendment to report - 78-week dietary carcinogenicity study with MTI-446 in mice, [redacted] report no. 6648-130, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1998 b	A.3.10.2	Teratogenicity study of MTI-446 given orally to rats, Nippon Experimental [redacted], report no. H-97163, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1998 e	A.3.10.2	Teratogenicity study of MTI-446 given orally to rabbits, [redacted]	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			report no. H-97166, GLP, unpublished					
[redacted]	2013	A.3.10.2	Dinotefuran: Prenatal Developmental Toxicity Study in Rabbits, [redacted] report no. SR12005, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001	A.3.10.1.	MTI-446 technical preliminary two generation study in the Han Wistar rat, [redacted] report no. 774990, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002	A.3.10.1.	MTI-446 two-generation reproduction study in the Han Wistar rat by oral (dietary) administration, [redacted] report no. 775192, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001a	A.3.2.4. A.3.12	Acute oral gavage neurotoxicity study with MTI-446 in rats, [redacted] report no. CHW 6648-147, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001b	A.3.12	13-week dietary neurotoxicity study with MTI-446 in rats, [redacted] report no. CHW 6648-148, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2006a	A.3.1	Transfer of [14C]MTI-446 into milk of lactating rats after oral administration, [redacted] report no. A29136, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2009	A.3.12	Oral (Diet) Dosage-range finding developmental neurotoxicity and immunotoxicity study of MTI-446 (Dinotefuran) in [redacted]:CD (SD)	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			rats, [redacted], report no. SRY00001, GLP, unpublished					
[redacted]	2010	A.3.10.2. A.3.12	Oral (Diet) developmental neurotoxicity study of MTI-446 (Dinotefuran) in [redacted]:CD (SD) rats, [redacted], report no. SRY00002, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
Reference product								
[redacted]	2010 a	B.5.3	Acute oral toxicity of New GOK1 to the rat - limit test -, [redacted] report no. 02 G 09 024, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 b	B.5.3	Amendment to Final Report - Acute oral toxicity of New GOK1 to the rat - limit test -, [redacted] report no. 02 G 09 024, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 c	B.5.3	Acute oral toxicity of New GOK1 to the mouse - limit test -, [redacted] report no. 02 G 09 025, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 d	B.5.3	Amendment to final report - acute oral toxicity of New GOK1 to the mouse - limit test -, [redacted] report no. 02 G 09 025, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2009 a	B.5.3	Acute dermal toxicity test with New GOK1 in the rat - limit test -, [redacted] report no. 02 G 07 011, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 e	B.5.3	Amendment to final report - Acute dermal toxicity test with New GOK1 in the rat - limit test -,	Y	Mitsui Chemicals Agro, Inc.	N	Y	N

			[redacted] report no. 02 G 07 011, GLP, unpublished					
[redacted]	2009 b	B.5.3	Acute dermal toxicity test with New GOK1 in the mouse - limit test -, [redacted] report no. 02 G 07 010, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010f	B.5.3	Amendment to Final Report - Acute Dermal Toxicity Test with New GOK1 in the Mouse - Limit Test -, [redacted] report no. 02 G 07 010, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 a	B.5.4	Acute dermal irritation/corrosion test (patch test) of New GOK 1 in rabbits[redacted] report no. 25219, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 b	B.5.4	Acute eye irritation/corrosion test of New GOK 1 in rabbits, [redacted] report no. 25220, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 a	B.5.5	Skin sensitisation test of New GOK 1 in guinea pigs-according to the E.V. Buehler method-, [redacted] report No. 25221, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N
[redacted]	2010 b	B.5.5	Amendment No.1 to final report - Skin sensitisation test of New GOK 1 in guinea pigs-according to the E.V. Buehler method[redacted] report no. 25221, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	N	Y	N

Data protection from this renewal *–(end five years from the first day of the month following the date of the adoption of a decision in accordance with Article 14(4))*

