Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine

EC Number: -
CAS Number: 165252-70-0

CLH-O-0000007342-79-01/F

Adopted

14 September 2023

14 September 2023

CLH-O-0000007342-79-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has **adopted on 14 September 2023 by consensus** an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine**

EC Number: **-**

CAS Number: **165252-70-0**

Rapporteur, appointed by RAC: **Raili Moldov** *supported by Jana Saksa (Adviser)*

Co-Rapporteur, appointed by RAC: **Anja Menard Srpčič**

Administrative information on the opinion

Belgium has submitted on **13 October 2022** a CLH dossier containing a proposal together with the justification and background information documented in a CLH report.

The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **5 December 2022**.

Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 February 2023**.

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The following table provides a summary of the Current Annex VI entry, Dossier submitter proposal, RAC opinion and potential Annex VI entry if agreed by the Commission.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 submitters 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 Wng	H410		M=10 M= 10	
RAC opinion	TBD	dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	-	165252-70-0	Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410		oral: ATE = 2000 mg/kg bw M=10 M= 10	
Resulting Annex VI entry if agreed by COM	TBD	dinotefuran (ISO); (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	-	165252-70-0	Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410		oral: ATE = 2000 mg/kg bw M=10 M= 10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Dinotefuran, with molecular formula $C_7H_{14}N_4O_3$, is registered under the REACH Regulation (EC) No 1907/2006 and is manufactured in and/or imported to the European Economic Area at ≥ 10 to < 100 tonnes per annum. The substance is approved for use as a biocide (insecticide). It should be noted that a large majority of the parameters/endpoints described in the CLH report prepared by the Dossier Submitter (DS) - Belgium - 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 1 June 2015. Belgium has taken over the function as evaluating competent authority for the dinotefuran dossier due to departure of the United Kingdom from the European Union, and more precisely for the renewal of the assessment report for dinotefuran for product type 18.
There is no current harmonised classification for the active substance dinotefuran according to Annex VI of Regulation (EC) no 1272/2008.

Toxicokinetics

The toxicokinetics of dinotefuran has been investigated in two *in vivo* absorption, distribution, metabolism and excretion studies, one in adult rats (2000a), the other in neonates (2000c) and in an *in vivo* dermal absorption study (2006b). Additionally, an oral study investigating the transfer of dinotefuran to the milk of lactating rats (2006a) was also provided by the DS.

Radioactivity derived from orally administered [14C]-dinotefuran is rapidly and almost completely absorbed from the GI tract, and is widely distributed throughout the tissues and fluids of the body. The elimination is rapid, predominantly by urinary excretion, and almost complete within 7 days after administration. Further, [14C]-dinotefuran is rapidly transferred to the foetus in utero and to maternal milk post-partum, but the elimination is rapid. 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. 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. The absorption, distribution, metabolism and elimination of [G-14C]-dinotefuran are similar in neonatal and young adult rats. Radioactivity is rapidly transferred to foetuses and rapidly distributed to the foetal tissues. Systemic absorption of the dermally applied dinotefuran is very low (less than or equal to 2.1 % of the applied dose).

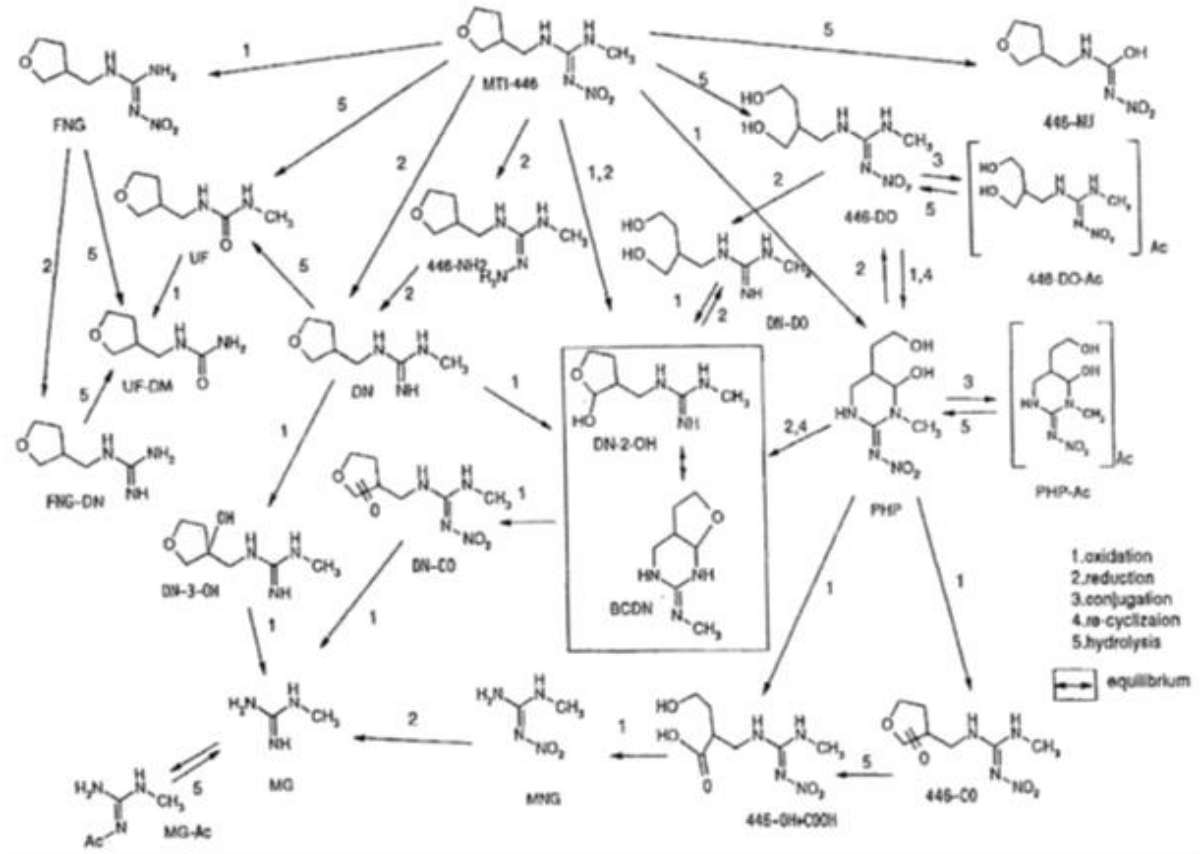
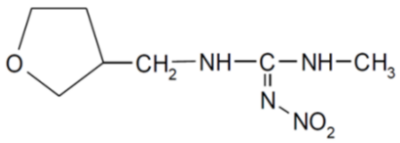


***Figure**: Generalised metabolic pathway for dinotefuran in the rat*

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Dinotefuran is a crystalline solid. The structural formula of the substance is:



Explosives

The substance contains chemical groups other than oxygen associated with explosive properties. Dinotefuran was tested according to EC Council Directive 92/69/EEC, Annex, Part. A, Methods for the determination of physico-chemical properties, A.14 "Explosive properties" and the results did not show any thermal or mechanical (shock and friction) sensitivity under the conditions of the test.

Information on the exothermic decomposition energy is also available. The decomposition energy and decomposition onset temperature are < 500 J/g under the conditions of the test conducted

according to EU Annex IIA Point #2.1.2, OPPTS 830.7220, and OECD TG 103. The calculated exothermic decomposition energy (423.6 J/g) that is extrapolated from decomposition onset temperature of 208.3 °C. Accordingly, CLP Regulation criterion (c) is fulfilled, and the substance does not need to be classified.

In summary, it can be concluded that dinotefuran is not an explosive substance.

Flammable solids

Dinotefuran was tested according to EEC A.10 method and found not to be flammable. It 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 without producing smoke and a turbid melt remained. Based on the results of the preliminary test, the main test was not performed (ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, 7.1.10.3). The substance is therefore considered as not flammable.

Self-reactive substances and mixtures

Dinotefuran contains a feature (contiguous nitrogen atoms) associated with explosive properties. Dinotefuran was tested according to ECC A.16 (autoignition), EEC A.10, EEC A.14 method with no exothermic behaviour up to the melting temperature of 107.5 °C, no ignition after a two-minute exposure of the test substance to a flame, and no explosive properties being observed. The substance was also tested according to OECD TG 103 and the broad exothermic peak observed was above 200 °C. Considering the presented data on the physicochemical properties, there is no expectation that dinotefuran is a self-reactive substance, although the Guidance on the Application of the CLP Criteria (version 5.0, July 2017) states that neither the burning properties nor the sensitivity to impact and friction form part of the classification procedure for self-reactive substances and mixtures in CLP.

Pyrophoric solids

No experimental studies are available. Manufacture and handling of dinotefuran shows that the substance does not ignite spontaneously on coming into contact with air at normal temperatures. Additionally, data regarding flammability is presented as a supportive data, which shows that dinotefuran is not flammable. It could not be ignited during the preliminary test (EEC A.10) after contact with the ignition source for about 2 minutes. Dinotefuran melted producing smoke and a turbid melt remained. Therefore dinotefuran can be considered as not pyrophoric.

Self-heating substances and mixtures

Dinotefuran was tested according to ECC A.16 method and showed no exothermic activity up to the melting temperature of 107.5 °C, and no self-ignition was detected at < 400 °C. Although, it is stated in the Guidance on the Application of the CLP Criteria (version 5.0, July 2017) that EU test method A.16 as described in Regulation (EC) No 440/2008 is suitable for assessing self-heating properties, the CLP Regulation indicates the substances with a melting point < 160 °C do not need to be considered for classification as self-heating. It was further indicated that dinotefuran decomposes at approximately 208 °C.

Substances or mixtures which in contact with water emit flammable gases

Dinotefuran does not fulfil any of the criteria for classification in this hazard class because the chemical structure does not contain metals or metalloids. Additionally, experience in production or handling shows that the substance does not react with water (is washed with water) and the substance is soluble in water. The hydrolysis study (OECD TG 111; 1998; report no. 95/MTO098/1216) conducted with dinotefuran concluded that dinotefuran is hydrolytically stable

under acid, neutral and weakly basic conditions, although it becomes unstable under more strongly basic conditions.

Oxidising solids

Dinotefuran was tested according to the method O.1, part III, sub-section 34.4.1. Conical piles were ignited, and potassium bromate was used as the reference substance. The study was not GLP compliant but was well reported and sufficient information provided to determine whether it was conducted in accordance with the test guidelines. The study is considered by the DS to be reliable and relevant for the classification purpose. 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.

