Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

Indoxacarb and Indoxacarb

(enantiomeric reaction mass S:R 75:25)

ECHA/RAC/CLH-O-0000001735-72-01/F

Adopted

1 June 2011

Annankatu 18 | P.O. Box 400 | 00121 Helsinki | Finland
www.echa.eu | Tel.: + 358 9 68.61.80

1 June 2011
CLH-O-0000001735-72-01/F

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

In accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: ***Indoxacarb and Indoxacarb (enantiomeric reaction mass S:R 75:25)***

EC Number: ***There are no EC-numbers assigned to Indoxacarb (S-enantiomer) or Indoxacarb (enantiomeric reaction mass S:R 75:25).***

CAS Number: ***173584-44-6 (Indoxacarb - S-enantiomer)***

There is no CAS-number assigned to Indoxacarb (enantiomeric reaction mass S:R 75:25).

The proposal was submitted by ***United Kingdom and the Netherlands***
and received by RAC on ***11 October 2010***

The proposed harmonised classification

Indoxacarb (pure S enantiomer)

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	none	none
Current proposal for consideration by RAC	Acute tox 3 - H301 Acute tox 4 - H332 Skin Sens 1 - H317 STOT RE 1 - H372 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410 M-factor: 1	T; R25 Xn; R20 - 48/22 R43 N; R50/53 SCLs: N; R50/53: C≥ 25% N, R51/53: 2.5% ≤ C <25% R52/53: 0.25% ≤ C <2.5%
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	Acute tox 3 - H301 Acute tox 4 - H332 Skin Sens 1 - H317 STOT RE 1 - H372	T; R25 Xn; R20 - 48/22 R43 N; R50/53

	Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410 M-factor: 1	SCLs: N; R50/53: C≥ 25% N, R51/53: 2.5% ≤ C <25% R52/53: 0.25% ≤ C <2.5%

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	none	none
Current proposal for consideration by RAC	Acute tox 3 - H301 Acute tox 4 - H332 Skin Sens 1 - H317 STOT RE 1 - H372 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410 M-factor: 1	Xn; R20/22 – 48/22 R43 N; R50/53 SCLs: N; R50/53 C≥ 25% N; R51/53: 2.5% ≤ C <25% R52/53: 0.25% ≤ C <2.5%
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	Acute tox 3 - H301 Acute tox 4 - H332 Skin Sens 1 - H317 STOT RE 1 - H372 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410 M-factor: 1	Xn; R20/22 – 48/22 R43 N; R50/53 SCLs: N; R50/53 C≥ 25% N; R51/53: 2.5% ≤ C <25% R52/53: 0.25% ≤ C <2.5%

PROCESS FOR ADOPTION OF THE OPINION

United Kingdom and the Netherlands have 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp on ***27 August 2010*** Parties concerned and MSCAs were invited to submit comments and contributions by ***11 October 2010***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Riitta Leinonen***
Co-rapporteur, appointed by RAC: ***Agnes Schulte***

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37 (4) of the CLP Regulation
The RAC opinion on the proposed harmonised classification and labelling has been reached on ***1 June 2011,*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by consensus.

OPINION OF RAC

The RAC adopted the opinion that ***Indoxacarb and Indoxacarb (enantiomeric reaction mass S:R 75:25)*** should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation:

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 statement Code(s)	Suppl. Hazard statement Code(s)		
	Indoxacarb	not yet assigned	173584-44-6	Acute tox 3	H301	GHS06	H301			
				Acute tox 4	H332	GHS08	H317			
				Skin Sens 1B	H317	GHS09	H332			
				STOT RE 1	H372	Dgr	H372			
				Aquatic Acute 1	H400		H410		Acute M=1	
				Aquatic Chronic 1	H410				Chronic M=1	
	Indoxacarb [enantiomeric reaction mass S:R 75:25]	not yet assigned	144171-61-9	Acute tox 3	H301	GHS06	H301			
				Acute tox 4	H332	GHS08	H317			
				Skin Sens 1B	H317	GHS09	H332			
				STOT RE 1	H372	Dgr	H372			
				Aquatic Acute 1	H400		H410		Acute M=1	
				Aquatic Chronic 1	H410				Chronic M=1	

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	Indoxacarb	not yet assigned	173584-44-6	T; R25-48/25 Xn; R20 R43 N; R50/53	T; N R: 20-25-43-48/25-50/53 S: (1/2-)45-24-37-60-61	N; R50/53: C ≥ 25 % N; R51/53: 2,5 % ≤ C < 25 % R52/53: 0,25 % ≤ C < 2,5 %	
	Indoxacarb [enantiomeric reaction mass S:R 75:25]	not yet assigned	144171-61-9	T; R48/25 Xn; R20/22 R43 N; R50/53	T; N R: 20/22-43-48/25-50/53 S: (1/2-)45-24-37-60-61	N; R50/53: C ≥ 25 % N; R51/53: 2,5 % ≤ C < 25 % R52/53: 0,25 % ≤ C < 2,5 %	