Not confidential (as per article 66):

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	2015	3.7.1.	Expert Statement - Dinotefuran: Proposal to revise NOAEL values in specified dietary studies justified by data generated in an investigative pair-feeding and palatability study in the rat, [redacted] report no. 15-LKC-10, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2022	3.7.1.	Amendment to Expert Statement - Dinotefuran: Proposal to revise NOAEL values in specified dietary studies justified by data generated in an investigative pair-feeding and palatability study in the rat, [redacted] report no. 15-LKC-10, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
Reference product								
[redacted]	2014	B.5.2	Dinotefuran: Percutaneous Penetration of [14 C]-Dinotefuran Formulated as Dinotefuran 2% Gel	Y	Mitsui Chemicals Agro, Inc.	N	Y	N

			Through Human Split-thickness Skin Membranes (in vitro), [redacted] report no. D80138, non-GLP; unpublished					

Confidential (as per article 66) :

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	1998 a	A.3.7.1.	Repeated Dose Toxicity Test of MTI-446 by Forced Oral Administration for One Week Using Dogs, [redacted], report no. H 97326, non-GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1998 b	A.3.7.1.	Repeated Dose Toxicity Test of MTI-446 Mixed in the Diet for One Week Using Dogs, [redacted], report no. H 97327, non-GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2019	A.3.8.2.	Micronucleus Test in Bone Marrow Cells of Mouse with Dinotefuran Technical, [redacted] Report no. 8721, GLP; unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2003	A.3.10.2.	A Study for Effects of Dinotefuran on Fertility and Early Embryonic Development to Implantation in Rats Following Oral Administration, [redacted] Report no. MA02198, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted].	2004	A.3.10.2.	Study for Effects of	Y	Mitsui Chemical	Y	Y	Y

			Dinotefuran on Pre- and Postnatal Development, Including Maternal Function, in Rats Following Oral Administration, [redacted] Report no. MA02200, GLP, unpublished		s Agro, Inc.			
[redacted]	2015 a	A.3.16	Study in Sprague Dawley Rats for 4 Weeks, [redacted] Report no. MCW0059, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2015 b	A.3.16	Report amendment 1 - Study in Sprague Dawley Rats for 4 Weeks, [redacted], Report no. MCW0059, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2020	A.3.15	Health report of workers who manufacture dinotefuran, [redacted] Report no. not specified, non-GLP, unpublished.	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2011 a	A.3.14	FIRST AMENDMENT TO REPORT - MTI-446 two-generation reproduction study in the Han Wistar rat by oral (dietary) administration, [redacted] report no. 775192, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	N
[redacted]	2011 b	A.3.14	SECOND AMENDMENT TO REPORT - MTI-446 two-generation reproduction study in the	Y	Mitsui Chemicals Agro, Inc.	Y	Y	N

			Han Wistar rat by oral (dietary) administration, [redacted] report no. 775192, GLP, unpublished					
[redacted]	2013	A.3.14	THIRD AMENDMENT TO REPORT - MTI-446 two-generation reproduction study in the Han Wistar rat by oral (dietary) administration, [redacted] report no. 775192, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	N
[redacted]	2004	A.3.4	LX-1434-04 (Dinotefuran Technical): Acute eye irritation study in rabbits, [redacted] Report No. 8394-04, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	N (EFSA MRL Article 10 application (import tolerance application in various crops)	Y

Environmental part:

Data protection from the first approval *- 01/06/2015 - 31/11/2024*

Confidential (as per article 66) :

