Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Benzovindiflupyr (ISO);
***N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide**

EC number: -
CAS number: 1072957-71-1

CLH-O-0000001412-86-28/F

Adopted

04 December 2014

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4 December 2014

CLH-O-0000001426-86-28/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 (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name:
***N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoro methyl)-1-methyl-1*H*-pyrazole-4-carboxamide; benzovindiflupyr (ISO)**

EC number: -
CAS number: 1072957-71-1

The proposal was submitted by **France** and received by the RAC on **10 April 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted 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 **29 April 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 June 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Paola Di Prospero Fanghella**

Co- rapporteur, appointed by RAC: **Joao Carvalho**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 December 2014**. The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

RAC adopted the opinion that **benzovindiflupyr** should be classified and labelled as follows:

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

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard stateme nt Code(s)		
Current Annex VI entry	**No current Annex VI entry**										
Dossier submitters proposal	616-218-00-X	benzovindiflupyr (ISO); *N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide	-	1072957-71-1	Acute Tox. 3 Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H301 H331 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410		M = 100 M = 100	
RAC opinion	616-218-00-X	benzovindiflupyr (ISO); *N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide	-	1072957-71-1	Acute Tox. 3 Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H301 H331 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410		M = 100 M = 100	
Resulting Annex VI entry if agreed by COM	616-218-00-X	benzovindiflupyr (ISO); *N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide	-	1072957-71-1	Acute Tox. 3 Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H301 H331 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410		M = 100 M = 100	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal
The results of the tests on physico-chemical properties indicate that benzovindiflupyr is neither explosive, flammable nor self-reactive. The dossier submitter (DS) proposed no classification for physical hazards.

Comments received during public consultation
No comment were received during the public consultation.

Assessment and comparison with the classification criteria
RAC agrees with the DS that no classification for physical hazards is warranted.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal
Three studies on acute toxicity, one for each route of exposure, were included in the CLH report. In an acute oral toxicity study (conducted in accordance with OECD test guideline (TG) 425) with female rats, mortalities were observed at the middle dose (55 mg/kg bw, 1 animal) and at the high dose (175 mg/kg bw, all animals) (Tavaszi, 2010). No deaths were observed in an oral single dose neurotoxicity study up to the highest dose of 80 mg/kg bw (Sommer, 2011a).
Based on the results of these two studies, the acute oral median lethal dose (MLD) for benzovindiflupyr was estimated to be >55 and <175 mg/kg bw. The DS proposed to classify benzovindiflupyr as Acute Tox. 3; H301.

A dermal limit dose study (conducted in accordance with OECD TG 402) reported no mortalities when male and female rats were administered 2000 mg/kg bw (Zelenák, 2010a). No classification was proposed for acute dermal toxicity.

The acute inhalation toxicity was evaluated in a GLP study (OECD TG 403) in rats. In this study, one female was found dead on day 1, while significant clinical signs were noted during exposure in all animals. The median lethal concentration (MLC) was estimated to be >0.56 mg/L. The DS proposed to classify benzovindiflupyr as acute Tox. 3; H331 in accordance with the classification criteria for inhalation of dusts and mists.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
RAC agrees with the assessment of the DS that the MLD for benzovindiflupyr is >55 and <175 mg/kg bw, and therefore based on the comparison of the oral MLD with the criteria, RAC agrees with the conclusion of the DS that benzovindiflupyr should be classified as acute Tox. 3; H301.

For the inhalation route, RAC discussed the feasibility of classification based on the a minimum MLC value , i.e. >0.56 mg/L (proposed by the DS), which may be considered inconclusive.
Based on evident toxicity observed during the fixed dose study the classification as acute Tox. 3; H331 is warranted.

RAC concludes, in agreement with the DS proposal, to classify the substance for inhalation toxicity as acute Tox. 3; H331 in accordance with CLP.

As the dermal LD_{50} was estimated to be >2000 mg/Kg RAC agrees with the conclusion of the DS that benzovindiflupyr should not be classified for dermal toxicity in accordance with CLP.