SCIENTIFIC GROUNDS FOR THE OPINION

Indoxacarb (enantiomeric reaction mass 75:25 S:R) was approved for Annex I listing under both the Biocidal Products Directive (98/8/EC) (July 2009) and the Plant Protection Products Directive (91/414/EEC) (2006). Recent development allowed pure production of Indoxacarb, which refers only to the S enantiomer (CAS: 173584-44-6, Producers code DPX-KN128) and which is the insecticidally active form. This opinion contains proposals on all hazard classes for harmonised classification and labelling for each substance.

1 HUMAN HEALTH HAZARD ASSESSMENT

1.1 Acute toxicity

1.1.1 Summary and discussion of acute toxicity

Indoxacarb (pure S enantiomer)

Acute **oral** studies with Indoxacarb (pure S enantiomer) result in an LD_{50} of 179 mg/kg bw for female rats. Males were less susceptible (LD_{50} of 843 mg/kg bw), probably due to differences in toxicokinetics. Based on the low LD_{50} in female rats, according to Directive 67/548/EEC, classification with T; R25 (range 25 – 200 mg/kg bw) is appropriate and Acute Tox Cat 3; H301 according to Regulation EC 1272/2008 (range 50 – 300 mg/kg bw).

No data were available for acute **inhalation** exposure to Indoxacarb (pure S enantiomer). In an acute inhalation study with Indoxacarb (enantiomeric reaction mass 75:25 S:R)-MUP in rats, the LD_{50} was above 5.5 mg/L, the highest dose applied. However, the concentration of Indoxacarb (enantiomeric reaction mass 75:25 S:R) in Indoxacarb (enantiomeric reaction mass 75:25 S:R)-MUP is only 70% and the concentration of the S enantiomer only 52.5% (70% * 0.75). Single inhalation exposure of Indoxacarb (racemic mixture 50:50 S:R) to rats resulted in an LC_{50} above 5.4 mg/L in males and in an LC_{50} of 4.2 mg/L in females. The results with Indoxacarb (racemic mixture 50:50 S:R), are considered also relevant for Indoxacarb (pure S enantiomer) because the acute oral studies indicate that the acute toxicity of the S-enantiomer might be slightly higher compared to the R-enantiomer. Therefore, classification with Xn; R20 (harmful by inhalation) is appropriate according to Directive 67/548/EEC (range 1 – 5 mg/L) and Acute Tox Cat 4; H332 according to Regulation EC 1272/2008 (range 1 – 5 mg/L).

No data were available for acute **dermal** exposure to Indoxacarb (pure S enantiomer). In an acute dermal toxicity study in rats, application of Indoxacarb (enantiomeric reaction mass 75:25 S:R) at a dose of 5000 mg/kg bw did not induce mortality or evidence of systemic toxicity. These values are above the classification limits according to Directive 67/548/EEC (2000 mg/kg bw) and Regulation EC 1272/2008 (2000 mg/kg bw). The results with Indoxacarb (enantiomeric reaction mass 75:25 S:R) are considered also relevant for Indoxacarb (pure S enantiomer) even though the acute oral studies indicate that the acute toxicity of the S-enantiomer might be slightly higher compared to the R-enantiomer.

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

The acute **oral** toxicity study with Indoxacarb (enantiomeric reaction mass 75:25 S:R) resulted in an LD_{50} of 268 mg/kg bw for female rats. The slightly higher LD_{50} than observed for Indoxacarb (pure S enantiomer) may be explained by the lower concentration of the S

enantiomer in Indoxacarb (enantiomeric reaction mass 75:25 S:R). Based on these results classification with Xn; R22 (range 200 – 2000 mg/kg bw) is appropriate for Indoxacarb (enantiomeric reaction mass 75:25 S:R) according to Directive 67/548/EEC and Acute Tox Cat3; H301 according to Regulation EC 1272/2008 (range 50 – 300 mg/kg bw).

