Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Tralkoxydim

EC No.: Not assigned

CAS No.: 87820-88-0

ECHA/RAC/CLH-O-0000001911-78-03/F

Adopted

14 September 2012

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14 September 2012
CLH-O-0000001911-78-03/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 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

Chemical name: Tralkoxydim

EC No.: Not assigned

CAS No.: 87820-88-0

The proposal was submitted by **United Kingdom**
and received by RAC on **30/08/2011**

The proposed harmonised classification

	Regulation (EC) No 1272/2008	**Directive 67/548/EEC**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	–	–
Proposal by dossier submitter for consideration by RAC	Carc. 2 – H351 Acute Tox. 4 – H302 STOT RE 2 – H373 (liver) Aquatic Chronic 2 – H411	Carc. Cat. 3; R40 Xn; R22 Xn; R48/22 N; R51/53
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Carc. 2 – H351 Acute Tox. 4 – H302 STOT RE 2 – H373 (liver) Aquatic Chronic 2 – H411	Carc. Cat. 3; R40 Xn; R22 Xn; R48/22 N; R51/53

PROCESS FOR ADOPTION OF THE OPINION

The **United Kingdom** 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/web/guest/harmonised-classification-and-labelling-consultation*** on **30/08/2011**. Parties concerned and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14/10/2011**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Marja Pronk**

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 **14 September 2012**, 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 **tralkoxydim** should be classified and labelled as follows:

Classification & Labelling in accordance with Regulation (EC) No 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 state-ment Code(s)		
606-146-00-7	Tralkoxydim	–	87820-88-0	Acute Tox. 4 Carc. 2 Aquatic Chronic 2	H302 H351 H411	GHS07 GHS08 GHS09 Wng	H302 H351 H411			

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

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
606-146-00-7	Tralkoxydim	–	87820-88-0	Carc. Cat. 3; R40 Xn; R22 N; R51/53	Xn, N R: 22-40-51/53 S: 36/37-60-61	N; R51/53: C ≥ 25% R52/53: 2.5% ≤ C < 25%	

SCIENTIFIC GROUNDS FOR THE OPINION

Tralkoxydim is a cyclohexanedione oxime herbicide that was included as an active substance in Annex I of the Plant Protection Products Directive (91/414/EEC) in 2008. This opinion on harmonised classification and labelling relates to all hazard classes.

HUMAN HEALTH HAZARD ASSESSMENT

Acute toxicity and specific target organ toxicity – single exposure (STOT SE)

The RAC conclusion for both of these endpoints together is presented further below.

Summary of Dossier submitter's proposal

Acute toxicity

Comparison with criteria

The LD_{50} values from the acute oral toxicity studies range from 934 to 1258 mg/kg. These are within the range of 300-2000 mg/kg for classification under CLP as Acute Tox. 4; H302 (Directive 67/548/EEC, DSD; 200-2000 mg/kg, Xn; R22).

In an acute inhalation study, the LC_{50} was found to be > 3.5 mg/l. The target particulate concentration in the study was 5 mg/l (the cut-off for classification under both CLP and Directive 67/548/EEC) but the actual concentration tested (which was the maximum achievable concentration) was 3.5 mg/l. Given the results of this study no classification is proposed.

The LD_{50} from the acute dermal toxicity study was > 2000 mg/kg which is above the classification cut-off (2000 mg/kg) under both CLP and Directive 67/548/EEC. Therefore no classification is proposed.

Dossier submitter's conclusion

CLP: Acute Tox. 4 – H302
Directive 67/548/EEC: Xn; R22

Specific target organ toxicity – single exposure (STOT SE)

The clinical signs that were apparent after single oral, dermal and inhalation exposure included decreased activity, lachrymation, dehydration, hypothermia, piloerection, pinched sides, upward curvature of the spine, reduced righting reflexes, depressed respiration, miosis, prostration and urinary incontinence.

Comparison with criteria

Substances that have produced significant toxicity in humans or that on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure are classified in STOT SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

Classification in STOT SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

The signs that were apparent after single oral, dermal and inhalation exposure to tralkoxydim were indicative of non-specific, general acute toxicity. As there was no clear evidence of specific toxic effects on a target organ or tissue, no signs of respiratory tract irritation or narcotic effects, no classification for specific target organ toxicity (single exposure) under CLP was proposed.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

RAC assessment of acute toxicity and STOT SE

The evaluation by RAC relates to the proposal of the dossier submitter to classify tralkoxydim for acute toxicity (for the oral route only), but not for specific target organ toxicity upon single exposure. During public consultation, support was expressed for the proposed classification for acute toxicity; no comments were received on specific target organ toxicity after single exposure.

Following a comparison of the available LD_{50} and LC_{50} values in rats with the criteria, RAC supported the conclusion of the dossier submitter that tralkoxydim should be classified for acute oral toxicity with **Acute Tox. 4 – H302** (CLP) and **Xn; R22** (DSD), but not for acute dermal or inhalation toxicity.

RAC also concluded that the clinical signs observed in the acute toxicity studies with tralkoxydim do not fulfill the CLP criteria to classify for STOT SE, in line with the justification provided by the dossier submitter.

RAC conclusion

CLP: Acute Tox. 4 – H302
Directive 67/548/EEC: Xn; R22

Irritation

Summary of Dossier submitter's proposal

Skin

Very slight or well-defined erythema (average scores from 24-72 hours ≤ 1 in all animals) and very slight, slight or moderate oedema (average scores from 24-72 hours ≤ 1 in all animals) were observed. All reactions had resolved within 7 days of application.

Comparison with criteria

As the scores for erythema and oedema were ≤ 1 in all animals tested and only slight desquamation persisted in one animal until the end of the study no classification is proposed.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Eye

There were no effects on the cornea or iris (all scores were 0). Slight to moderate conjunctival redness and chemosis were observed (average scores from 24 to 72 hours ≤ 1 in all animals). All effects had resolved by day 4.