***Table**: Results of the oxidising solids study (2004)*

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

Based on the available burn times, dinotefuran was not considered to be an oxidising solid.

Corrosive to metals

According to the DS, dinotefuran is a solid with a melting point higher than 55 °C and that may not become liquid during transport. Dinotefuran does not contain acidic or basic functional groups, does not contain halogens, and it is not able to form complexes with metals. It is therefore not considered to be corrosive to metals.

Comments received during consultation

No comments on physical hazards were received during the consultation.

Assessment and comparison with the classification criteria

Explosives

Dinotefuran has not shown explosive properties in tests using analogous test methods that are described in Part I of the UN RTDG, Manual of Tests and Criteria for the determination of explosive properties.

According to the CLP Regulation, a substance or mixture shall not be classified as explosive if:

"(c) The organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties, but the exothermic decomposition energy is less than 500 J/g, and the onset of exothermic decomposition is below 500 °C."

The available experimental results confirm that the substance has no explosive properties, and although dinotefuran contains chemical groups associated with explosive properties other than oxygen (contiguous nitrogen atoms), decomposition energy is < 500 J/g and decomposition onset temperature is < 500 °C.

Considering this, RAC agrees with the DS that dinotefuran does not warrant classification as explosive.

Flammable solids

According to the CLP Regulation, a powdered, granular, or pasty substance shall be considered as a readily combustible solid when the time of burning of one or more of the test runs, performed in accordance with the test method described in Part III, sub-section 33.2.1, of the UN RTDG, Manual of Tests and Criteria, is less than 45 seconds or the rate of burning is more than 2.2 mm/s.

According to the data from the available EEC Guideline A.10, dinotefuran does not meet this criterion and RAC agrees with the DS that dinotefuran does not require classification as a flammable solid.

Self-reactive substances and mixtures

According to the CLP Regulation I.2.8.4.2. the classification procedure for self-reactive substances need not be applied if:

a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties; or

b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT for a 50 kg package is greater than 75 °C or the exothermic decomposition energy is less than 300 J/G.

Dinotefuran contains a feature (contiguous nitrogen atoms) associated with explosive properties. The calculated exothermic decomposition energy is 423.6 J/g. Thus, none of the screening criteria are fulfilled.

RAC concludes that dinotefuran does not warrant classification as a self-reactive substance due to a lack of data.

Pyrophoric solids

According to the CLP Regulation, a pyrophoric solid shall be classified in Category 1 if the solid ignites within 5 minutes of coming into contact with air.

The screening procedure for pyrophoric solids need not be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e., the substance is known to be stable at room temperature for prolonged periods of time (days)).

The DS has reported that the substance is known to be stable at room temperature for prolonged periods of time (days); experience in manufacture and handling of dinotefuran shows that the substance does not ignite spontaneously on coming into contact with air at normal temperatures; dinotefuran is not considered as a flammable solid.

Based on these considerations RAC agrees with the DS that dinotefuran does not warrant classification as pyrophoric solid.

Self-heating substances and mixtures

According to Guidance on the Application of the CLP Criteria Version 5.0 – July 2017 (CLP Annex I: 2.11.4.2.), substances with a low melting point (< 160 °C) should not be considered for classification in this class since the melting process is endothermic and the substance-air surface is drastically reduced.

RAC recognises the negative results obtained in EEC A.16. RAC also recognises that the substance has a melting point lower than 160 °C. Thus, RAC agrees with the DS that no classification is warranted.

Substances or mixtures which in contact with water emit flammable gases

According to the CLP Regulation I.2.12.4.1, the classification procedure for this class need not be applied if:

(a) the chemical structure of the substance or mixture does not contain metals or metalloids; or
(b) experience in production or handling shows that the substance or mixture does not react with water, *e.g.*, the substance is manufactured with water or washed with water; or
(c) the substance or mixture is known to be soluble in water to form a stable mixture.

The DS stated that during production, the substance does not react with water (it is washed with water). Taking into account the fact that dinotefuran does not contain metals or metalloids in the structure, is soluble in water, and is hydrolytically stable under acid, neutral and weakly basic conditions, RAC agrees with DS that dinotefuran does not warrant classification.

Oxidising solids

According to the UN RTDG, Manual of Tests and Criteria, a substance is not an oxidizing solid if in both the 4:1 and 1:1 sample-to-cellulose ratio (by mass) tested, does not ignite and burn, or exhibits mean burning times greater than that of a 3:7 mixture (by mass) of potassium bromate and cellulose.

Taking into account the results of the test provided by the DS, RAC agrees that dinotefuran does not warrant the classification as an oxidising solid.

Corrosive to metals

According to Guidance on the Application of the CLP Criteria (Version 5.0 – July 2017), application of classification criteria in the UN-MTC, Section 37.4 excludes solids, while 'liquids and solids that may become liquids (during transport)', have to be considered for such a classification. Solids having a melting point lower than 55 °C (which is the test temperature required in UN Test C.1) must then be taken into consideration. Dinotefuran is a solid with a melting point at 107.5 °C and it may not become liquid during transport.

Additionally, Guidance on the Application of the CLP Criteria states that the following substances and mixtures should be considered for classification in this class:

- substances and mixtures having acidic or basic functional groups;
- substances or mixtures containing halogen;
- substances able to form complexes with metals and mixtures containing such substances.

Dinotefuran does not contain acidic or basic functional groups, it does not contain halogens, and it is not able to form complexes with metals. Thus, RAC agrees with no classification as corrosive to metals.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

No classification for dinotefuran has been proposed by the DS for acute oral toxicity based on the results from two GLP compliant acute oral studies (reliability 1).

In the first **acute oral toxicity study (1997a)**, performed according to OECD TG 401, groups of 5 male and 5 female rats were exposed to dinotefuran by gavage followed by a 14-day observation period.

In a range-finding study one male and one female were exposed to 500, 1 000, 3 000 and 5 000 mg/kg bw dinotefuran. In Phase I of the main study, females only were exposed to 1 000 and 3 000 mg/kg bw while both males and females were exposed to 5 000 mg/kg bw dinotefuran. In Phase II, males and females were exposed to 1 000, 2 000 and 3 000 mg/kg bw dinotefuran with an additional group of males exposed to 5 000 mg/kg bw dinotefuran and an additional group of females exposed to 4 000 mg/kg bw dinotefuran.

No death occurred in males in the dose range-finding study and in Phase I of the main study. In Phase II of the main study no deaths occurred in males exposed to 1 000 and 2 000 mg/kg bw respectively. Deaths occurred in males exposed to 3 000 (3/5 deaths) and 5 000 (5/5 deaths) mg/kg bw dinotefuran in Phase II of the main study.

No death occurred in females in the dose range-finding study exposed to 500 and 1 000 mg/kg bw and in Phase I of the main study. Deaths occurred in the dose range-finding study at concentration of 3 000 (1/1 deaths) and 5 000 mg/kg bw (1/1 deaths) and in Phase II of the main study at concentrations of 2 000 (3/5 deaths), 3 000 (4/5 deaths) and 4 000 (5/5 deaths) mg/kg bw, respectively.

Most deaths occurred on the day of treatment or on day 1. The 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. Clinical signs were generally transient and included red staining of the face from 1 000 mg/kg bw dinotefuran and hypoactivity, staggering gait, hunched posture, prostration miosis, lacrimation, salivation, tachypnoea, dyspnoea, soft faeces, convulsions and tremors at dose levels ≥ 2 000 mg/kg bw dinotefuran. All survivors, except one female exposed to 5 000 mg/kg bw in Phase I, gained weight during the observation period. No treatment related gross lesions were observed at necropsy in any animal. LD_{50} values of 2 804, 2 000 and 2 450 mg/kg bw dinotefuran were identified for males, females and for the sexes combined respectively. The Dossier Submitter concluded that dinotefuran exhibited low acute oral toxicity in male and female rats.

In a **second study** (1997b, 2000), groups of 5 male and 5 female mice were exposed to dinotefuran by gavage followed by a 14-day observation period. Doses were based on the results of a range-finding study in which one male and one female were exposed to 500, 1 000, 3 000 and 5 000 mg/kg bw dinotefuran. In the main study, males and females were exposed to 1 000, 2 000 and 3 000 mg/kg bw dinotefuran. Deaths occurred in males and females exposed to

≥ 2 000 mg/kg bw dinotefuran; in the range finding study 1/1 male died following exposure to 3 000 mg/kg bw and both male (1/1) and female (1/1) mice exposed to 5 000 mg/kg bw dinotefuran died. In the main study, male and female mice died following exposure to 2 000 (1/5 males, 2/5 females) and 3 000 (4/5 males and females) mg/kg bw dinotefuran. All deaths occurred on the day of treatment. Clinical signs were apparent on the day of treatment only and included hypoactivity, staggering gait, dyspnoea, convulsions and tremors at dose levels ≥ 2 000 mg/kg bw dinotefuran. Slight weight loss was recorded in 4 females exposed to 1 000 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. LD_{50} values of 2 450, 2 275 and 2 371 mg/kg bw dinotefuran were identified for males, females and for the sexes combined respectively. The Dossier Submitter concluded that dinotefuran exhibited low acute oral toxicity in male and female mice.

Additionally, data from a reliable GLP compliant acute neurotoxicity study in rats is presented. A single gavage dose of 0 (0.5 % CMC vehicle only), 325, 750 or 1 500 mg/kg bw was administered. There were no deaths or treatment-related clinical signs during the study at any dose level. 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 was identified for acute toxicity in the rat.

The DS proposed an acute toxicity estimate (ATE) of dinotefuran via the oral exposure route of 2371 mg/kg bw based on average value from the mouse study.

Acute dermal toxicity

The DS proposed no classification of dinotefuran for acute dermal toxicity based on the result from a reliable and GLP compliant study performed according to OECD TG 402 (1997c). Dinotefuran was applied dermally to 5 male and 5 female rats at a limit dose of 2 000 mg/kg bw for 24 h followed by a 14-day observation period. No deaths were observed during or post-exposure. 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. 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.

The DS proposed a LD_{50} of dinotefuran via the dermal exposure route of > 2 000 mg/kg bw.