In an acute **inhalation** study with Indoxacarb (enantiomeric reaction mass 75:25 S:R)-MUP in rats, the LD_{50} was above 5.5 mg/L, the highest dose applied. However, the concentration of Indoxacarb (enantiomeric reaction mass 75:25 S:R) in Indoxacarb (enantiomeric reaction mass 75:25 S:R)-MUP is only 70% (52.5% S and 17.5% R). Single inhalation exposure of Indoxacarb (racemic mixture 50:50 S:R) to rats resulted in an LC_{50} above 5.4 mg/L in males and in an LC_{50} of 4.2 mg/L in females. The results with Indoxacarb (racemic mixture 50:50 S:R), are considered also relevant for Indoxacarb (enantiomeric reaction mass 75:25 S:R), given the reduced concentration of Indoxacarb (enantiomeric reaction mass 75:25 S:R)-in the MUP and considering that the acute oral studies indicate that the acute toxicity of the S-enantiomer might be slightly higher compared to the R-enantiomer. Therefore, classification with Xn; R20 (harmful by inhalation) is appropriate according to Directive 67/548/EEC (range 1 – 5 mg/L) and Acute Tox Cat 4; H332 according to Regulation EC 1272/2008 (range 1 – 5 mg/L).

In an acute **dermal** toxicity study in rats, application of Indoxacarb (enantiomeric reaction mass 75:25 S:R) at a dose of 5000 mg/kg bw did not induce mortality. These values are above the classification limits according to Directive 67/548/EEC (2000 mg/kg bw) and Regulation EC 1272/2008 (2000 mg/kg bw).

Indoxacarb (pure S enantiomer)
Directive 67/548/EEC: T; R25 Xn; R20
CLP: Acute Tox. 3: H301
Acute Tox. 4: H332
Indoxacarb (enantiomeric reaction mass 75:25 S:R)
Directive 67/548/EEC: Xn; R20/22
CLP: Acute Tox 3: H301
Acute Tox 4: H332

1.2 Specific Target Organ Toxicity – Single Exposure (STOT-SE)

Indoxacarb (pure S enantiomer)

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

There is some concern on neurofunctional disorder at dose below guidance value for STOT SE Cat 1. However, effects occur at doses that are also relevant for acute toxicity and acute toxic effects do not justify a classification for STOT-SE.

1.3 Irritation

Indoxacarb (pure S enantiomer)

For Indoxacarb (pure S enantiomer), no data on irritation potential are available. However, because irritation depends on reactivity and since the reactivity of both enantiomers is probably similar, read-across from Indoxacarb (enantiomeric reaction mass 75:25 S:R) to Indoxacarb (pure S enantiomer) is justified.

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

Indoxacarb (enantiomeric reaction mass 75:25 S:R) is not irritating to skin and only slightly irritating to the eyes with all effects reversible within 72 hours. Mean scores were below those that would require classification, all effects were reversible within 72 h or 14 days.

In an acute inhalation study with Indoxacarb (enantiomeric reaction mass 75:25 S:R)-MUP no evidence of irritating effect in the respiratory tract was observed. It can thus be concluded that Indoxacarb (enantiomeric reaction mass 75:25 S:R) does not need to be classified for irritation.

1.4 Sensitisation

1.4.1 Summary of skin sensitisation data

1.4.2 Summary and discussion of sensitisation

Indoxacarb (pure S enantiomer)

Read across from a positive response with Indoxacarb (enantiomeric reaction mass 75:25 S:R) to Indoxacarb is justified as it is considered that the skin sensitisation potential is independent of the chiral form. Classification of Indoxacarb (pure S enantiomer) as a skin sensitiser (R43) is appropriate according to Directive 67/548/EEC and Skin Sens Cat 1: H317 according to Regulation EC 1272/2008 (skin sens. category 1B:H317 under the new criteria of the CLP regulation (2nd ATP)).

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

A positive response in more than 30% of animals was obtained in a guinea pig maximisation test with Indoxacarb (enantiomeric reaction mass 75:25 S:R). According to the classification into potency categories as described in the Guidance on the Application of the CLP-criteria, Indoxacarb (enantiomeric reaction mass 75:25 S:R) is a moderate skin sensitiser. Therefore, classification of Indoxacarb (enantiomeric reaction mass 75:25 S:R) as a skin sensitiser (R43) is appropriate according to Directive 67/548/EEC and Skin Sens Cat 1B: H317 according to Regulation EC 1272/2008.

The generic concentration limit of 1% is allocated.

Indoxacarb (pure S enantiomer)

Directive 67/548/EEC: Xi; R43

CLP: Skin Sens. 1 (Skin Sens 1B*) H317

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

Directive 67/548/EEC: Xi; R43

CLP: Skin Sens.1 (Skin Sens 1B*) H317

* according to the new criteria of CLP Regulation (2nd ATP)

1.4.3 Respiratory system

No information is available with regard to the respiratory sensitisation potential of Indoxacarb (pure S enantiomer) and Indoxacarb (enantiomeric reaction mass 75:25 S:R). Both forms of Indoxacarb have no structural relationships with known respiratory sensitisers. Therefore, there is no data available showing or indicating a potential for respiratory sensitisation.

No classification is proposed for this endpoint.