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

Summary of the Dossier submitter's proposal

All clinical signs observed in the acute toxicity studies via the oral, dermal and inhalation routes were considered to be non-specific signs of general acute toxicity. The acute neurotoxicity study demonstrated no evidence of neurotoxicity at 80 mg/kg bw. Therefore, the dossier submitter concluded that no classification is warranted for STOT SE.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

The signs that were apparent after single oral and inhalation exposure (no adverse effects were observed after dermal exposure) to benzovindiflupyr were indicative of non-specific, general acute toxicity. There was no clear evidence of specific effects on a target organ or tissue that were independent of mortalities, no definitive signs of respiratory tract irritation or narcotic effects.

In the absence of constant and identifiable effects, RAC agrees with the DS conclusion that benzovindiflupyr need not be classified for STOT SE in accordance with CLP.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

One rabbit skin irritation study, conducted according to OECD TG 404, was summarised in the CLH report (Zelenák, 2010b). No signs of oedema were observed in any animal; the mean scores for each of the three rabbits at 24, 48 and 72h were all equal to zero. Very slight erythema was seen in all rabbits at 1 hour which persisted to 24 hours in one animal; the mean scores at 24, 48 and 72h were 0.3, 0 and 0 respectively. The DS proposed no classification for skin corrosion/irritation.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

Dermal exposure to benzovindiflupyr did not result in any significant signs of skin corrosion/irritation.
Therefore, RAC agrees with the DS that benzovindiflupyr should not be classified for skin corrosion/ irritation in accordance with CLP.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

One rabbit eye irritation study, conducted according to OECD TG 405, was summarised in the CLH report (Mallaun, 2011). In this study, conjunctival redness was noted in all animals one hour after application, which persisted in two animals until 72 hours after treatment and in one animal until 7 days after treatment. There were no corneal or iridial effects in any animal and all animals showed full recovery at 10 days after treatment. Dossier Submitter proposes no classification for this endpoint.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

Benzovindiflupyr was mildly irritating to the eyes with transient signs of irritation (conjunctival redness) that reversed after 10 days post-treatment.

All mean irritation scores were <2, therefore, RAC agrees with the DS conclusion that no classification is required in accordance with CLP.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

A local lymph node assay (LLNA) in female mice was conducted according to OECD TG 429 (Török-Bathó, 2010). Stimulation index values for the test item were all <3 (0.6, 0.9 and 0.4 at concentrations of 25, 10 and 5% (w/v), respectively and 0.8, 0.7 and 0.8 at concentrations of 1.0, 0.1 and 0.01% (w/v), respectively). The positive control substance had a stimulation index >3.0. Benzovindiflupyr was negative for skin sensitisation potential in the mouse LLNA and according to the DS does not meet the criteria for classification according to CLP.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

Benzovindiflupyr was negative for skin sensitisation potential in the mouse local lymph node assay. The stimulation index values for the test item were all <3. The Guidance on the Application of the CLP Criteria, version 4.0 – November 2013 (CLP Guidance) indicates that a substace may be classified as a skin sensitiser on the basis of positive results in an LLNA (criteria for a positive result include a stimulation index >3).

Therefore RAC concludes that the substance does not meet the criteria for classification according to CLP.

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

Summary of the Dossier submitter's proposal

The CLH report contained a detailed description and assessment of the benzovindiflupyr data on repeated dose toxicity (RDT). The RDT of benzovindiflupyr has been evaluated by the oral route in rats (28 day study equivalent to OECD TG 407; Marr, 2010 and 90 day study, OECD TG 408; Robertson, 2010a), mice (28 day study, OECD TG 407; Shearer, 2010 and 90 day study, OECD TG 408; Mackay, 2011) and dogs (90 day study OECD TG 409; Pothman, 2010, 1 year study OECD TG 452; Braun, 2011; in both studies capsules were provided in the diet) and by the dermal route in a 28 day study in rat (OECD TG 410; Sommer, 2010). In all species tested, the main effect observed after short-term oral administration was an initial body weight loss or a reduction in body weight gain. No evidence of toxicity was seen following dermal exposure. Toxic effects were minor and are summarised below:

Bodyweight

Effects on body weight were observed in all the species at different doses but this was associated with a decrease in food consumption in the oral studies. Thus this effect was not considered severe enough to support classification in itself.