Acute Inhalation Toxicity

The DS proposed no classification of dinotefuran for acute inhalation toxicity based on the result from a reliable and GLP compliant study performed according to OECD TG 403 (1999, 200a, b). 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. 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, but the authors of the study stated that this was the minimum attainable MMAD. No deaths were observed during or post-exposure. 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.

LC_{50} was estimated to be > 4.09 mg/L in both male and female rats.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

Acute oral toxicity studies in rats and in mice are available. LD_{50} values of 2 804 and 2 000 mg/kg bw dinotefuran were identified for male and female rats, respectively. LD_{50} values of 2 450 and 2 275 mg/kg bw dinotefuran were identified for male and female mice, respectively. Noting that reported data show variation in sensitivity between males and females towards acute oral toxicity and since the median lethal dose of dinotefuran in the acceptable acute oral toxicity study in female rats was equal to 2 000 mg/kg bw, RAC is of the opinion that the substance warrants classification as Acute Tox. 4, H302: Harmful if swallowed, with an ATE of 2 000 mg/kg bw.

Since the median lethal dose of dinetofuran in the acceptable acute dermal toxicity study in rats was above 2 000 mg/kg bw, RAC agrees with the DS proposal of no classification for acute dermal toxicity.

Since the median lethal dose LC_{50} of dinetofuran in the acceptable acute inhalation toxicity study was estimated to be > 4.09 mg/L in both male and female rats, RAC agrees with the DS's proposal of no classification for acute inhalation toxicity.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

There are no human data available. Series of the standard studies are presented by the DS to investigate the potential of dinotefuran to cause specific target organ toxicity (single exposure). 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 acute neurotoxicity study in rats was available. Based on the results of these reliable and GLP compliant studies the DS proposed no classification in this hazard class.

In the acute oral toxicity studies treatment-related clinical signs were apparent at dose levels of ≥ 2 000 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 tonic convulsions and tremors. Clinical signs were generally transient but occasionally persisted for up to 3 days after treatment, all these effects were considered to be a manifestation of general toxicity.

In an acute neurotoxicity study the only treatment related change reported was a reduction in motor activity score at 1500 mg/kg bw during the first 10 minutes after administration. Beyond 10 minutes, no change was observed regarding the motor activity.

The DS presented three developmental toxicity studies conducted according to OECD 414 (1998b; 2013) and one study conducted according to OECD TG 426 (2010) to assess the narcotic effects. In one rabbit developmental toxicity study (1998e) dinotefuran was administered at the concentrations of 52, 125, 300 mg/kg bw/d, daily exposure for GD 6-18, 10-day post-exposure period. Hypoactivity, prone position, panting, flushing of the nose and ears and tremors from the start of treatment until day 14 of gestation were observed at concentration of 300 mg/kg bw/d. In the second rabbit developmental toxicity study (2013) all dams showed tachypnea at 500 mg/kg bw/day on days 6 and 7. No target organ toxicity has been observed in these studies.

The DS concluded that since there is no lack of coordination or ataxia observed, the lethargy alone cannot be imputable to a narcotic effect.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

Dinotefuran did not induce transient target organ effects such as respiratory tract irritation after single exposure. Transient effects (such as hypoactivity, staggering gait, dyspnea, tonic convulsions and tremors at lethal doses) observed in the acute oral toxicity studies (1997a, b) appeared rapidly after the start of the exposure and at dose levels where mortalities exist, therefore these effects were considered to be more relevant to acute toxicity. Effects (such as reduction in motor activity score at the highest dose level in 3 hours after dosing) observed in the acute neurotoxicity study (2001a) may be attributed to adaptation or effects (such as hypoactivity, prone position, panting, flushing of the nose and ears and tremors at highest dose) observed in the developmental toxicity study (1998e) may be attributed to general toxicity. There were no relevant effects for STOT SE 3 (narcotic effect) in the reliable developmental neurotoxicity (2010) study. Noting that in the presented acute oral, dermal and inhalation toxicity studies no adverse, systemic effects meeting classification criteria were described in animals after single exposure to dinotefuran at non-lethal doses or concentrations, RAC is of the opinion that this substance does not require classification for specific target organ toxicity – single exposure (STOT SE).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

No classification for dinotefuran has been proposed by the DS for skin irritancy/corrosivity based on the result from a reliable, GLP compliant and according to OECD TG 404 performed study (1998a, c). 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 a 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.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

The results of the acceptable skin irritation study in rabbits showed that the individual score was no greater than 0.33 in all tested rabbits, which is well below the classification criteria (≥ 2.3-≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals and that the observed skin inflammation was fully reversible within 7 days).

Overall, RAC agrees with the DS's proposal that no classification for skin irritation is warranted.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

No classification for dinotefuran has been proposed by the DS for eye damage/irritation based on the results from two GLP compliant eye irritation studies (reliability 1).

In a first study (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 irritant effects observed in both the unwashed and washed groups were no longer apparent on day 14.

In a second study (2004) 0.1 mL by volume (37.8 mg) of dinotefuran was placed into the conjunctival sac of the right eye of each animal. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24 h observation. The mean scores for corneal opacity, iris lesion, erythema and oedema were 0 at 24 h, 48 h and 72 h.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

According to the CLP criteria, a classification for eye irritation in Category 2 is justified if at least 4 out of 6 rabbits show a mean score per animal of:

i. ≥ 1 for corneal opacity and/or
ii. ≥ 1 for iritis and/or
iii. ≥ 2 conjunctival erythema (redness) and/or
iv. ≥2 conjunctival oedema (swelling) (chemosis)

and which fully reverses within an observation period of normally 21 days.

Dinotefuran does not fulfil the classification criteria for eye irritation as only one animal show mean scores for corneal opacity ≥ 1, only 1 animal show mean score ≥ 2 for conjunctival redness and only 1 animal show score ≥ 2 for conjunctival oedema. The observed effects were fully reversed within an observation period of < 21 days (14 days). Overall, RAC agrees with no classification for serious eye damage/eye irritation.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The DS has stated that there are no animal and/or human data available for evaluation respiratory sensitisation of dinotefuran.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

This hazard class was not assessed by RAC due to lack of data.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

No classification for dinotefuran has been proposed by the DS for skin sensitisation.

The DS provided a reliable, GLP compliant, according to OECD TG 406 performed skin sensitisation study of dinotefuran in guinea pigs (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. 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. 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 DS concluded that the skin sensitisation potential of dinotefuran has been adequately tested.

Comments received during consultation

No comments were received during the public consultation.

Assessment and comparison with the classification criteria

According to the CLP Regulation p.3.4.2.2.3.1, for Category 1, when an adjuvant type test method for skin sensitisation is used, a response of at least 30 % of the test animals is considered as positive.

RAC recognises the uncertainties regarding the challenge concentration of 25 % dinotefuran and notes that the initial Magnusson and Kligman procedure allowed to test solids that are finely

pulverized and preferably incorporated in petrolatum at a concentration of 25 %, providing not excessively irritation or injurious to general health. RAC also notes the maximum technically achievable concentration and that a 10 % sodium lauryl sulfate pre-treatment was applied. Overall, RAC agrees with the DS's proposal that no classification for skin sensitisation is warranted.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The DS provided several repeated dose toxicity studies by the oral, inhalation and dermal routes in rats, mice and dogs. For the oral (dietary) route, the main effects reported in all species tested are minor reductions in body weight gain and food consumption for sub-acute, sub-chronic and chronic exposures. A bespoke pair-feeding/palatability study (2015) in the rat demonstrated lower food consumption due to unpalatability and as the result decrease of body weight gain. 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. The DS did not propose a classification for dinotefuran in this hazard class.

Oral route

In a **28-day oral dietary study in Sprague-Dawley rats** (OECD TG 407), the substance was administered at concentrations of 0, 5 000, 25 000 and 50 000 ppm (1997a). There were no treatment related mortalities or clinical signs. Body weight gain and food consumption were reduced in a dose related manner in both sexes at 25 000 and 50 000 ppm. These changes were accompanied by minor clinical chemistry changes which may have been secondary to the reduced body weight gain, namely increased serum cholesterol at 2 500 and 50 000 ppm and reduced serum glucose at 50 000 ppm. There were no treatment related haematology, ophthalmoscopy, urinalysis, organ weight, macroscopic pathology or histopathology findings or macroscopic pathology findings. Decrease of body weight gain was linked to reduced food consumption due to unpalatability of the diet. Since the unpalatability of dinotefuran was proved at dose 20 000 and 50 000 ppm in the provided study it is concluded that the NOAEL for this study is 50 000 ppm (3 720 / 4 222 mg/kg bw/day, M/F).

In a **28-day oral dietary study in CD-1 mice** (OECD TG 407), the substance was administered at concentrations of 0, 5 000, 25 000 and 50 000 ppm (1997b). There were no treatment related mortalities or clinical signs. Body weight gain was markedly reduced at 25 000 and 50 000 ppm in both sexes. Excessive food spillage in the 25 000 and 50 000 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 5 000 ppm. The only clinical chemistry difference considered to be treatment related was increased serum protein and albumin concentrations in males at 50 000 ppm. There were no treatment related haematology, organ weight, macroscopic pathology or histopathology findings. In this study there was no decrease of food consumption in the two highest doses, thus the decreased body weight gain cannot be imputable to the unpalatability. Therefore, the DS concluded that the NOAEL for this study is 5 000 ppm (equivalent to 901 and 1 043 mg/kg bw/d, M/F respectively).

Additionally, the effects on body weight and food consumption in the **developmental toxicity studies in rats and in rabbits** were consistent with the findings in the oral dietary studies. In rats (dose levels 0, 100, 300, 1 000 mg/kg bw/day, GD 6-15), dinotefuran elicited maternal

toxicity only at 1 000 mg/kg/day, observed as reduced body weight gain and food consumption during the early part of the dosing period and increased water consumption towards the end of the dosing period.

Supplementary information about the impact of dinotefuran on body weight gain in rats is available from a **dietary immunotoxicity study** (2012). The substance was administered dietary at dose levels 0, 2 240, 5 600, 14 000 ppm for 28 days. There were no treatment-related clinical signs at any dose level or in the cyclophosphamide-treated group and no animals died prematurely. Food consumption was persistently lower than control for both sexes receiving 14 000 ppm. 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, Plaque forming cell (PFC)/106 viable 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 14 000 ppm was the maximum tolerated dose for this study type and duration. The DS concluded based on the observation of reduced body weight gain and food consumption at 14 000 ppm that the NOAEL for general toxicity is 5 600 ppm (intake 425 mg/kg bw/day in males and 430 mg/kg bw/day in females).