1.5 Repeated dose toxicity

1.5.1 Repeated dose toxicity: oral

1.5.2 Summary and discussion of repeated dose toxicity

The results of the 90-day oral rat studies demonstrate that Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb (racemic mixture 50:50 S:R) show similar dose-response characteristics. Consequently, the results of the additional studies in which animals have been exposed to Indoxacarb (racemic mixture 50:50 S:R) are

considered to be relevant to the prediction of the toxicity and the classification of Indoxacarb (pure S enantiomer) and Indoxacarb (enantiomeric reaction mass 75:25 S:R).

The main findings included mortality (observed at 8.94 mg/kg bw) and haemolytic anaemia (observed at 3.78 mg/kg bw). In addition there was evidence of neurotoxicity from ≥ 30 mg/kg bw and of myocardial necrosis from ≥17 mg/kg in mice.

In most studies in the rat, females appeared to be more sensitive to the effects compared to males. Species differences were also observed with the rat more sensitive than mice and dogs to the toxicological effects.

The most sensitive effects of oral exposure to Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb (racemic mixture 50:50 S:R) in both rats and dogs by the oral route are regenerative haemolytic anaemia and severe decreases in body weight parameters (> 25%) and/or nutritional status. Concurrent with Muller et al., 2006, anaemic effects of more than 20% reduction in the circulating red cell mass (as stand-alone effect) were considered sufficient for classification. Methaemoglobulin (MetHb) formation (4%) was observed in some studies but was not determined in all studies. As a reduction in Haemoglobin and an increase in MetHb both result in a decrease in oxygen transport, these effects should be combined. However, since MetHb has not been determined in all studies this is difficult. Therefore, reductions in Hb somewhat below 20% are also considered sufficient as a stand-alone criterion for classification. Also premature deaths or a combination of less severe reduction in Hb (>10%) and haemolysis-related adverse effects (such as haemoglobinuria, haemosiderinuria or haemosiderosis) require classification.

Although there are in-vitro data that suggest that humans are less sensitive than rats and dogs to glutathione oxidation in red blood cells that were interpreted by the rapporteur MS in a way that humans were thought to be less sensitive to haemolysis induced by oxidative stress. In contrast, the guidance document of Muller et al., 2006 mentions that rats and mice are less sensitive to methaemoglobin production than man and dogs. The proposed mechanism underlying the regenerative haemolytic effects of Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb (racemic mixture 50:50 S:R) is yet to be clearly established. Therefore, for classification, these differences in sensitivity are not taken into account.

Depending on severity anaemia could be reversible by regenerative proliferation of blood cell precursors as long as no blood stem cells/early precursor cells are damaged. Indications on irreversible damage of erythrocyte precursor were seen at doses of ≥640 ppm (17.5 mg/kg bw/d) in dogs (Mertens, 1997). However, also at doses below 17.5 mg/kg bw/d haemolytic anaemia and related haemosiderin deposition are considered as serious health effects since there is no clearance mechanism for accelerated deposition of haemosiderosis in organs, and it could not be ruled out that premature deaths are related to haemotoxicity.

Indoxacarb (pure S enantiomer)

In a 90-day study with Indoxacarb (enantiomeric reaction mass 75:25 S:R) in rats, at 8.94 mg/kg bw/day mortality in females was reported (≤10 mg/kg bw/d, guidance value for CLP Cat1, 90 day). In addition, in 28-day toxicity studies with Indoxacarb (racemic mixture 50:50 S:R) in rats and mice, delayed mortality was observed at 23.5 and 34 mg/kg bw/day, respectively) ((≤30 mg/kg bw/d, guidance value for CLP Cat1, 28 day). Since the results of the repeated dose studies with Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb (racemic mixture 50:50 S:R) show similar dose-response characteristics, the results of the additional studies in which animals have been exposed to Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb (racemic mixture 50:50 S:R) are considered to be also relevant to the prediction of the toxicity and the classification of Indoxacarb (pure S enantiomer).

In a 90-day dietary study in rats with Indoxacarb (pure S enantiomer) (the only repeated dose toxicity study available for Indoxacarb (pure S enantiomer)) severely reduced body weight gain (> 32%), food intake (> 11%) and adverse effects on haematology parameters (RBC, Hb and Ht change > 10%, max. 17%) were observed in females at doses ≥ 50 ppm (4.1 mg/kg bw/day). At the same doses, also significantly higher incidences of splenic erythrocytic and bone marrow hyperplasia was observed in males as well as females. In females increased haemosiderin deposition in liver (significantly higher incidence at 100 ppm, 8.5 mg/kg bw/d) and in spleen (significantly higher incidences ≥20 ppm, 1.7 mg/kg bw/d (10/10 females ≥20 ppm compared to 0/10 in controls, no data on severity grades) was seen. Secondary effects to the haemosiderosis were not observed in this 90 day study. The combination of effects such as Hb reduction ≥10% plus increased haemosiderosis occurred at 50 ppm (4.1 mg/kg bw/d), which is below the guidance value for Cat 1 (10 mg/kg bw/d, 90 days, CLP) and also below the guidance value of 5 mg/kg bw/d for T; R48/25 (DSD). Although no data are reported on the average severity scores, markedly increased incidences of haemolytic anemia-related effects below guidance doses are relevant for classification.