Liver

In the rat, minor changes in the liver included increased liver weight and centrilobular hypertrophy in both the 28 day and 90 day toxicity studies at doses of 36 mg/kg bw/day and above. There was no evidence of liver toxicity in mice or dogs. Increased liver weight and liver histopathology was seen in rats at the LOAEL (400 ppm, 36 mg/kg bw/day in the 28 day study and

750 ppm, 53 mg/kg bw/day in the 90 day study). Investigative studies have demonstrated that benzovindiflupyr induces hepatic UDP glucuronyltransferase (UDPGT) leading to hepatocellular hypertrophy and increased liver weight (Robertson, 2012b). The available data also showed that the mode of action in the rat has no relevance in humans due to the well documented qualitative and quantitative differences in response to UDPGT induction between rats and humans (Lake, 2012a; Lake, 2012B; Green, 2012).

Therefore, these adaptive changes do not warrant classification as STOT RE.

Kidney
Minimal tubular basophilia was seen in female rats in the 28 day study at 400 ppm (36 mg/kg bw/day; Marr, 2010) and above but not in the 90 day study at higher doses (1500 and 750 ppm, 108.8 and 58.8 mg/kg bw/day; Robertson, 2010a). These effects are observed above the concentration limits described in the CLP (based on 90 day studies). In the mouse, tubulointerstitial nephritis was observed in both sexes at 500 ppm (81.8 mg/kg bw/day) in the 28 day study but not in the 90 day study at the same dose level. There was no indication of kidney toxicity in the dog.
Effects on kidney were observed in in 28 day studies in rats (Marr, 2010) and mice (preliminary studies; Shearer, 2010) at high dose levels but not in the 90 day studies at similar dose levels.

All effects were minor, occurred at dose levels associated with body weight effects and, as such, provide no evidence of specific target organ toxicity and do not warrant classification.

Gastrointestinal tract
In the 90 day mouse study, an increased incidence of soft faeces and hyperplasia in the colon and rectum was observed in both sexes at 300 and 500 ppm (55.6/59.6 mg/kg bw/day and 97.9/102.8 mg/kg bw/day). In the 1 year dog study, vomiting and mucoid faeces were observed in both sexes at 250 and 500 mg/kg/day. Some evidence of gastrointestinal disturbance was seen in mice and dogs (soft faeces and mucosal hyperplasia in the rectum and colon in mice; vomiting, mucoid faeces in dogs). These effects were accompanied by effects on body weight, were of minimal severity and there was no evidence of organ dysfunction.

Study	NO(A)EL (mg/kg bw/d)	LO(A)EL effects (mg/kg bw/d)
Rat 28 d (dietary)	9.0 (male and female)	36.0 (male and female) Minimal tubular basophilia in kidneys (female). Centrilobular hepatocyte hypertrophy in liver (male).
Mouse 28 d (dietary)	15.,6 and 19.0 (male and female)	47.5 and 57.9 (male and female) ↓ bw in males
Rat 90 d (dietary)	7.6 and 8.2 (male and female)	53.8 and 58.8 (male and female) ↓ bw, bw gain, food consumption, food utilization in both sexes; ↑ adjusted liver weights in females; Centrilobular hepatocyte hypertrophy in males (4/10).
Mouse 90 d (dietary)	17.0 and 20.9 (male and female)	55.6 and 59.6 (male and female) ↑incidence of soft faeces in males; ↓ bw, bw gain, food consumption in males and females; Minor changes in clinical chemistry: ↓ plasma triglycerides in males, ↑ plasma calcium level in females Distended large intestine was observed in one animal of each sex. Mucosal hyperplasia of the colon in males (6/10) and in females (5/10) and/or mucosal hyperplasia of the rectum in males (3/10) and in females (5/10)
Dog 13 w (capsule)	30.0	375.0 (male and female) ↓ bw and bw gain in males ↓ plasma calcium level in males (w8 and w13).
Dog 1y (capsule)	250.0	500.0 (male and female) ↓ body weight gain in males and females

The DS proposed no classification for STOT RE.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

There is no evidence that benzovindiflupyr produces specific target organ toxicity (repeated exposure) i.e. produces significant health effects considered to impair function, both reversible and irreversible. Significant effects observed in the liver (increased weight and histopathology) in rat were considered to be adaptive changes resulting from UDPGT induction and are not relevant to human health. The effects do not support classification for specific target organ toxicity following repeated exposure and fall within the effects mentioned in Annex I: 3.9.2.8.1 of the CLP Guidance. Based on the data presented, RAC concludes that the substance should not be classified for STOT RE.