In another reliable **4-week immunotoxicity study in mouse** (2011) dinotefuran was administered at concentrations of 1 120, 2 800, 7 000 ppm. No evidence of general toxicity as well as no effects on the humoral T-lymphocyte-dependent response against antigen on sheep red blood cells (SRBC) in the dinotefuran groups. The NOAEL for all effects is 7 000 ppm (equivalent to 1 053 (M) and 1 438 (F) mg/kg bw/d) and the NOEL for immunotoxicity 7 000 ppm (equivalent to 1 053 (M) and 1 438 (F) mg/kg bw/d).

In a **7-day oral capsule administration study in beagle dogs** (not GLP, reliability 2, supportive study) the substance was administered to male and female animals at concentrations of 0, 30, 100, 300 mg/kg bw/day (1998a). Clinical signs of diarrhoea or vomiting were observed in the 300 mg/kg bw/day group at the beginning of the test period. The changes observed in the weight of both male and female genital organs were considered attributable to sexual immaturity of the subjects. There were no treatment related mortalities. There were no adverse effects on body weight gain or food consumption. There were no treatment related haematology, urinalysis, organ weight changes, macroscopic pathology or histopathology findings. The DS concluded that the NOEL for this study is 100 mg/kg bw/day, M/F).

In a second **7-day oral dietary study (1998b) in beagle dogs** (not GLP, reliability 2, supportive study), the substance was administered to male and female dogs at concentrations of 0, 1 250, 5 000, 20 000, 30 000, 40 000 ppm. 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 40 000 and the 30 000 ppm dose groups, suggestive of reduced palatability of the test diets. There were no treatment related haematology, urinalysis, organ weight changes, macroscopic pathology or histopathology findings. The DS concluded that the NOAEL for this study is 40 000 ppm (770/924 mg/kg bw/day (M/F) respectively).

In a **13 week oral dietary study in Sprague-Dawley rats** (according to OECD TG 408, GLP compliance, reliability 1), the substance was administered to males and females at concentrations of 0, 500 (34/38 mg/kg bw/day male and female respectively), 5 000 (336/384 mg/kg bw/day (m/f)), 25 000 (1 623/1 871 mg/kg bw/day (m/f)) and 50 000 ppm (3 156/3 616 mg/kg bw/day (m/f)) (1997c). There were no treatment related mortalities or clinical signs. Body weight gain was reduced in a dose related manner in both sexes at 25 000 and 50 000 ppm and in females at 5 000 ppm. Food consumption was reduced for much of the study in both sexes at 25 000 and

50 000 ppm. There were no treatment related haematology, clinical chemistry, ophthalmoscopy, urinalysis, organ weight or macroscopic pathology findings. Treatment related histopathological findings were limited to increased cytoplasmic vacuolation of the adrenal cortex in both sexes treated at 25 000 and 50 000 ppm and in males at 5 000 ppm. Mostly, the lesions were 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. This finding is not considered as an adverse since there were no correlating clinical pathology findings indicating functional deficit. According to scientific literature, effects on the adrenal gland can arise as a secondary effect of stress rather than as a direct effect (Marty M. *et al.*, 2018; -DePeyster A. *et al*, 2014). In the presented study the stress related response could be due to the food consumption and body weight gain differences. Moreover, this histopathological alteration did not occur at dose levels in excess of 3 000 mg/kg bw/day for 4 weeks or after 26, 52, 78 and 104 weeks of 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 25 000 and 50 000 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 50 000 ppm included initial body weight loss. However, in the investigative study food consumption was reduced by up to 10 and 38 % at 20 000 and 50 000 ppm, respectively, with concomitant decreases in body weight gain of up to 32 and 60 %, respectively, including initial body weight loss at 50 000 ppm. Since these effects have been shown in the investigative study and considered to be due to unpalatability of the test diets, the effects on food consumption and body weight gain in the 13-week study were also considered to be due to diet palatability and do not therefore represent adverse effects of treatment. The DS concluded that the NOAEL for this study is 50 000 ppm (3 156/3 616 mg/kg bw/day, males/females, respectively).

In a **13 week oral dietary study in CD-1 mice** (according to OECD TG 408, GLP compliant, reliability 1), the substance was administered to males and females animals at the concentrations of 0, 500, 5 000, 25 000 and 50 000 ppm (1997b). There were no treatment related mortalities or clinical signs. Body weight gain was significantly reduced at 50 000 ppm in both sexes. Body weight gain for females at 500, 5 000 and 25 000 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 25 000 and 50 000 ppm groups in the 1st week and at 50 000 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. The DS concluded that the NOAEL for this study is 25 000 ppm (intake of 4 442 mg/kg bw/day in males and 5 414 mg/kg bw/day in females).

In a **13-week oral dietary study in beagle dogs** (according to OECD TG 409, GLP compliant, reliability 1), the substance was administered to males and females animals at the concentrations of 0, 1 600, 8 000 and 40 000 ppm (1997c). The highest dose level was progressively reduced to 30 000 ppm on day 5 and to 24 000 ppm on day 12 following the observation of severe reductions in food consumption and body weight 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 30 000 or 40 000 ppm, included black, liquid/mucoid, few or no faeces, thinness, slightly reduced activity, pale gums. Body weights for both sexes in highest dose recovered after the dose level reductions, though these remained lower that controls for the remainder of the study. Body weights were also significantly lower for females at 1 600 and 8 000 ppm during the second half of the study; although a dose-response relationship was not

apparent, similar body weight changes were present in females at dietary dose levels of 3 200 and 16 000 ppm in the 52-week dog study (1999c), and therefore these lower body weights were considered to be 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 24 000 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. In the absence of evidence for any other general or specific organ toxicity a NOAEL of 8 000 ppm for both sexes (307/323 mg/kg bw/day, M/F) was assigned.

A **dietary neurotoxicity study in rats** is presented to provide a supplementary information on repeated dose subchronic toxicity in rats (Section 3.9.1, 2001b). Dietary levels of 0, 500, 5 000 and 50 000 ppm were administered for 13 weeks. At 50 000 ppm only, reduced body weight gain and food consumption in both sexes were reported. A NOAEL of 5 000 ppm (intake 327 mg/kg bw/day for males and 400 mg/kg bw/day for females) was identified for general toxicity.

A **dietary 2-generation reproduction study** was presented (Section 3.8.2, 2002) to provide a supplementary information on repeated dose sub-chronic toxicity. Dietary dose levels 0, 300, 1 000, 3 000, 10 000 ppm were administered. NOEL for general parental toxicity of 3 000 ppm (intake of at least 241 and 268 mg/kg bw/day in parental males and females, respectively) was identified based on body weight and food consumption reductions at 10 000 ppm.

In a **52-week oral dietary study in beagle dogs** (according to OECD TG 452, GLP compliant, reliability 1) the substance was administered to males and females at 0, 640, 3 200 and 16 000 ppm (1999c). There were no treatment related mortalities or clinical signs. A treatment related reduction in mean body weight gain was observed in both sexes at 16 000 ppm and in females at 3 200 ppm throughout the study, though only the changes in females achieved statistical significance. In females the body weight 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 (2005). The DS concluded with a NOAEL of 16000 ppm for both sexes (559 / 512 mg/kg bw/day, m/f).

The information from the **78-week oral dietary carcinogenicity study in CD-1 mice** (OECD TG 451, GLP compliant, reliability 1) was presented to provide some relevant information on chronic toxicity (2000d, e). Dietary levels of 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, body weight gain was reduced throughout most of the study and platelet count was reduced at termination at 25 000 ppm. There were no treatment related organ weight changes or non-neoplastic histopathology changes. A NOAEL of 2 500 ppm (intake of 345 mg/kg bw/day in males and 441 mg/kg bw/day in females) was set for non-neoplastic effects.

The supplementary information from a **104-week oral dietary chronic/carcinogenicity study** was presented to assess the effect on food consumption and body weight gain at 0, 60, 200, 2 000 and 20 000 ppm (2000c). 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 20 000 ppm at the interim week 78 kill, which can be regarded as secondary to the reduced body weight gain. The effect on food consumption and body weight gain at 20 000 ppm

in the 104-week study during the first 4 weeks of treatment was very similar to the effect at 20 000 ppm in the palatability investigative study (2015), but the effects tended to persist until termination at 104 weeks, particularly in females. The low overall body weight gain in females at 20 000 ppm (weeks 1-104) was considered to reflect the marked retardation of body weight gain 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 food consumption and body weight gain in the 104-week study were also considered to be due to diet palatability and do not therefore represent adverse effects of treatment. A NOAEL of 20 000 ppm for both sexes (991 / 1 332 mg/kg bw/day, M/F) was identified.

Dermal route

In a 28-day dermal study in Sprague-Dawley rats (according to OECD TG 410, GLP compliant, reliability 1) the substance was administered at doses of 0 (CMC vehicle control), 40, 200 and 1 000 mg/kg bw/day (2001b). No evidence of systemic or local toxicity was observed. A NOAEL of 1 000 mg/kg bw/day was identified.

Inhalation route

In a 28-day inhalation study (OECD TG 412, GLP compliant, reliability 1), Wistar rats were exposed nose only to dinotefuran dust atmospheres of 0, 0.22, 0.66, 2.08 mg/L, for 6 h/day (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 body weight gain and food consumption in males only during the 1st week in all the dinotefuran groups (though only the body weight differences achieved statistical significance). However, body weight gain for weeks 2 to 4 in all treated groups was similar to controls. The DS concluded that a NOAEC for males was not identified, and a LOAEC of 0.22 mg/L was assigned; for females the study NOAEC was 2.08 mg/L.