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	2012 a	A.4.2.2	Toxicity testing of dinotefuran technical - on microorganisms with the activated sludge respiration inhibition test, [redacted] unpublished report no. S11-03209, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	1999	A.4.2.3.1	Acute Toxicity of MTI-446 to Rainbow Trout (Oncorhynchus mykiss) in a 96-Hour Static Test, [redacted] unpublished report no. 740924, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001 a	A.4.2.3.1	MTI-446 technical : a 96-hour flow-through acute toxicity test with the sheepshead minnow (Cyprinodon variegatus), [redacted] unpublished report no. 236A-105, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 a	A.4.2.3.1	Acute Toxicity of MTI-446 to bluegill sunfish (Lepomis macrochirus) in a 96-Hour Static	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			Test, [redacted] unpublished report no. 740946, GLP, unpublished					
[redacted]	2000 b	A.4.2.3.1	Acute Toxicity of MTI-446 to common carp (Cyprinus carpio) in a 96-Hour Static Test, [redacted] unpublished report no. 741003, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002 a	A.4.2.3.1	DN Phosphate Determination of Acute Toxicity to Rainbow Trout (96 h, Semi-static), [redacted] unpublished report no. 19814, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002 b	A.4.2.3.1	DN Phosphate Determination of Acute Toxicity of Bluegill Sunfish (96-Hour Semi-static), [redacted] unpublished report no. 19799, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 c	A.4.2.3.1	Acute toxicity of MTI-446 to Daphnia magna in a 48-hour immobilization test, [redacted] unpublished report no. 740968, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001 b	A.4.2.3.1	DN phosphate determination of acute toxicity to Daphnia (48 h, Static), [redacted] unpublished report no. 20122, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 d	A.4.2.3.1	Toxicity of MTI-446 to Pseudokirchneriella subcapitata (Formerly Selenastrum capricornutum) in a 96-hour algal growth inhibition test, [redacted] unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			report no. 740981, GLP, unpublished					
[redacted]	2002 c	A.4.2.3.1	DN phosphate alga, growth inhibition test (96 h), [redacted] unpublished report no. 19849	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2002 d	A.4.2.3.1	Toxicity of MTI-446 to the aquatic higher plant Lemna gibba in a 7-day semistatic growth inhibition test, [redacted] unpublished report no. 827752, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2001 c	A.4.2.3.1	Toxic effects of MTI-446 to Rainbow trout (Oncorhynchus mykiss) in an early-life stage toxicity test, [redacted] unpublished report no. 794338, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000 e	A.4.2.3.1	Influence of MTI-446 on survival and reproduction of Daphnia magna in a semistatic test over three weeks, [redacted] unpublished report no. 752106, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2000f	A.4.2.3.2	Acute toxicity of MTI-446 to first-instar larvae of Chironomus riparius, [redacted] unpublished report no. 752128, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2003 a	A.4.2.3.2	Effects of MTI-446 on the development of sediment-dwelling larvae of Chironomus riparius in a water sediment system, [redacted]	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

			Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 844569, GLP, unpublished					
[redacted]	2007	A.4.2.3.2	Effects of DN phosphate on the development of sediment-dwelling larvae of Chironomus riparius in a water-sediment system with spiked sediment, [redacted] unpublished report no. 844571, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y

Author (s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[3] (Yes/No)	Applicability	
							CAR/RAR	CLH
[redacted]	2012 b	A.4.1.1.2 Biotic degradation, initial studies, P 40; Appendix VII, 4.1.1	Ready biodegradability of dinotefuran technical in a manometric respirometry test[redacted] unpublished report no. 70891163, March 8, 2012	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	1998	A.4.1.1.1 Abiotic degradation Hydrolysis p35, Appendix VII, 5.1.1 study 1	MTI-446: Determination of hydrolysis as a function of pH. [redacted] unpublished report no. 95/MTO098/1216 (MRID 45640101), July 29, 1998.	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2002 e	A.4.1.1.1 Abiotic degradation ;phototransformation in water p36, Appendix VII, 5.1.1 study 2	Aqueous Photolysis of 14C-MTI-446 under Laboratory Conditions and Determination of Quantum Yield. [redacted] unpublished report no. 729011, MRID 45640105, February 7, 2002.	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2000k	A.4.1.1.1 Abiotic deg radation; Photo-oxydation in air	Estimation of the degradation of MTI-446 by photo-oxidation in air. [redacted], unpublished report no. 731160, (MRID 45640110), September 22, 2000.	yes	Mitsui Chemicals Agro, Inc.	yes	y	y