In conclusion, RAC agrees with the DS that no classification is warranted for STOT RE in accordance with CLP.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Benzovindiflupyr showed no genotoxic activity in a reverse gene mutation assay in bacteria using six tester strains (Sokolowski, 2009), in a mammalian cell gene mutation assay (Wollny, 2010) and in an *in vitro* mammalian chromosome aberration test (Bohnenberger, 2010). All studies were tested both in the presence and absence of exogenous metabolic activation and used positive and negative controls to confirm the validity of the tests.

Negative results were obtained also in a rat micronucleus assay after treatment with Benzovindiflupyr (Innes, 2010).
The negative results in both *in vitro* and *in vivo* assays, lead the DS to propose no classification for mutagenicity.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
Genotoxicity of benzovindiflupyr was tested in three *in vitro* and one *in vivo* test. The results of all studies were negative whilst positive and negative controls demonstrated the validity of the tests.

RAC concludes that benzovindiflupyr can be considered not to be genotoxic and no classification is warranted in accordance with CLP.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal
The carcinogenicity potential of benzovindiflupyr was evaluated in a 2 year study in rat and in an 80 weeks study in mice conducted according to OECD TG 453 and 451 respectively.
The carcinogenicity study for benzovindiflupyr in rats showed the induction of thyroid tumors in male rats as reported in the table below:

	Dietary concentration benzovindiflupyr (ppm)			
	0	25	100	600
Thyroid follicular cell adenoma	1/53 (2%)	4/52 (7.6%)	5/52 (9.6%)	9/52* (17.3%)
Thyroid follicular cell carcinoma	1/52	0/52	1/52	0/52

The available data, as reported in the CLH report, also demonstrated that the mode of action of this kind of tumor is species-specific and not relevant for humans.
Based on the evaluation of the mode of action studies and on the regulatory toxicology database the following has been demonstrated:

- Benzovindiflupyr has no direct effect on thyroid peroxidase
- Induction of UDPGT leading to an increase in conjugation and excretion of (triiodothyronine) T3 and thyroxine (T4)
- A decrease in serum T3 and T4 levels
- A compensatory increase in thyroid stimulating hormone (TSH) levels secreted via the hypothalamus-pituitary-thyroid (HPT) axis
- Under the chronic proliferative stimulus of TSH, thyroid follicular cells eventually progress to form follicular cell adenomas

All these findings supported the conclusion of the DS that the mode of action that has been shown in the rat has no relevance to humans due to the well documented qualitative and quantitative differences in response to UDPGT induction and increased T3/T4 clearance between rats and humans.

The carcinogenicity study in the mouse showed an increased incidence of Harderian gland adenomas at all doses compared with control. These Harderian gland tumours were considered not treatment related for the following reasons:

- There was no dose-response relationship. The Harderian gland tumour incidence at the low dose was higher than the historical control range whereas the incidence in the mid-dose was within the historical range.
- There was no statistical significance using pairwise tests and there was no statistically significant trend using the Peto trend test.
- There were no indications of any pre-neoplastic micropathology findings in the Harderian gland.
- There were no increases in the incidence of adenocarcinoma in the Harderian gland in the mouse.
- There were no increases in the incidence of adenocarcinoma in the Harderian gland and there was no indication of any increase in tumour incidence in the Harderian gland in the rat.

Moreover this kind of tumor is not relevant for classification; in fact, according to CLP guidance paragraph 3.6.2.3.2:

" *Tumours in the Harderian glands. Harderian glands are found in all vertebrates that possess a nictitating membrane, or third eyelid. They are located behind the eyeball in the orbit nictitating membrane, encircling the optic nerve. Humans have a rudimentary one* "
"…the assumed mode of action is required to decide if these findings would support a classification. However, tumours observed only in these tissues, with no other observed tumours are unlikely to lead to classification. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered..."

Taken together, the DS concluded that benzovindiflupyr does not pose a carcinogenic hazard to humans.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
Carcinogenicity studies in rats and mice showed an increased incidence of thyroid follicular cell adenoma in rats but no evidence of carcinogenicity in the mouse.
Certain tumour types observed in animal carcinogenicity studies are of questionable or no relevance to humans. This is the case of thyroid tumor observed in rats. In fact, benzovindiflupyr induced thyroid tumours in male rats are attributable to induction of hepatic UDP-glucuronsyltransferase (UDPGT), which results in a series of downstream events, ultimately leading to tumourigenesis (as reported in the annex of the CLH report).