Additionally, to elaborate the effects on body weight gain the DS provided a pair-feeding/palatability investigative study (2015). Based on results of this study the dossier submitter concluded that unpalatability of dinotefuran is proved at the concentrations 20 000 and 50 000 ppm. Thus, effects on weight gain and food consumption at these concentrations reported in several toxicity studies with a high probability may be attributed to unpalatability of treated diet. More in detail, groups of individually-caged rats treated with dinotefuran (20 000 and 50 000 ppm) 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. Additionally, 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 produced an immediate (from Day 1) decrease in the food consumption by 40 and 50 % (males and females respectively) at 20 000 ppm and by 80 and 68 % (males and females respectively) at 50 000 ppm which persisted throughout the four-week treatment period. 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 20 000 and 50 000 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 20 000 ppm ingested a higher dose on Day 1 (1 434 mg/kg bw) than the males treated at 50 000 ppm (1 195 mg/kg bw), but the effect on food consumption was much greater at 50 000 ppm than at 20 000 ppm. In females the effect was less clear because the dose ingested at 50 000 ppm (1 750 mg/kg bw) was slightly higher than the dose ingested at 20 000 ppm (1 078 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 20 000 ppm dinotefuran, and a less marked and more transient rejection of diet containing 4 000 ppm. 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 4 000-50 000 ppm.

In the group-matched phase, body weight change in the groups treated with 20 000 or 50 000 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). Overall body weight gain at both 20 000 and 50 000 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.

Comments received during consultation

No comments on this hazard class were received during public consultation.

Assessment and comparison with the classification criteria

Studies conducted by the oral route show a decrease in food consumption with a corresponding decrease in body weight. In the diet studies, low palatability is suspected to be involved in the reduction in food consumption.

Increased cytoplasmic vacuolation of the adrenal cortex was found in a 13-week rat study. The severity of the lesion was graded as minimal or slight (except for one female at 50 000 ppm that was graded as moderate). Minimal to moderate adrenal cortical vacuolation is considered not to be an adverse finding in this study, since there were no correlating clinical pathology findings indicating a functional deficit.

RAC agrees with the DS that no classification is warranted for this hazard class.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Based on negative results in the available *in vitro* and *in vivo* genotoxicity studies the DS concluded that the criteria for classification for germ cell mutagenicity are not fulfilled and dinotefuran should not be classified to this hazard class.

The DS provided several *in vitro* and *in vivo* studies of genotoxicity summarised below for the evaluation of germ cell mutagenicity:

***In vitro* studies**

Test system, Method, Guideline GLP Reliability	**Organism/ strain(s)**	**Concentrations tested**	**Result**		**Remark**	**Reference**
			– S9	**+ S9**		
Bacterial reverse mutation assay OECD TG 471 (1994), OECD TG 472 (1994), GLP, Reliability 1	*S. typhimurium:* TA 98, TA 100, TA 1535, TA 1537 *E. coli* WP2uvrA	1.2-5 000 µg/plate	neg.	neg.	Cytotoxicity or precipitation of test substance in the medium were not observed, but the highest conc. tested was the limit concentration	1996, **Key study**
Bacterial DNA repair assay Japan MAFF (1985), GLP, Reliability 1	Bacillus subtilis: M45 Rec- & H17 Rec+	0 (solvent DMSO control), 62.5-16 000 µg/disc	neg.	neg.	-	1999, **Key study**
Chromosomal aberration assay, OECD TG 473, GLP, Reliability 1	Chinese hamster lung cells	500-2 000 µg/mL (up to ~0.01M)	neg.	neg.	Cytotoxicity or precipitation of test substance in the culture medium were not observed, but the highest concentration tested was the limit concentration.	1996, **Key study**
Gene mutation in mammalian cells, according to OECD TG 476, GLP, Reliability 1	Mouse lymphoma L5178Y cells	7.81 (preliminary study) and 400 (main study)–2 022 µg/mL (up to ~0.01M)	neg.	neg.	Cytotoxicity or precipitation of test substance in the culture medium were not observed, but the highest concentration tested was the limit concentration.	2002, **Key study**

***In vivo* studies**

Test system, Method, Guideline GLP Reliability	**Organism/ strain(s)**	**Concentrations tested**	**Result**	**Remark**	**Reference**
Erythrocyte micronucleus test similar to OECD TG 474 (1997) but not compliant, GLP, Reliability 1	*Mouse (BDF1 strain)*	Daily, gavage, for 2 days, 270-1 080 mg/kg/day. Sampling times; 24 h after last dose, sampled from bone marrow	Negative. No general toxicity in main study; deaths at 1 800 mg/kg/day in a pilot study. An appropriate response was seen in the positive control group.	Not OECD 474 compliant due to only 1 000 polychromatic erythrocytes/animal were assessed for the presence of micronuclei.	1995, **Key study**

Test system, Method, Guideline GLP Reliability	Organism/ strain(s)	Concentrations tested	Result	Remark	Reference
Erythrocyte micronucleus test, OECD TG 474 (2016), GLP, Reliability 1		Single exposure to 0 (vehicle, corn oil), 500, 1 000 and 2 000 mg/kg bw, by gavage.	Negative. No deaths and no signs of general toxicity. 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.	5 animals per sex per dose. 48 hour post exposure period. The study addressed the aneugenicity endpoint and demonstrated exposure in plasma.	2019, **Key study**

Dinotefuran was non-mutagenic in bacterial and mammalian gene mutation tests, with and without metabolic activation as well as *in vitro* chromosomal aberration assay. All tests were conducted in compliance with the relevant OECD TG. Dinotefuran was also tested in a non-standard bacterial DNA repair assay (*B. subtilis*) and showed negative result. Furthermore, dinotefuran was negative in two *in vivo* bone marrow micronucleus tests conducted in mice. One study is considered as supportive because only 1 000 polychromatic erythrocytes/animal were assessed for the presence of micronuclei, rather than the 2 000 polychromatic erythrocytes/animal recommended in the TG. The second study was performed in accordance with the OECD TG and without deficiencies. There was no evidence of general toxicity or a reduction of the PCE/NCE ratio. The presence of dinotefuran in plasma was demonstrated and therefore exposure of the bone marrow to the test material. The study showed no test item related increase in bone marrow micronuclei up to the top dose of 2 000 mg/kg bw in the mouse. It was concluded that dinotefuran is neither aneugenic nor clastogenic.

Comments received during consultation

No comments on this hazard class were received during public consultation.

Assessment and comparison with the classification criteria

The CLP Regulation states that the results from mutagenicity or genotoxicity tests *in vitro* and in mammalian somatic and germ cells *in vivo* can be considered in classifying substances within this hazard class.

The germ cell mutagenicity potential of dinotefuran has been assessed in relevant *in vitro* and *in vivo* tests. The substance was negative in all tested assays.

RAC therefore agrees with the DS that no classification is warranted for this hazard class.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

No information on carcinogenic potential in humans was available. To investigate the carcinogenic potential of dinotefuran the DS provided two standard, GLP compliant chronic/carcinogenicity dietary studies, conducted in rats and mice. Based on the results of these studies, the DS proposed no classification for dinotefuran in this hazard class.

In the reliable, GLP compliant, **104-week oral dietary rat** (Sprague Dawley) study (2000c), conducted according to OECD TG 453, the substance was administered at dose levels of 0, 60, 200, 2 000 and 20 000 ppm. Survival was not affected by treatment. The body weight gains of both sexes were reduced by treatment at 20 000 ppm from week 2 but the effect was more severe in the females with an overall (week 1-104) reduced body weight gain by 5.1 and 35.6 % in males and females, respectively. The mean weekly food consumption for animals treated at 20 000 ppm 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 2 000 ppm. There were no treatment related effects on the nature and incidence of adverse non-neoplastic histopathological findings at any dose level. However, males treated at 20 000 ppm showed higher incidences of renal changes, pelvic mineralisation, lymphohistiocytic infiltrate, tubular epithelial basophilia and thickening of the basement membrane. None of the renal changes was 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 20 000 ppm. Similarly, increased incidences of thymic lymphocyte depletion and prostatic chronic active inflammation in males at 20 000 ppm was considered not to be adverse effects since they occur commonly in the rat.

The incidence of thyroid C-cell adenoma in males was statistically significantly increased (26 %) at 20 000 ppm (11.9 % in concurrent 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 (28 %) in females at 20 000 ppm (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 %.

***Table**: Terminal sacrifice and decedents from carcinogenicity:*

Findings	**Males: dose level (ppm)**				
	0	**60**	**200**	**2 000**	**20 000**
Thyroid - No. examined	59	60	60	58	60
- C-cell adenoma(b)	7 (11.9 %)	10 (17 %)	10 (17 %)	12 (21 %)	15 (26 %)
Historical control % range	8.0-26.7 % [from 13 carcinogenicity studies, completed Jun 1998-April 2002]				
Finding	**Females: dose level (ppm)**				
	0	**60**	**100**	**2 000**	**20 000**
Thyroid - No. examined	58	59	53	56	58
- 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	**6**	**200**	**2 000**	**20 000**
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 %**				
Finding	**Females: dose level (ppm)**				
	0	**60**	**200**	**20 000**	**20 000**
Mammary gland - no. examined	60	60	60	58	60
Adenoma (b)	11 (18.3 %)	11 (18.3 %)	7 (11.6 %)	9 (15.5 %)	9 (15 %)
- 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.

The incidences of thyroid C-cell adenoma and mammary gland carcinoma 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. Thus, the higher incidences of thyroid C-cell adenoma and mammary gland carcinoma are considered as not treatment-related.

The incidence of interstitial cell adenoma (Leydig cell adenomas) was increased at the top dose only (8.4 % at 20 000 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 mode of action 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 reduced the concern that the Leydig cell adenomas were 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 was not considered to be treatment-related or biologically significant as there was no dose response, a lack of statistical significance and no increase in Leydig cell hyperplasia. The NOAEL was set at 20 000 ppm.

In the reliable 78-week oral dietary carcinogenicity study (2000d,c) in CD-1 mice conducted according to OECD TG 451, the substance was administered at 0, 25, 250, 2 500 and 25 000 ppm. Survival was not affected by treatment. The only non-neoplastic effects were reduced body weight gain and reduced platelet counts at 25000 ppm. There were no differences in the incidence of neoplastic findings in treated groups as compared to the controls.

Comments received during consultation

No comments on this hazard class were received during public consultation.

Assessment and comparison with the classification criteria

No epidemiologic studies in humans investigating the carcinogenic potential of dinotefuran are available.

The DS presented the results of two reliable chronic toxicity/carcinogenicity studies via the oral route of exposure in rats and mice.

The incidences of benign testicular interstitial cell tumours, benign endometrial stromal polyps, thyroid C-cell adenomas and the incidence of mammary gland carcinomas were observed only in one species, without a clear dose-response relationship and within or close to the historical control range.