Therefore, based on the mortality observed at 8.94 mg/kg/day in the 90-day study with Indoxacarb (enantiomeric reaction mass 75:25 S:R) and supported by the mortality observed from 23.5 and 34 mg/kg/day in the 28-day studies with Indoxacarb (racemic mixture 50:50 S:R) and supported by the effects related to haemolytic anaemia in the 90-day study on Indoxacarb (pure S enantiomer), classification with T; R48/25 seems justified for Indoxacarb (pure S enantiomer) according to Directive 67/548/EEC (guidance value below 5 mg/kg bw), and STOT-RE Cat 1: H372 according to Regulation EC 1272/2008 (< 10 mg/kg bw). Proposal for classifications according to Dir 67/548/EEC and CLP are corresponding taking mortalities (at 8.94 mg/kg/) and haemolytic anaemia (at 50 ppm = 4.1 mg/kg bw/d), in combination with accelerated haemosiderin deposit in the spleen (≥20 ppm, 1.7 mg/kg bw/d) and in the liver (at 100 ppm, 8.5 mg/kg bw/d) into account in comparion to the guidance values (< 10 mg/kg bw for STOT-RE Cat 1 and < 5 mg/kg bw for T; R48/25).

Although the original CLH dossier of the dossier submitter proposed Xn; R48/22 for DSD, RAC considers the original proposal as a borderline case where simultaneous classification should be proposed in accordance to DSD and CLP. It is proposed to apply guidance values less strictly to differentiate Xn; R48/22 from T; R48/25. Taking into account haemotoxic/spleen/liver effects from 4.1 mg/kg bw/d in rats and as for other substances a harmonised classification on both regulations is therefore proposed.

According to the CLP criteria it is proposed to add the target organs to the hazard statement: Causes damage to organs (blood, nervous system, heart) through prolonged or repeated exposure.

No studies on repeated dermal exposure to Indoxacarb (pure S enantiomer) are reported. However, short-term (28-day) dermal exposure to Indoxacarb (enantiomeric reaction mass 75:25 S:R) in rats revealed similar effects as were observed after oral exposure, but, with a LOAEL of 50 mg/kg bw/day. Dose-related effects on body weight gain (reduction > 25%) and anaemia (decreased circulating erythrocytes and increased reticulocytes) were observed at the LOAEL. Whilst these effects occurred at doses below the classification cut-off, they are not considered severe enough (in comparison to the criteria of Muller et al., 2006) or do not comply for combined effects required to justify for classification for this route.

No data were available for long term inhalation exposure to Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) or Indoxacarb (racemic mixture 50:50 S:R).

Indoxacarb (enantiomeric reaction mass 75:25 S:R)

Based on results from 90 day studies, mortality in females was reported at 8.94 mg/kg b/day between day 8 and 19, deaths of females were also reported at 6.09 mg/kg bw/day (without any data on the time of death). Based on this mortality, and supported by the mortality data of 28 day toxicity studies with Indoxacarb (racemic mixture 50:50 S:R) in rats and mice (mortality at 23.5 and 34 mg/kg bw/day), classification with Xn; R48/22 is proposed for Indoxacarb (enantiomeric reaction mass 75:25 S:R) according to Directive 67/548/EEC (range 5-50 mg/kg bw for 90-day studies), and STOT-RE Cat 1: H372 according to Regulation EC 1272/2008 (< 10 mg/kg bw for 90-day studies).

Surviving rats of the same 90-day dietary study in rats with Indoxacarb (enantiomeric reaction mass 75:25 S:R) (the only oral repeated dose toxicity study available for Indoxacarb (enantiomeric reaction mass 75:25 S:R)) demonstrated reduced body weight gain (≥ 38%) in females at doses ≥ 3.78 mg/kg bw/day and in males at 15 mg/kg bw/d . In addition, reduced RBC (> 10%-15%) was reported in females at ≥3.78 mg/kg bw/d, reduced RBC and Hb (-16% and -11%, resp.) , as well as haemosiderin deposit in liver (in females ≥3.78 mg/kg bw/d), in kidneys (females at 100 mg/kg bw/d) and spleen (females at ≥0.67 mg/kg bw/d, males ≥6.01 mg/kg bw/d). The dose of 15 mg/kg bw/d which caused Hb reduction > 10% in males and increased incidences of haemosiderosis is below the guidance value for STOT-RE Cat 2.