This situation is also clearly stated in paragraph 3.9.2.5.3 of the CLP Guidance: …. "such a mechanism/effect cannot be directly extrapolated to humans, i.e. these thyroid effects observed in rodents caused by an increase in hepatic UDPG-transferase are therefore considered of insufficient concern for classification."

In conclusion, RAC agrees that benzovindiflupyr acts by a mode of action that is not relevant to humans and concluded that no classification for carcinogenicity is needed in accordance with CLP.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal
The reproductive toxicity of benzovindiflupyr was investigated in a two generation reproduction toxicity study in the rat (Whitlow, 2011a) and the developmental toxicity of benzovindiflupyr was assessed in preliminary and full developmental toxicity studies in rats and rabbits (Whitlow, 2011c, 2011d; Sawhney Coder, 2011a, 2011b).

As part of the alignment with the approval of new PPP active substances, to which benzovindiflupyr is subject to, and to better analyse the reproductive toxicity, additional

information about spermatological parameters was received from the DS after the public consultation. The analysis showed that in the P and F1 generations the sperm motility, morphology and sperm head count values were not affected by treatment with the test item. Statistical differences in motility were noted in the 100 ppm dose group but not at 600 ppm, therefore they were considered unrelated to treatment (see tables below, in the DAR, B.6.6.1-8a and B.6.6.1-8b).

Table B.6.6.1-8a: P generation sperm analysis

Observation	Dose Group (mg/kg/day)				HCD
	0	25	100	600	2002-2007
Progressive motile (%)	71	71	63*	70	53-63
Stationary motile (%)	13	13	17*	13	22-35
Not motile (%)	17	17	20	17	9-17
Normal, complete sperm	93.6	-	-	91.7*	89.7-94
Complete sperm, misshapen hook	0.7	-	-	1.5**	0.4-1.2
Complete sperm, abnormally curved hook	2.2	-	-	3.2**	1.1-3.8
Complete sperm, reversed head	0.1	-	-	0.0*	0.0-0.2

* Statistically significant difference from control group mean, p<0.05 (Dunnett test)
** Statistically significant difference from control group mean, p<0.01 (Dunnett test)

Table B.6.6.1-8b: F1 generation sperm analysis

Observation	Dose Group (mg/kg/day)				HCD
	0	25	100	600	2002-2007
Progressive motile (%)	60	58	57	58	44-64
Stationary motile (%)	25	26	27	25	24-33
Not motile (%)	15	16	16	16	10-27
Normal, complete sperm	90.9	-	-	90.6	90.6-94.5
Complete sperm, misshapen hook	1.6	-	-	1.9	0.4-1.1
Complete sperm, abnormally curved hook	3.2	-	-	2.7	2.4-3.2
Complete sperm, reversed head	0.0	-	-	0.1	0.0-0.1

Mating performance and fertility were not affected by treatment with benzovindiflupyr. The follicle and corpora lutea count made during micropathological examination of ovarian tissues from females of the F1 generation showed a statistically significantly lower number of growing follicles and corpora lutea in the high dose group compared to the control group.

No evidence of treatment-related effects on fertility, sexual function or other parameters of reproductive performance were seen.

The developmental toxicity studies were reported as follows (see Table 20 of the CLH report):

Study	Dose Levels	NO(A)EL (mg/kg/day)	LOAEL (mg/kg/day)	Effects
Developmental toxicity in the rat (gavage) Whitlow S, (2011b)	0, 7.5, 15 & 30 mg/kg/day	Maternal: 15 mg/kg/day	At 30 mg/kg/d: Clinical signs: ↓ activity, hunched posture, ataxia, ruffled fur; ↓ body weight gain, food consumption,	At 30 mg/kg/d: Clinical signs: ↓ activity, hunched posture, ataxia, ruffled fur; ↓ body weight gain, food consumption,
		Foetal: 15 mg/kg/day	Foetal: 30 mg/kg/day	At 30 mg/kg/d: ↓ foetal weight, slight delay in ossification in ossification at 30 mg/kg/day.
Range-finding Developmental toxicity in the rabbit (gavage) Coder P, (2011a)	25, 50 & 100 mg/kg/day	Not applicable – range-finding study	Not applicable – range-finding study	At 100 mg/kg/day: ↓ body weight (+++) and food consumption resulting in early termination of all animals. ↓ body weight (++) and food consumption also led to abortion and moribundity in some animals at 50 mg/kg/day.
Developmental toxicity in the rabbit (gavage) Sawhney Coder P, (2010b)	0, 10, 20 & 35 mg/kg/day	Maternal: 35 mg/kg/day	Maternal: None	Maternal: none
		Foetal: 35 mg/kg/day	Foetal: None	Foetal: None

In the rat study (Whitlow, 2011b) foetal weights were statistically significantly reduced and at skeletal examination a slight delay in ossification was observed at 30 mg/kg/day. At this dose clear signs of maternal toxicity were observed. Therefore no biologically significant morphological alterations, including teratogenicity, were observed in this study.