Based on the above mentioned and on lack of evidence of mutagenicity, RAC agrees with the DS that no classification is warranted for this hazard class.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Fertility

No classification of dinotefuran for sexual function and fertility has been proposed by the DS based on the absence of effects on reproduction in a GLP-compliant two-generation study performed according to OECD TG 416 (key study, reliability 1) and in a two-generation pilot study.

In a **pilot two-generation rat study**, dinotefuran was administered to 6/sex/group at 0, 10 000 (the parental intake 700/779 mg/kg bw/day (M/F)) and 20 000 ppm (1 340/1 507 mg/kg bw/day (M/F)) (2001). There were no treatment related F0 mortalities or clinical signs. F0 parental body weight gain and food consumption were reduced in a dose related manner at both 10 000 and 20 000 ppm. Treatment related necropsy findings were limited to the observation of small thymus in F0 females. There were no effects on fertility or mating performance, although the numbers of implantation sites and live births was reduced at 20 000 ppm. F1 pup body weights during lactation and food consumption post weaning were reduced; pup viability was unaffected. The LOAEL for general parental and neonatal toxicity was 10 000 ppm; the NOAEL for reproductive parameters was 1 000 ppm.

In a **two-generation dietary rat study**, the substance was administered at 0, 300, 1 000, 3 000, 10 000 ppm daily for 10 weeks prior to mating and through to weaning of F1 offspring (2002). One F0 high dose female died during the study on PND 21. Parental clinical signs of toxicity were limited to soft faeces during the lactation period in F0 females at 10 000 ppm. For both sexes at 10 000 ppm, F0 and F1 body weight 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. NOEL (general toxicity) 3 000 ppm (equivalent to 241 (M) and 267.9 (F) mg/kg bw/day); NOEL (neonatal toxicity) 3 000 ppm, NOEL (reproduction toxicity) 10 000 ppm (822 (M) and 907 (F) mg/kg bw/day)

Developmental toxicity

The DS provided several studies for evaluation of developmental toxicity in rats and rabbits summarised below.

<u>Rat studies</u>

In a GLP-compliant, performed according to OECD TG 414, **rat developmental toxicity study**, the substance was administered by gavage at 0 (0.5 % CMC vehicle), 100, 300 and 1 000 mg/kg bw/day (1998b). The dosing period was shorter than required for the guideline. However, the DS

does not consider this to have compromised the validity of the study. Maternal toxicity signs such as reduced body weight gain and food consumption during the early part of the dosing period and increased water consumption towards the end of the dosing period were observed at 1 000 mg/kg bw/day. Mean pre-implantation loss was noticeably higher at 1 000 mg/kg/day than controls (24 % vs 9 %), but because implantation was complete 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 1000 mg/kg bw/day. The NOAEL (maternal toxicity) is 300 mg/kg bw/d;

The NOAEL (developmental toxicity) is 1 000 mg/kg/d The DS concluded that dinotefuran is not a developmental toxicant in rats.

In the study investigating the effects of dinotefuran on **fertility and early embryonic development to implantation in rats** (OECD Guidance 150, level 4) the substance was administered by gavage at 0 (0.5 % CMC-Na vehicle), 100, 300 and 1 000 mg/kg bw/day daily for 14 days (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 1 000 mg/kg bw group; this is due to the non-significant increase of the number of implantation at dose 1 000 mg/kg bw compared with the control group. Therefore, this increase is not considered by the DS as adverse. The NOAEL (general toxicity) is 1 000 mg/kg bw/d; The NOAEL (reproductive function M/F) is 1000 mg/kg;

In the study investigating the effects of dinotefuran on **pre- and post-natal development, including maternal function in rats** (OECD Guidance 150, level 4), the substance was administered by gavage at 0 (0.5 % CMC-Na vehicle), 100, 300 and 1 000 mg/kg bw/day daily exposure from Day 7 of gestation until Day 20 of lactation (2004). Signs of general toxicity were observed at 1 000 mg/kg bw/d: decrease of body weight gain (Day 8-20 gestation) and food consumption (Day 8-15 gestation). One dam in this group died during delivery, but the relationship between the death and treatment with the test article was unclear. 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. F1 development: decrease of body weight gain birth to 70 days old. In embryos (F2), no treatment-related effects were noted on the number of implantations or live embryos or pre- or post-implantation loss (%). No treatment-related effects 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. The NOAEL (general toxicity) is 300 mg/kg bw/d; the NOAEL (F1 development) is 300 mg/kg bw/day and the NOAEL (reproductive function) 1 000 mg/kg bw/d.

In a GLP compliant, reliable, conducted according to OECD TG 426, **rat developmental neurotoxicity study** dinotefuran was administered dietary daily exposure on Day 6 of gestation until Day 21 of lactation at 0, 1 000, 3 000 or 10 000 ppm (equivalent to 0, 79, 237, 784 mg/kg bw/day, respectively) (2010). The following developmental parameters were assessed - preputial separation/vaginal opening, motor activity, acoustic startle inhibition response, learning and memory, neurohistopathology, brain weight and brain morphometry and no treated related effects were found. Evidence of maternal toxicity was limited to the observation of reduced body weight gain during gestation (GD 6-21) at 10 000 ppm only. For the F1 offspring, there was no evidence of general neonatal toxicity, because litter size, clinical condition, pup viability and body weights were comparable for all groups. The NOAEL (maternal) is 237 mg/kg bw/day; the NOAEL (neonatal toxicity and developmental neurotoxicity) is 784 mg/kg bw/day.

Rabbits

In the first GLP compliant, reliable, conducted according to OECD TG 414 **rabbit developmental toxicity study**, dinotefuran was administered by gavage at dose levels of 0 (0.5 % CMC vehicle), 52, 125 and 300 mg/kg bw/day, daily exposure for gd 6-18, 10-day post-exposure period (1998e). It should be noted that the dosing period was shorter than required for the guideline. However, the DS does not consider this to have compromised the validity of the study. Signs of maternal toxicity were observed at 300 mg/kg/day: reduced body weight gain (50 %), food consumption and water consumption (23 % and ~25 % respectively); 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 body weight gain from gd 19 was greater that controls. The body weight reduced during the early part of the dosing period at 125 mg/kg bw/day. Additionally, 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; the gastric mucosa was thickened in two mothers at 300 mg/kg bw/day. 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. The NOEL (maternal toxicity) is 52 mg/kg bw/day and NOEL (developmental toxicity) 300 mg/kg bw/day.

In the second GLP compliant, reliable, conducted according to OECD TG 414 **rabbit developmental toxicity study**, dinotefuran was administered by gavage at dose levels of 0 (0.5 % CMC vehicle), 60, 175, 500 mg/kg bw/d, daily exposure for gd 6-27, 10-day post-exposure period (2013). Signs of marked maternal toxicity were observed at 500 mg/kg bw/day (tachypnoea) on gd 6 and 7, reduced body weights (from gd 6, by 7 % gd 24) and reduced food consumption (22-54 %, up to 53 % on gd 12-15), and the death of one mother on gd 27 after a prolonged period of very low food consumption and body weight loss. There were no treatment-related macroscopic necropsy changes in the maternal organs. All dams at 500 mg/kg bw/day showed tachypnea on days 6 and 7, and increased incidences of small amount or no feces and reduced urine output. Three out of the 24 pregnant mothers (12.5 %) at 500 mg/kg bw/day aborted, between gd 25 and 28, each after a prolonged period of very low food consumption; these abortions were 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 (8 %), but these were regarded as not being related to dinotefuran treatment because abortion remained within the historical control range (0-8.3 %), 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.

Effects on or via lactation

In the two-generation study, the neonates, F1 and F2 body weights during lactation were reduced by 12-15 % at 10 000 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 body weight (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 was considered by the DS that there was no evidence that dinotefuran caused a specific adverse effect on pups via lactation, therefore classification for lactational effects was not proposed.

Comments received during consultation

No comments on this hazard class were received during public consultation.

Assessment and comparison with the classification criteria

Fertility

According to the Guidance on the Application of the CLP Criteria Version 5.0 – July 2017 (CLP Annex I: 3.7.2.2.1.1.) adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes.

In the pilot two-generation study (2001) females treated at 10 000 and 20 000 ppm showed treatment- and dose-related decrease in food consumption and body weight gain throughout the treatment period: at 10000 ppm body weight gain in females was reduced by 31 % and food consumption was reduced up to 17 % (both week 1-2); at 20 000 ppm decreased body weight gain of 62 % in females and of 61 % in males (week 1-2) was noted and food consumption was reduced in females up to 22 % and 17 % in males (week 1-2). Additionally, decreased number of implantation sites (21 %) and decreased birth index (16 %) was observed at 20 000 ppm.

In the two-generation study (2002) the group mean body weight gain during the pre-pairing period were reduced in P generation males and females at 10 000 ppm. The slightly lower body weights of P and F1 generation females at 10 000 ppm persisted during the gestation and lactation periods. There was no effect of treatment at any dose level in either generation on the duration of the oestrous cycle. There were no treatment-related effects at any dose level in either generation on fertility and mating performance, duration of gestation, number of implantations, post-implantation loss, litter size at birth, pup mortality, litter size at weaning and sex ratio. Apart from two parameters with non-dose-related statistically significant occurrences (higher neonatal pup mortality at 300 ppm and higher number of empty implantation sites at 3 000 ppm), all reproductive data in the treated groups were comparable to, and not significantly different from, the control group. There were no treatment-related effects on sperm motility, morphology and counts in either P or F1 generation males at any dose level. All histopathological findings recorded in the reproductive organs, pituitary and adrenal glands of P and F1 generation males and females is considered to be within the range of background lesions commonly observed in rats of this strain and age.

RAC agrees with the DS and is of the opinion that no classification for effects on sexual function and fertility is warranted.

Developmental toxicity

Reported prenatal toxicity studies do not provide evidence that dinotefuran may impair in utero development of rats and rabbits.

In the pilot two-generation study decrease in pup body weight (25 % at weaning) and food consumption post weaning (up to 54 %) was observed at 10 000 ppm; decrease in pup body weight (38 % at weaning) and decrease in food consumption post weaning (up to 64 %) was observed at 20 000 ppm. The results of the study were used for dose selection for the main study.