Beyond findings in male rats, Hb reduction of -11% in combination with haemosiderin deposit in liver of female rats at ≥3.78 mg/kg bw/d argues for STOT-RE Cat 1. Although delayed mortilities of 5/10 females in the same study are lead for the original classification proposal from dossier submitter, haemolytic anaemia in combination with liver haemosiderosis observed in female rats at ≥3.78 mg/kg bw/d are in support of T; R48/25.

RAC considers the original proposal to classify with Xn; R48/22 as a borderline case where simultaneous classification should be proposed in accordance to DSD and CLP. It is proposed to apply guidance values less strictly to differentiate Xn; R48/22 from T; R48/25. Taking into account haemotoxic/liver effects from 3.78 mg/kg bw/d in rats and as for other substances a harmonised classification on both regulations is therefore proposed.

Although anaemic effects on blood cells could be reversible depending on its severity by regenerative proliferation of blood cell precursors, haemosiderin deposition is a non-reversible process. There is no clearance mechanism for accelerated deposition of haemosiderosis in organs, deposition in liver and kidney is a pathological finding irrespective of the severity. It could not be ruled out that premature deaths are related to haemotoxicity.

According to the CLP criteria it is proposed to add the target organs to the hazard statement: Causes damage to organs (blood, nervous system, heart) through prolonged or repeated exposure

Similar effects were observed in rats after short-term (28d) dermal exposure to Indoxacarb (enantiomeric reaction mass 75:25 S:R) in rats, but, with a LOAEL of 50 mg/kg bw/day. Dose-related effects on body weight gain (reduction > 25%) and anaemia (decreased circulating erythrocytes and increased reticulocytes) were observed at the LOAEL. Whilst these effects occurred at doses below the classification cut-off, they are not considered severe enough (in comparison to the criteria of Muller et al., 2006) or do not comply for combined effects required to justify for classification of this route.

No data were available for long term inhalation exposure to Indoxacarb (pure S enantiomer), Indoxacarb (enantiomeric reaction mass 75:25 S:R) or Indoxacarb (racemic mixture 50:50 S:R).

Indoxacarb (pure S enantiomer) Directive 67/548/EEC: T; R48/25 CLP: STOT RE. 1; H372 Causes damage to organs (blood, nervous system, heart) through prolonged or repeated exposure

Indoxacarb (enantiomeric reaction mass 75:25 S:R) Directive 67/548/EEC: T; R48/25 CLP: STOT RE.1; H372 Causes damage to organs (blood, nervous system, heart) through prolonged or repeated exposure

1.6 Mutagenicity

No classification is proposed for this endpoint.

1.7 Carcinogenicity

No classification is proposed for this endpoint.

1.8 Toxicity for reproduction

1.8.1 Effects on fertility

1.8.2 Developmental toxicity

No classification is proposed for this endpoint.

1.9 Flammability

No classification is proposed for this endpoint.

1.10 Oxidising potential

No classification is proposed for this endpoint.

2 ENVIRONMENTAL HAZARD ASSESSMENT

The S enantiomer is the insecticidally active form. During the early development of the product it was not possible to produce the pure S enantiomer on a commercial scale and, consequently, a technical material was produced consisting of approximately a 3:1 ratio of the S:R enantiomers Indoxacarb (enantiomeric reaction mass S:R 75:25). This technical material has been used to formulate products in the EU. However, recent developments have meant that it is now viable to manufacture a material that contains only trace amounts of the insecticidally inactive R enantiomer and this 'pure' form is now used for product formulations.

For the purpose of Indoxacarb classification, the observed toxicity for tested mixtures of S:R enantiomers is assumed to be due to the insecticidally active S enantiomer with the R enantiomer being inactive. Therefore the results from studies with various ratios of S:R enantiomers can be read-across.

Ecotoxicity studies conducted using Indoxacarb (enantiomeric reaction mass 75:25 S:R) show that the substance is acutely toxic to fish and invertebrates with a 96-h LC_{50} of 0.65 mg/l and a 48-h EC_{50} of 0.6 mg/l. Both values are above the experimental solubility in pure water (0.225 ± 0.036 mg/l at 20°C) but within the solubility limit in the test water. Although effects were observed in algal growth inhibition studies using Indoxacarb (enantiomeric reaction mass 75:25 S:R), the E_rC_{50} is considered to be above the solubility of this substance in test media.

Chronic toxicity tests were conducted using Indoxacarb (enantiomeric reaction mass 75:25 S:R). A 90-day NOEC for fish is 0.15 mg/l, a 21-day NOEC for Daphnia magna is 0.09 mg/l and a 72-h NOE_rC for algae is 0.46 mg/l.