The potential for benzovindiflupyr to induce developmental effects has been assessed using two species, rodent and non-rodent. The experimental results showed no evidence of teratogenicity in both species and no evidence of developmental effects in the absence of maternal toxicity.

In conclusion the reprotoxicity data showed no evidence of treatment-related effects on fertility, sexual function or other parameters of reproductive performance and there was no indication of developmental toxicity.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

Overall, RAC considers that the data do not provide evidence that benzovindiflupyr induces adverse effects on the reproductive organs or fertility and no classification is supported for fertility.

There is no evidence that benzovindiflupyr produces developmental toxicity effects. In the rat developmental toxicity study the reduction in the body weight and the retardation of ossification were seen in association with maternal toxicity. As reported in the CLP guidance 3.7.2.4.3 "…..*Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity."*

RAC therefore agrees with the DS that classification is not justified for reproductive toxicity in accordance with CLP.

RAC evaluation of neurotoxicity, immunotoxicity and specific investigation

Summary of the Dossier submitter's proposal

Specific studies were performed to investigate the potential for neurotoxicity (acute and sub-chronic studies), immunotoxicity and to generate data on the proposed mode of action with regard to the thyroid tumours in rats (Robertson, 2010b, 2012a, 2012b; Lake, 2012a, 2012b; Green, 2012).

In the acute neurotoxicity study, single gavage doses of 0, 10, 30 or 80 mg/kg did not produce any functional or pathological indications of neurotoxicity, although signs of general toxicity were observed at 30 mg/kg and above (Sommer, 2011a). In the sub-chronic neurotoxicity study, 90 days dietary administration at 0, 100, 250 (male and female) or 800 ppm (males)/500 ppm (females) did not result in any indications of functional or pathological neurotoxicity (Sommer, 2011b).

A 28 day dietary immunotoxicity study was conducted in CD-1 female mice (Wasil, 2012). Benzovindiflupyr was administered in the diet for 28 consecutive days at dietary concentrations of 0, 100, 200 or 400 ppm. A positive control group was dosed with cyclophosphamide via intraperitoneal injection (50 mg/kg bw/day) for 4 consecutive days. Additionally, all mice were immunised with an intravenous injection of sheep red blood cells (sRBC) on study day 24, approximately 96 hours prior to the scheduled necropsy on study day 28. The liver, spleen, and thymus were weighed. Spleen cell suspensions were prepared, spleen cell counts were performed and the number of specific IgM antibody forming cells directed towards the sRBC was determined. There was no indication that benzovindiflupyr is immunotoxic.

Mechanistic studies included a 28 day study (Robertson, 2010b, 2012a), a 14 day dietary thyroid mode of action study (Robertson, 2012b), an in vitro study for effects on thyroid peroxidase activity (Lake, 2012a) and an investigation of hepatic UDPGT activity towards thyroxine as substrate (Lake, 2012b). In addition, a position paper considering all the available data supporting the weight of evidence arguments for the postulated mode of action was prepared (Green, 2012). All these data were reported in the annex of the CLH report.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

The data presented in the CLH report showed no indication that benzovindiflupyr has neurotoxic or immunotoxic potential and investigative studies supported the proposed mode of action for thyroid cancer formation (for details see the paragraph on carcinogenicity).

RAC concludes that no classification is necessary for neurotoxicity and immunotoxicity in accordance with CLP.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Benzovindiflupyr has no environmental classification and labelling in Annex VI of CLP Regulation.

The DS proposed to classify benzovindiflupyr as Aquatic Acute 1 (H400) with an M-factor = 100 and Aquatic Chronic 1 (H410) with an M-factor = 100. The classification was based on the substance being not rapidly degradable, non-bioaccumulative and very toxic to fish. The relevant

lowest acute toxicity value was an LC_{50} (96h) of 0.0035 mg/L on *Cyprinus carpio* and the lowest chronic toxicity value was a NOEC (32d) of 0.00095 mg/L on *Pimephales promelas*.