In the two-generation rat study at 10 000 ppm: decrease in pup body weight (F1 and F2) in males and females (by 12-15 % at weaning) was observed. There were no treatment-related abnormalities in pups at any dose level in F1 or F2 generation during the pre-weaning period. Decreased relative spleen weight (both F1 and F2) at weaning in males and females (9-15 %) was noted. The mean brain weight relative to body weight was also significantly ($p < 0.01$) elevated in these animals but is considered to be due to the lower body weights of the group. There was no effect on thymus weight at any dose level. Absolute and relative spleen weight were significantly ($p < 0.05$ or 0.01) reduced to a similar extent in both sexes of the F2 generation at 10 000 ppm. In the F1 generation, statistically significant differences from the control was noted for progressively motile and stationary sperm at 10 000 ppm and for progressive sperm at

1 000 ppm. Since the differences in the mean values were numerically small and did not show clear dose dependency, these findings are considered to be incidental to treatment.

Abortions observed in the developmental toxicity study in rabbits at the highest dose occurred after a prolonged period of low food consumption. These abortions may be related to treatment although likely to be secondary to the decreased maternal food consumption. Abortion was also seen in the control group. RAC is of the opinion that no classification for developmental toxicity is warranted.

Effects on or via lactation

There is no evidence that dinotefuran caused a specific adverse effect on pups via lactation. RAC agrees with the DS that no classification for effects on or via lactation is warranted.

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

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.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

Hazard class not relevant for this dossier.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Dinotefuran is a biocidal active substance used as insecticide. The substance is currently not listed in Annex VI of Regulation (EC) No 1272/2008.

The Dossier Submitter (DS) proposed to classify the substance as:

- Aquatic Acute 1 (H400) with M-factor of 10, based on a 48 h LC_{50} value of 0.0721mg/L for *Chironomus riparius.*
- Aquatic Chronic 1 (H410) with M-factor of 10, based on lack of rapid degradation and a 27 d NOEC value of 0.00254 mg/L for *C. riparius.*

Degradation

A hydrolysis study according to OECD TG 111 and Method C7 of Commission Directive 92/69/EEC (1998) was run at pH 4, 7, 9, 11 and 13 and at 50 °C in the dark. 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 1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF). As there was < 11 % hydrolysis observed following 7 d of incubation in buffer solutions of pH 4, 7, and 9 at 50 °C, dinotefuran was considered to be hydrolytically stable. Based upon results obtained at an 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 focused specifically on measuring dinotefuran, it is stated that UF was the "expected major hydrolysate". A DT_{50} value for dinotefuran normalised to 12 °C was calculated as 39.2 d at pH 11 and 3.66 d at pH 13.

In the photolysis study performed according to Directive 95/36/EEC, Directive 94/37/EEC, SETAC guidance and US-EPA OPPTS 835.2210 guidelines, dinotefuran 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 degradation of dinotefuran in the aquatic environment. Photolytic breakdown of dinotefuran gave rise to 18 degradation products with the major degradant (present at > 10 %) being UF, 1-methylguanidine (MG), 1-(2-hydroxytetrahydro-3-furylmethyl)-3-methylguanidine (DN-2-OH), 1-(3-hydroxytetrahydro-3-furylmethyl)-3-methylguanidine (DN-3-OH) and 3-(methylamino)-9-oxa-2-aza-4-azoniabicyclo[4.3.0]non-3-ene (BCDN), plus an unidentified mixture of at least two components coded as M2.

In the ready biodegradation study OECD TG 301F and Commission Regulation 440/2008/EC: Method C.4-D, dinotefuran was considered not readily biodegradable as mean biodegradation (consumption of oxygen (BOD)) of dinotefuran over 28 days was determined as 0 %.

Three aerobic water/sediment degradation studies are available. First study (2000l) carried out according to EPA 162-4, SETAC Guideline 8.2, Commission Directive 95/36/EC, equivalent to OECD TG 308, was run for 320 days in dark aerobic condition at 20 ± 1 °C using pond (Judenweiher, Switzerland) and river (Mumpf, Switzerland) systems. The degradation half-lives (DT_{50}) for the total system at 20 °C were 56.7 d (river) and 44.5 d (pond). When normalized to 12 °C, DT_{50} values were 112 d (river) and 88.2 d (pond). As the study demonstrated significant relocation of the test material to the sediment phase, dissipation half-lives (DT_{50}) at 20 °C for dinotefuran of 49.2 d (river) and 23.0 d (pond) were derived. When normalized 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, 1-methyl-2-nitroguanidine (MNG), and Nitroguanidine (NG) at < 4.0 % AR), only one main transformation product was characterised – 1-methyl-3-(tetrahydro-3-furylmethyl)guanidine (DN). There is evidence to show that DN underwent further degradation in both systems as levels 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.

The second study (2011c) performed according to OPPTS 835.4300, OPPTS 835.4400, equivalent to OECD TG 308, was run for 100 days in dark aerobic and anaerobic conditions at 20 ± 2 °C using two water sediment systems (Swiss Lake and Calwich Abbey Lake). In the aerobic experiment the degradation half-lives (DT_{50}) values for the total system at 20 ± 2 °C were 24.2 d (Calwich Abbey Lake) and 64.0 d (Swiss Lake). When normalised to 12 °C, DT_{50} values would be 55.81 d (Calwich Abbey Lake) and 145.4 d (Swiss Lake). A significant metabolite was DN, which accounted up to 69.9 % AR. A number of minor degradation products were found, each accounting for 9.6 % AR in both systems.

The third study (2020a) carried out according to OECD TG 308, was run for 14 d under natural sunlight (outdoor) at 20-25 °C using two natural water/sediment systems (Calwich Abbey Lake and Emperor Lake). The degradation half-lives (DT_{50}) for the total system at 20 °C were 2.19 d (Calwich Abbey Lake) and 3.07 d (Emperor Lake). When normalised to 12 °C, DT_{50} values would be 5.24 d (Calwich Abbey Lake) and 6.78 d (Emperor Lake).

There were two soil degradation studies available. The degradation half-lifes (DT_{50s}) of dinotefuran in soils ranged from 17.8 to 124.2 days at 12 °C. Dinotefuran degraded in soil to form MNG as a major metabolite.

Based on available data, the DS concluded that dinotefuran is considered not rapidly degradable.

Bioaccumulation

No experimental bioaccumulation studies were available, dinotefuran has an estimated partition coefficient n-octanol/water (log K_{ow}) of -0.549 (25 ºC, pH 7). The lack of potential for bioconcentration was further supported with result calculated with 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. 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. Additional BCF modelling performed to the Mackay BCF regression model (Mackay, 1982) indicated a potential bioaccumulation factor of 0.014.

Data on bioaccumulation for the major metabolite DN in the aquatic environment was available. The predicted log K_{ow} of DN was -0.18 (US-EPA EPISuite v4.11 (KOWWIN)) which was converted to BCF_{fish} value of 0.14. The results indicated that DN would not trigger a concern for bioconcentration or bioaccumulation.

Based on available data, the DS concluded that dinotefuran can be considered as not bioaccumulative in the aquatic environment.

Aquatic Toxicity

The test results from available acute and chronic toxicity studies for all three trophic levels performed with dinotefuran are summarised in the following table (the key endpoints used in hazard classification are highlighted in bold).

Studies on acute aquatic toxicity on the major metabolite 1-methyl-3-(tetrahydro-3-furylmethyl)guanidinium dihydrogen phosphate (DN phosphate) for all three trophic levels are also available. Based on the available data, the DS did not consider DN phosphate more toxic than the parent substance and it is therefore not considered further for classification purposes. All reported LC_{50}/EC_{50} values are > 100 mg/L.

Table*: Summary of the reported studies on aquatic toxicity of dinotefuran*

Method	Species	Endpoint	Toxicity value (mg/L)	Reference
Short-term toxicity				
OPPTS 850.1075, EEC C.1, OECD TG 203 (1992)	*Oncorhynchus mykiss*	96 h LC_{50}	> 100 n	Anonymous (1999) 1st amendment, Author, 2000, IUCLID 9.1.1
OPPTS 850.1075, EEC C.1, OECD TG 203 (1992)	*Cyprinodon variegatus*	96 h LC_{50}	> 109 mm	Anonymous (2001a) IUCLID 9.1.1

Method	Species	Endpoint	Toxicity value (mg/L)	Reference
OPPTS 850.1075, EEC C.1, OECD TG 203, (1992)	*Lepomis macrochirus*	96 h LC_{50}	> 100 n	Anonymous (2000a) 1st amendment, XXXXX, 2000a, IUCLID 9.1.1
OPPTS 850.1075, EEC C.1, OECD TG 203 (1992)	*Cyprinus carpio*	96 h LC_{50}	> 100 n	Anonymous (2000b) IUCLID 9.1.1
OPPTS 850.1010, EEC C.2, OECD TG 202 (1984)	*Daphnia magna*	48 h EC_{50}	> 1 000 n	Anonymous (2000b) 1st amendment, Author, 2000b, IUCLID 9.1.2
OPPTS 850.1035, EPA Subdivision E, Series 72-3	*Americamysis bahia*	96 h EC_{50}	0.79 mm	Anonymous (2001e) IUCLID 9.1.2
Based on OECD TG 202; EEC C.2; BBA guideline, 1995; OECD 219;	*Chironomus riparius*	48 h LC_{50}	**0.0721 n**	Anonymous (2000f) IUCLID 9.1.9
OECD TG 201 (1984), EEC C.3 (1992), OPPTS 850.5400	*Pseudokirchneriella subcapitata*	96 h E_rC_{50}	> 100 n	Anonymous (2000d) 1st and 2nd amendment, Author, 2000, IUCLID 9.1.3
OPPTS 850.4400, OECD TG 221 (draft 2000)	*Lemna gibba*	7 d EC_{50}	n.a.	Anonymous (2002d) IUCLID 9.1.10
Long-term toxicity				
Early life stage (ELS) OECD TG 210, OPPTS 850.1400	*Oncorhynchus mykiss*	94 d NOEC	10.1 mm	Anonymous (2001d) IUCLID 9.1.6.1
OPPTS 850.1300, OECD TG 211	*Daphnia magna*	21 d NOEC	100 n	Anonymous (2000e) IUCLID 9.1.6.2
OECD TG 219 (draft 2001), BBA-Guideline (draft 1995)	*Chironomus riparius*	27 d NOEC	**0.00254** n	Anonymous (2003a) IUCLID 9.1.9
OPPTS 850.1350	*Americamysis bahia*	35 d NOEC	0.089 mm	Anonymous (2011b) IUCLID 9.1.9
OECD TG 201 (1984), EEC C.3 (1992), OPPTS 850.5400	*Pseudokirchneriella subcapitata*	96 h NOEC/EC_{10}	n.a.	Anonymous (2000d) 1st and 2nd amendment, Author, 2000, IUCLID 9.1.3
OPPTS 850.4400, OECD TG 221 (draft 2000)	*Lemna gibba*	7 d NOEC	> 110 n	Anonymous (2002d) IUCLID 9.1.10

Note: mm – mean measured concentration; n – nominal concentration; n.a. - not available;

Acute aquatic toxicity

For fish, four limit tests with four different fish species were available. In all studies, 96 h LC_{50} values of > 100 mg/L were reported.