[3] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process. For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

[redacted]	2000 l	A.4.1.1.3.2Biodegradation in freshwater, p.42 Appendix VII, 4.1.1	14C-MTI-446 : Degradation and Metabolism in Aquatic Systems. [redacted] unpublished report no. 709604, October 20, 2000	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2001e	A.4.1.2.1 Adsorption onto/desorption from soils	Adsorption/desorption of 14C-MTI-446 on soils; [redacted]; unpublished report no. 728998; September 19, 2001.	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2001e	A.4.1.2.1 Adsorption onto/desorption from soils	Adsorption/desorption of 14C-MTI-446 on soils; [redacted]; unpublished report no. 728998; September 19, 2001.	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2003b	A.4.1.1.3.6.1	14C MTI-446 metabolism in one soil incubated under aerobic conditions, [redacted], GLP, unpublished	yes	Mitsui Chemicals Agro, Inc.	yes	y	y
[redacted]	2003c	A.4.1.1.3.6.1	14C MTI-446: Anaerobic soil degradation and metabolism, [redacted], GLP, unpublished	yes	Mitsui Chemicals Agro, Inc.	yes	y	y

Data protection from this renewal *–(end five years from the first day of the month following the date of the adoption of a decision in accordance with Article 14(4))*

Confidential (as per article 66) :

Author (s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[1] (Yes/No)	Applicability	
							CAR/RAR	CLH
ACTIVE SUBSTANCE								
[redacted]	2011e	A.4.2.3.3	MTI-446 technical : a 96-hour flow-through acute toxicty test with the saltwater mysid (Mysidopsis bahia), [redacted] unpublished report no. 236A-104A, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2011b	A.4.2.3.3	Dinotefuran: a flow-through life-cycle toxicity test with the saltwater mysid (Americamysis bahia), [redacted] unpublished report no. 236A-141B, GLP, unpublished	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2011c	A.4.1.1.3.2Biodegradation in freshwater, p.42 Appendix VII, 4.1.1	aerobic & anaerobic water-sediment degradation/key / Dinotefuran/(RS)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine /165252-70-0; OECD / Biodegradation in water and sediment: simulation tests	Y	Mitsui Chemicals Agro, Inc.	Y	Y	Y
[redacted]	2020a	A.4.1.1.3.2Biodegradation in freshwater, p.42 Appendix VII, 4.1.1	aerobic water-sediment degradation/ /key / Dinotefuran / (RS)-1-methyl-2-nitro-3-	Y	Mitsui Chemicals Agro, Inc.	yes	y	y

			(tetrahydro-3-furylmethyl)guanidine / 165252-70-0: OECD / Biodegradation in water and sediment: simulation tests					
[redacted]	2001e	A.4.1.1.3.6.1	Degradation rate of MTI-446 in 11 agricultural soils from Germany incubated under aerobic conditions, [redacted], Report n° 734422, GLP, unpublished	y	Mitsui Chemicals Agro, Inc.	y	y	y
[redacted]	2020b	A.4.1.1.3.2	Re-evaluation of the water sediment degradation kinetics studies conducted with Dinotefuran; [redacted]; GMP, unpublished	y	Mitsui Chemicals Agro, Inc.	y	y	y
[redacted]	2020c	A.4.1.1.3.2	Dinotefuran: assessment of environmental persistence, [redacted], report n° 20-LKC-04, GLP, unpublished	y	Mitsui Chemicals Agro, Inc.	y	y	y

Appendix VI: Confidential information

See the Confidential Annex (separate document).

Appendix VII: Study summaries (relevant for the CLH proposal)

Study summaries are presented in the Annex I report (separate document).