Degradation
The substance degrades by indirect aqueous photolysis (DT_{50} of 5.0 days) and slower by direct aqueous photolysis in sterile buffer (DT_{50} of 44.2 days) according to OECD TG 316.

The substance was found to be hydrolytically stable for up to five days at pH 4, 5 and 7 after the preliminary test carried out according to OECD TG 111. No hydrolysis products were detected.

Regarding biodegradation, one study on ready biodegradability and another study on biodegradation in water/sediment tests were included in the CLH report. The ready biodegradability test was performed according to OECD TG 301F and GLP. Benzovindiflupyr was degraded by an average of 1% after 28 days and was considered not-readily biodegradable under these test conditions. The substance did not show inhibitory effects on the activated sludge microorganisms at the tested concentration.

The degradation of benzovindiflupyr was also investigated in a standard water/sediment system with two different sediments (silt loam and sandy loam) according to OECD TG 308 under GLP conditions. In this study standard aerobic and anaerobic degradation was investigated under dark conditions, which resulted in c.a. 90% of the applied benzovindiflupyr remaining not degraded after an exposure period of 100 days. Both aerobic and anaerobic mineralization ranged between 0.1-0.3% after 100 days. No metabolites were observed above 3% of applied radioactivity. The total system degradation rates (DT_{50} and DT_{90}) were extrapolated to >500 and 1000 days, respectively.

The DS concluded that benzonvidiflupyr is considered not rapidly biodegradable.

Bioaccumulation
The substance has a measured log Kow of 4.3, according to OECD TG 107. A BCF was determined in bluegill sunfish (*Lepomis machrochirus*) in a GLP study conducted according to OECD TG 305. The BCF of benzovindiflupyr based on the characterisation of the residues in the whole fish tissues was 76 L/kg. After normalisation for lipid content of the test organisms (3.09%) the final experimentally normalised steady state BCF was estimated to be 123 L/kg based on an assumed 5% lipid content. This value was used for normalisation. The clearance of accumulated residue from the whole body was rapid, with a depuration half-life of 0.54 days. The DS concluded that based on experimental results accumulation of the substance in fish is not expected.

Aquatic Toxicity
Acute and chronic aquatic toxicity data are available for the three trophic levels (fish, aquatic invertebrate and algae) resulting in fish being shown to be the most sensitive species from both acute and chronic tests.

Acute toxicity
Five acute toxicity tests on **fish** were included in the CLH dossier, all of which were carried out according to OECD TG 203: four with freshwater fish and one with a saltwater species (*Cyprinodon variegatus*). The substance was less toxic to saltwater fish than freshwater fish species by one order of magnitude. Studies were reliable and considered adequate for classification purposes: an LC_{50} (96h) for *C. carpio* of 3.5 µg/L, LC_{50} (96h) for *P. promelas* of 4.7 µg/L, LC_{50} (96h) for *Oncorhynchus mykiss* of 9.1 µg/L, LC_{50} (96h) for *L. machrochirus* of 26 µg/L and LC_{50} (96h) for *C. variegatus* of 27 µg/L. The lowest acute toxicity value for freshwater species, the LC_{50} (96h) of 3.5 µg/L in carp (*C. carpio*) was selected by the DS for classification purposes. The study was carried out under GLP and under flow-through conditions and the test substance concentrations were analytically monitored during the course of the study.

Three reliable acute toxicity tests on aquatic **invertebrates** were included in the CLH dossier: one with the freshwater *Daphnia magna* (EC_{50} (48h) of 85 µg/L) carried out according to OECD TG 202

and two tests with a saltwater species: the mysid *Americamysis bahia* (LC_{50} (96h) of 56 µg/L), conducted according to EPA OPPTS 850.1035 and the bivalve *Crassostrea virginica* (EC_{50} (96h) of 160 µg/L), conducted according to the EPA OPPTS 850.1025.

Regarding the acute information for **algae and aquatic plants**, two algal studies were included in the dossier carried out according to OECD TG 201: one with *Pseudokirchneriella subcapitata* (ErC_{50} (72h) >890 µg/L) and other with *Skeletonema kostatum* (ErC_{50} (72h) of 550 µg/L). Additionally, an aquatic plant study with *Lemna gibba* was included in the dossier resulting in a EC_{50} (7d) value >880 µg/L based on the change in frond number produced.