Three acute toxicity studies with three different aquatic invertebrates were available. The sediment dwelling organism *C. riparius* was the most sensitive species tested, with nominal 48 h LC_{50} value of 0.0721 mg/L.

There was only one acute toxicity study available for algae with a nominal 96 h E_rC_{50} value of > 100 mg/L for *Pseudokirchneriella subcapitata.*

For aquatic plants, one acute toxicity study with *Lemna gibba* is available which resulted in nominal 7 d NOEC value of > 110 mg/L. The 7 d EC_{50} value is not available.

From the available aquatic toxicity data, invertebrates are the most acutely sensitive trophic level. Therefore, the acute aquatic classification proposed by the DS was based on the *C. riparius* (48 h LC_{50} of 0.0271 mg/L). The DS proposed classification as **Aquatic Acute 1** (H400) with **M-factor of 10**.

Chronic aquatic toxicity

There was one long-term toxicity study for fish available, with a mean measured 94 d NOEC value of 10.1 mg/L for *Oncorhynchus mykiss.*

Two chronic toxicity studies with two different aquatic invertebrates were available. The sediment dwelling organism *C. riparius* was the most sensitive species tested, with a nominal 27 d NOEC value of 0.00254 mg/L.

For algae, one toxicity study with *P. subcapitata* was available but no NOEC/EC_{10} value was reported.

There was one study available for aquatic plants with nominal 7 d NOEC of > 110 mg/L for *Lemna gibba.*

From the available long-term aquatic toxicity studies, invertebrates were the most sensitive trophic level. Therefore, the chronic aquatic classification proposed by DS was based on the insect *C. riparius* study (27 d NOEC of 0.00254 mg/L). The DS proposed **Aquatic Chronic 1 (H410)**, with **M-factor of 10**, as the substance is not rapidly degradable.

Comments received during consultation

Two Member States (MS) and one National Authority provided comments. One MS agreed with the proposed classification for environmental hazards. Both MSs pointed out typo errors.

The MS commented that as the water/sediment degradation test Calwich Abbey Lake (2020a) was performed outdoors under natural sunlight it should not be considered for the calculation of the geometric mean DT_{50} in the total system. The study should be considered as additional information as it would otherwise, if included, provide an underestimate of the pure microbial degradation since photodegradation in water contributes to the breakdown of dinotefuran. The DS agreed and indicated that the worst-case value was considered for classification purposes.

The same MS asked for clarification regarding the two different DT_{50} values reported for the 2001e soil degradation study for Stolpe, Germany. In addition, the MS pointed out that normalisation to 12 °C is incorrect for the Stolpe, Germany. The DS clarified that there is a mistake and provided the correct values.

A National Authority agreed that *Chironomus* are the most acutely and chronically sensitive test species. The National Authority indicated that while the draft OECD TG 219 (Anonymous, 2003a in the CLH report) study employed a water-sediment test system, they agreed that the data described in the CLH report and in the RSS (ECHA, 2023) supported a long-term endpoint based on measured aquatic phase concentrations noting that ≤ 20 % losses were observed between initial measured (1 hour) and 27 day measured concentrations. The National Authority indicated that there are some uncertainties due to the fact that analytical verification did not cover all treatments results. They pointed out that the surrogate approach using the acute Chironomus endpoint (48 h LC_{50} = 0.0721 mg/L) also results in Aquatic Chronic 1 with an M-factor of 10. The

DS agreed that there are some uncertainties as the analytical verifications did not cover all test concentrations. However, the DS clarified that according to OECD TG 219 when the test substance is stable, its concentrations could be measured at least at the start (1 h after spiking the water) and at the end of the test, at the highest concentration and a lower one.

In addition, the National Authority also indicated that the REACH RSS included an EC_{10} endpoint based on nominal concentrations and asked for determination of an EC_{10} endpoint based on measured concentrations as EC_x are preferred to NOECs. The DS responded that the test in the CLH report (Anonymous, 2003a) and the one in the REACH RSS are the same. Consequently, the EC_{10} value from the REACH RSS could also be relevant. The DS pointed out that EC_{10} value (0.0046 mg/L) was based on nominal concentrations, while the NOEC value (0.00254 mg/L) was based on a mean measured concentration. The DS noted that both values are in the same range and would not change the outcome of the classification.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal to consider dinotefuran as **not rapidly degradable**, as:

- The substance is hydrolytically stable at environmentally relevant pHs (pH 4-9). The estimated hydrolytic half-life (DT_{50}) is more than 1 year at 12 °C.
- No degradation (0 % after 28 days) was observed in the ready biodegradability test, indicating that the substance is not readily biodegradable.
- The degradation half-life (DT_{50}s) values in the total system in three water/sediment system studies were 112 days (river), 88.2 days (pond), 5.24 to 145.4 days (lake) at 12 °C.

In addition, the degradation half-life (DT_{50}s) values in the soil from the two soil degradation studies ranged from 17.8 to 124.2 days at 12 °C.

Bioaccumulation

RAC agrees with the DS that dinotefuran has a low potential for bioaccumulation. In the absence of measured BCF data, the basis for this conclusion is the estimated log K_{ow} value of -0.549 that is well below the CLP criterion of 4. In addition, estimated BCF_{fish} values of 0.014 and 0.068 are also below the cut-off value of 500 given in the CLP Regulation.

Aquatic toxicity

Reliable short-term aquatic toxicity data are available for all three trophic levels. Aquatic invertebrates are the most acutely sensitive trophic level, and the lowest result is a nominal 48 h LC_{50} value of 0.0271 mg/L for *C. riparius*. RAC considers this study relevant and reliable, noting that the test system did not contain sediment. As this concentration is below the threshold value of 1 mg/L, RAC concludes that a classification as Aquatic Acute 1 (H400) with an M-factor of 10 ($0.01 < L(E)C_{50} \leq 0.1$ mg/L) is warranted.

Reliable long-term aquatic toxicity data are available for all three trophic levels. Aquatic invertebrates are the most chronically sensitive trophic level, with the most sensitive species *C. riparius*. RAC notes that the *Chironomus* toxicity study is a water-sediment study (OECD TG 219), and therefore exposure via sediment cannot be ruled out. However, according to adsorption/desorption study (OECD TG 106), dinotefuran sorbs weakly to soil (geometric mean K_{aoc} 25.4 L/kg). In the study, application of the test substance is done via the water column (spiked water). The measured concentrations in water column at the end of the test were 56 % to 61 % of the nominal concentrations. Therefore, RAC considers that exposure to dinotefuran

occurs primarily via the aqueous phase. Also, *Chironomus* spend their most sensitive larval stage (first instar) free swimming in the water and will therefore only be exposed to dinotefuran via the water in this stage. Additionally, *C. riparius* was the most sensitive acute species. Based on above, RAC considers this study relevant and reliable, therefore is appropriate to use this study for chronic classification of the substance. The lowest result is the mean measured 27 d NOEC value of 0.00254 mg/L (development and emergence).

In addition, a nominal 27 d EC_{10} value of 0.0046 mg/L (emergence rate) from the same study was provided in the RCOM by the DS. RAC notes that this EC_{10} value is in the same concentration range as NOEC value. However, in case of dinotefuran RAC considers more appropriate to use the mean measured NOEC value for aquatic classification because the EC_{10} value is based on nominal concentrations. In line with the ECHA Endpoint Specific Guidance R.7b, nominal concentrations can be used if measured concentrations were within 20 % of the nominal concentrations which is not the case for dinotefuran (measured concentrations not within ± 20 % of nominal).

RAC concludes to classify dinotefuran as Aquatic Chronic 1 (H410) with chronic M-factor of 10 (0.001 < NOEC ≤ 0.01 mg/L), based on the lowest chronic toxicity value of 0.00254 mg/L for *C. riparius* for a not rapidly degradable substance.

In summary, RAC supports the DS's proposal that dinotefuran warrants classification according to CLP as:

Aquatic Acute 1 (H400), M = 10

Aquatic Chronic 1 (H410), M = 10

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

No classification for hazards to the ozone layer was proposed by the DS.

Dinotefuran is not listed in Annex I to Regulation (EC) 1005/2009 on substances that deplete the ozone layer.

On the basis of the structure and on the physico-chemical properties of dinotefuran (absence of absorption bands in the atmospheric window, short atmospheric lifetime, the overall OH rate constant of dinotefuran is 156.066×10^{-12} cm³ per molecule s^{-1}, which equals a 24 h half-life of 0.1 day), absence of Cl, F, N or S functional groups in the molecule), dinotefuran is not expected to present a potential danger to the structure and/or functioning of the stratospheric ozone layer.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

RAC agrees with the DS's view that dinotefuran does not fulfil the criteria for classification for effects to the ozone layer.

Dinotefuran is not a member of any of the chemical classes expected to be an ozone depleting substance.

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.

RAC also notes that dinotefuran is not listed on the Annex I of Regulation (EC) 1005/2009 on substances that deplete the ozone layer.

In conclusion, RAC agrees with the DS that no classification for hazardous to the ozone layer is warranted.

Additional references

DePeyster, A., Mihaich, E., Kim, D.H., Elyea, W.A., Nemec, M.J., Hirakawa, B.P., Leggieri, S.E. Responses of the steroidogenic pathway from exposure to methyl-tertbutyl ether and tert-butanol. Toxicology 319 (2014), 23–37

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Schlede E., Eppler R., Testing for skin sensitization according to the notification procedure for new chemicals: the Magnusson and Kligman test. Contact Dermatitis (1995) 32. 1-4 (https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1600-0536.1995.tb00830.x)

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter and additional information (if applicable).

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).