An acute toxicity to fish study was performed with major degradant IN-JT333 (N-decarbomethoxylated Indoxacarb) which is formed in soil and sediment. The 96-h LC_{50} was 0.029 mg/l. Other degradants were observed to exhibit less acute toxicity than the parent substance.

It is noted that the S enantiomer is insecticidally active and following metabolism to IN-JT333 induces death after a few hours. The available acute testing includes limited testing with insects and it is recognised that other insect species may be more sensitive.

There is some experimental evidence to suggest that the S and R enantiomers are likely to undergo removal processes in the aquatic environment through aqueous photolysis, hydrolysis, adsorption to sediment and anaerobic and aerobic degradation. In water this is considered to occur at the same rates for both enantiomers. Most removal reflects adsorption to sediment and primary degradation with water DT_{50} values between 2 and 4 days at 12°C. Sediment DT_{50} values are longer, ranging between 64.5 days under anaerobic conditions and 9.5 days under aerobic conditions at 12°C.

However, various degradants are more persistent. This includes IN-JT333 which although not detected in water, was detected in aerobic and anaerobic sediment samples during a simulation study. The calculated DT_{50} values of IN-JT333 at 20°C in aerobic and anaerobic sediments are 29 days and 23 days. IN-JT333 is anticipated to further degrade to substances with DT_{50} values of 19 days and >1 year at 20°C.

The simulation study showed that mineralisation of the substance was minimal over 28 days. At day 28 the mean CO_2 residues were 1.8% AR in the anaerobic system and 7.1% AR in the aerobic system.

Therefore, although primary degradation of S and R enantiomers occurs in water and sediment fairly rapidly, significant degradation to non-toxic components does not occur with 28 days.

Based on available information, neither Indoxacarb nor Indoxacarb (enantiomeric reaction mass 75:25 S:R) are considered readily degradable as defined in Directive 67/548 for the purpose of classification.

Similarly under the CLP Regulation, neither Indoxacarb nor Indoxacarb (enantiomeric reaction mass 75;25 S:R)) are considered to undergo rapid degradation to non-toxic substances in the aquatic environment.

Measured fish BCF data indicate the S enantiomer (Indoxacarb) is not highly bioaccumulative (BCF_{fish} 77.3) whilst the R enantiomer (IN-KN127) is significantly more bioaccumulative (BCF_{fish} 1,848). As the BCF_{fish} is <100 for the S enantiomer, Indoxacarb is not considered bioaccumulative for the purpose of classification and labelling. The measured BCF_{fish} for Indoxacarb (racemic mixture 50:50 S:R) is 950. The BCF_{fish} for Indoxacarb (enantiomeric reaction mass 75:25 S:R) is anticipated to reflect the presence of the R enantiomer falling between 77.3 and 1,848. As the R enantiomer is a significant component of the Indoxacarb

enantiomeric 75:25 S:R mixture and the R enantiomer BCF_{fish} is considered bioaccumulative (i.e. > 100 and > 500 under CLP), the 75:25 S:R mixture is considered bioaccumulative for the purpose of classification and labelling.

The ratio of S:R enantiomers in water remained broadly 1:1 over the study period. However, the ratio of S:R enantiomers in fish tissue altered over the study period to approximately 1:19 based on measurement on days 21 and 28. One major metabolite (IN-JT333) was observed representing ~22-28% total radioactive residues (TRR) in fish fillets and ~23-30% TRR in fish viscera. It is possible that the difference in BCF_{fish} rates between S and R enantiomers is not a result of different uptake mechanisms and instead reflects metabolism of the insecticidally active S enantiomer (Indoxacarb) to IN-JT333 (N-decarbomethoxylated Indoxacarb).

Classification

The acute toxicity of both substances to aquatic organisms lies between 0.1 and 1 mg/l based on the 96-h LC50 of 0.65 mg/l to fish and on the 48-h EC50 of 0.6 mg/l to Daphnia magna. Both substances are not readily degradable neither do they fill the classification criteria of degrading biologically and/or abiotically in the aquatic environment to a level > 70 % within a 28 day period. The BCF 77.3 of Indoxacarb is below the classification limits 100 and 500 in Directive 67/548 and CLP Regulation respectively. However, the Indoxacarb (enantiomeric reaction mass 75:25 S:R) is considered bioaccumulative according to both criteria based on the BCF 1,848 of R enantiomer.

The specific concentration limits and M-factor are based on the acute toxicity values between 0.1 and 1 mg/l.