Chronic toxicity
One **fish** early life-stage toxicity study with *P. promelas* was conducted according to OECD TG 210 under GLP conditions. This study resulted in a NOEC (32d) of 0.95 µg/L, which was considered by the DS for classification purposes. The study, carried out under GLP, was a flow-through and the test substance concentrations were analytically monitored.

Regarding the chronic information for **aquatic invertebrates**, two chronic toxicity tests were included in the dossier: one with the freshwater *Daphnia magna* (NOEC (21d) of 15 µg/L) conducted according to OECD TG 211 and another test with a saltwater species: the mysid *A. bahia* (NOEC (28d) of 7.4 µg/L), according to EPA OPPTS 850.1350. Both studies are reliable and showed that aquatic invertebrates are less sensitive than fish to benzovindiflupyr.

Regarding the chronic information for **algae and aquatic plants**, two algal studies were included in the dossier carried out according to OECD TG 201: one with *P. subcapitata* (NOErC (72h) of 890 µg/L) and other with *S. kostatum* (NOErC (72h) of 400 µg/L). Additionally, an aquatic plant study (*Lemna gibba*) was included in the dossier (NOEC (7d) >880 µg/L).

Comments received during public consultation

Comments from six Member States (MS) were received during the public consultation (PC). All of them agreed with the classification proposed by the DS.

Regarding bioaccumulation, two MS indicated the need for lipid normalization of the BCF. The initial BCF of the test substance, based on the characterization of the residues in the whole fish tissues was estimated as 76 L/kg. After the normalization for lipid content of the test fish, the final experimentally steady state BCF is 123 L/kg. This correction has no effect on the proposed classification and labelling.

Also regarding bioaccumulation, one MS noted that there is no explanation why the BCF test was carried out with only one test concentration instead of two test concentrations. The DS explained that according to OECD TG 305, one test concentration can be considered sufficient when it is likely that the BCF is independent of the test concentration and the test concentration is as low as technically feasible. In the case of benzovindiflupyr, the concentration for the BCF test was 0.26 µg/L which is well below the solubility limit of the substance (water solubility of 0.98 mg/L).

Regarding ecotoxicity, one MS requested a clarification on two endpoints (larval survival and growth) mentioned in the CLH report which had only one value. The DS clarified this in their response in the RCOM.

Assessment and comparison with the classification criteria

Degradation

RAC evaluated the information in the CLH report and RCOM and agrees with the DS's proposal to consider benzovindiflupyr as a non-rapidly degradable substance based on 1% degradation in the OECD TG 301F study and 0.1-0.3% aerobic and anaerobic mineralization in the OECD TG 308 study. Both studies were performed under GLP.

Bioaccumulation

Despite the measured log Kow of 4.3 (OECD TG 117), RAC evaluated the information in the CLH report and RCOM and agrees with the DS that benzovindiflupyr has a low potential to

bioaccumulate based on rapid metabolism/depuration rates and a 5% lipid normalized BCF of 123 L/kg in the OECD TG 305 study which was performed under GLP.

Aquatic Toxicity
RAC evaluated the information in the CLH report and RCOM. Both acute and chronic aquatic toxicity data on fish, aquatic invertebrate and algae were available. All studies are reliable, carried out under GLP and are appropriate for classification purposes. Fish was determined to be the most sensitive species in both acute and chronic tests.

RAC agrees with the DS´s proposal to classify benzovindiflupyr as aquatic acute 1 and aquatic chronic 1 based on an LC_{50} (96h) in *C. carpio* of 3.5 µg/L (OECD TG 203) and a NOEC (32d) in *P. promelas* of 0.95 µg/L (OECD TG 210), respectively.

Based on the observed acute toxicity ($0.001 < LC_{50} \leq 0.01$) in fish and chronic toxicity ($0.0001 < NOEC \leq 0.001$) also in fish and non rapid degradation of the substance, RAC agrees with the DS's proposal to classify benzovindiflupyr as:

Aquatic Acute 1 (H400), M=100 and
Aquatic Chronic 1 (H410), M=100.

This classification was based on the substance being not rapidly degradable, non-bioaccumulative and very toxic to aquatic organisms.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

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