Classification of manufactured material Indoxacarb (enantiomeric reaction mass 75:25 S:R):
Following Directive 67/548/EEC, Indoxacarb (enantiomeric reaction mass 75:25 S:R) should be classified Dangerous for the Environment with the following risk and safety phrases:
N Dangerous for the Environment
R50 Very toxic to aquatic organisms
R53 May cause long term effects in the environment
S60 This material and its container must be disposed of as hazardous waste
S61 Avoid release to the environment. Refer to special instructions/Safety Data Sheet
Specific concentration limits:
N; R50-53: $C \geq 25$ %; N; R51-53: 2.5 % $\leq C < 25$ %; R52-53: 0.25 % $\leq C < 2.5$ %

Based on the CLP Regulation , Indoxacarb (enantiomeric reaction mass 75:25 S:R) should be classified as: Aquatic Acute 1, Aquatic Chronic 1
With the following hazard phrases: H400 ‘Toxic to aquatic life’ and H410 ‘Very toxic to aquatic life with long lasting effects’
Signal word: ‘Warning’
Pictogram with the Environment symbol.
Additionally: M factor 1 based on $0.1 < L(E)C_{50} \leq 1$ mg/l should apply.

Classification of Indoxacarb (pure S form)
Following Directive 67/548/EEC, Indoxacarb should be classified Dangerous for the Environment with the following risk and safety phrases:
N Dangerous for the Environment
R50 Very toxic to aquatic organisms
R53 May cause long term effects in the environment
S60 This material and its container must be disposed of as hazardous waste
S61 Avoid release to the environment. Refer to special instructions/Safety Data Sheet
Specific concentration limits:
N; R50-53: C ≥ 25 %; N; R51-53: 2.5 % ≤ C < 25 %; R52-53: 0.25 % ≤ C < 2.5 %

Based on the CLP Regulation , Indoxacarb should be classified as:
Aquatic Acute 1, Aquatic Chronic 1
With the following hazard phrases: H400 'Toxic to aquatic life' and H410 'Very toxic to aquatic life with long lasting effects'
Signal word: 'Warning'
Pictogram with the Environment symbol
Additionally: M factor 1 based on $0.1<L(E)C_{50}\leq 1$ mg/l should apply.

Classification according to the 2.ATP of the CLP Regulation

Acute hazard
There are no changes to the acute classification in the 2.ATP of the CLP Regulation. Consequently both substances are classified Acute Aquatic 1, M-factor 1 as described above in this Chapter.

Long-term hazard
Adequate chronic toxicity data for all three trophic levels is available for Indoxacarb (enantiomeric reaction mass 75:25 S:R) and Indoxacarb. In this case the classification is done according to Table 4.1.0 (b)(i) or (ii) depending on rapid degradation. The substances are non rapidly degradable and consequently Table 4.1.0 (b)(i) is used. The cut-off for chronic NOEC for classifying to Category Chronic 1 is ≤ 0.1 mg/l. Chronic NOEC values available for these substances are a 90-day NOEC for fish of 0.15 mg/l, a 21-day NOEC for Daphnia magna of 0.09 mg/l and a 72-h NOE_rC for algae of 0.46 mg/l. Based on the 21-day NOEC to Daphnia of 0.09 mg/l the substances will be classified to Category Chronic 1 with a chronic M-factor of 1.

The classification criteria in Table 4.1.0 (b)(iii) are the same as in CLP Regulation. The classification is based on acute toxicity, rapid degradability and bioaccumulation. The classification of these two substances according to this Table is Aquatic Chronic 1 as described above.

Classification of manufactured material Indoxacarb (enantiomeric reaction mass 75:25 S:R):

Based on the 2. ATP of the CLP Regulation, Indoxacarb (enantiomeric reaction mass 75:25 S:R) should be classified as: Aquatic Acute 1, Aquatic Chronic 1

With the following hazard phrases: H400 'Toxic to aquatic life' and H410 'Very toxic to aquatic life with long lasting effects'
Signal word: 'Warning'
Pictogram with the Environment symbol.
Additionally: Acute M-factor:
1 based on $0.1<L(E)C_{50}\leq 1$ mg/l and
Chronic M-factor:
1 based on on $0.01<NOEC\leq 0.1$ mg/l

Classification of Indoxacarb (pure S form)
Based on the 2.ATP of the CLP Regulation, Indoxacarb should be classified as:
Aquatic Acute 1, Aquatic Chronic 1
With the following hazard phrases: H400 'Toxic to aquatic life' and H410 'Very toxic to aquatic life with long lasting effects'
Signal word: 'Warning'
Pictogram with the Environment symbol
Additionally: Acute M-factor:
1 based on $0.1<L(E)C_{50}\leq 1$ mg/l and
Chronic M-factor:
1 based on on $0.01<NOEC\leq 0.1$ mg/l

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[1]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.