Comparison with criteria

Tralkoxydim did not produce effects on the cornea or iris and scores for conjunctival redness and chemosis were ≤ 1 in all treated animals. Therefore, tralkoxydim does not meet the criteria for classification.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Respiratory tract

No effects on the respiratory tract have been observed.

Comparison with criteria

No effects on the respiratory tract have been observed therefore tralkoxydim does not meet the criteria for classification.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter not to classify tralkoxydim for irritation (skin/eye/respiratory tract). This proposal/endpoint was not specifically commented on during public consultation.

In the rabbit studies for skin and eye irritation only slight, transient irritation was observed. Mean scores for erythema and oedema formation in the skin irritation study were below the threshold value of 2.3 for Skin Irrit. 2 – H315 (CLP) or 2 for Xi; R38 (DSD) in all (six) animals. Mean scores for conjuctival redness and chemosis in the eye irritation study were also below the threshold values for classification (2 for Eye Irrit. 2 – H319 (CLP) or 2.5 (redness) and 2 (chemosis) for Xi; R36 (DSD)) in all (six) animals. RAC therefore supported the conclusion of the dossier submitter that tralkoxydim should not be classified for skin or eye irritation, nor for respiratory tract irritation, given the absence of irritation effects in an acute inhalation study with rats (where only some abnormal respiratory noises were noted).

RAC conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Corrosivity

Summary of Dossier submitter's proposal

Tralkoxydim does not meet the criteria for classification as corrosive when tested in standard skin and eye irritation studies. Consequently, no classification is proposed.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter not to classify tralkoxydim for corrosion. This proposal/endpoint was not specifically commented on during public consultation.

RAC agrees with no classification for corrosivity, as justified by the dossier submitter.

RAC conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Sensitisation

Summary of Dossier submitter's proposal

Skin

Tralkoxydim gave a negative response in a guinea pig maximisation study (0/20 response) when tested at a challenge concentration of 75 %.

Comparison with criteria

A substance is classified as a skin sensitiser if, in a guinea pig maximisation study, a positive response is observed in 30% of treated animals. As 0/20 animals gave a response following treatment with tralkoxydim it can be concluded that it does not meet the criteria for classification in accordance with CLP or Directive 67/548/EEC.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Respiratory system

No data available.

Dossier submitter's conclusion

CLP: No classification proposed since no data is available
Directive 67/548/EEC: No classification proposed since no data is available

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter not to classify tralkoxydim for skin and respiratory sensitisation. This proposal/endpoint was not specifically commented on during public consultation.

RAC agrees with no classification for dermal or respiratory sensitisation, as justified by the dossier submitter.

RAC conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Repeated dose toxicity and specific target organ toxicity – repeated exposure (STOT RE)

Summary of Dossier submitter's proposal

The main target organ for toxicity following oral administration is the liver. In rats and hamsters, increased liver weights (ca 10% in rats and 20% in hamsters), with some minor histopathology in the hamster liver only (hepatocyte eosinophillia in one male and loss of hepatocyte vacuolation) were observed at high doses (≥ 205 mg/kg/day in rats and ≥ 600 mg/kg/day in hamsters).

In dogs, significant effects were noted from 50 mg/kg/day in a 90 day study and included increased liver weights (64% in males and 51% in females), slight fatty changes and vacuolation of hepatocytes in all animals. These effects were also noted in a 1-year study at 5 mg/kg/day in males (increased liver weight 8%, and 1/4 males with fatty changes in hepatocytes) and at 50 mg/kg/day in males and females (increased liver weights (ca. 70%) and 4/4 males and 2/4 females with moderate to marked fatty changes in hepatocytes).

In the mouse, significant liver effects were observed from 5 mg/kg/day in a number of 28 day studies. These effects included an increase in porphyrin, necrosis and hyperplasia and fibrosis of the bile ducts. Additional mechanistic studies have been conducted and it is proposed that the porphyrinogenic activity in mice following treatment with tralkoxydim is due to a species specific metabolic pathway which results in the formation of N-methyl protoporphyrin IX.

Dermal administration of tralkoxydim in a short-term repeated dose study did not result in any adverse effects.

Comparison with criteria under DSD

A substance is classified with R48 under Directive 67/548/EEC when it has produced or has been shown to have the potential to produce serious damage (clear functional disturbance or morphological change which has toxicological significance) following repeated exposure by the oral, dermal or inhalation routes. This can be on the basis of human data or evidence from studies in animals that cause such adverse effects at or below given guidance values (≤ 5 mg/kg/day or ≤50 mg/kg/day in a 90 day oral study in the rat).

There is no toxicological data available on tralkoxydim in humans relevant to STOT RE.

The main target organ of toxicity for tralkoxydim following oral administration to animals is the liver.

The effects in rats and hamsters occur above the relevant guidance values for classification with R48.

In dogs, toxicologically significant effects (slight to marked fatty changes in the liver) were noted at 50 mg/kg/day in a 90 day study and from 5 mg/kg/day in a 1 year study. Such effects at these dose levels are considered to show that classification with R48/22 is appropriate.

In the mouse, significant liver effects were observed from 5 mg/kg/day in a number of 28 day studies. These effects included an increase in porphyrin, necrosis and hyperplasia and fibrosis of the bile ducts. Additional mechanistic studies have been conducted and it is proposed that the porphyrinogenic activity in mice following treatment with tralkoxydim is due to a species specific metabolic pathway which results in the formation of N-methyl protoporphyrin IX. This has not been seen to occur in rats, or in hamsters and guinea pigs at significant levels or at low doses. In addition, *in vitro* investigations show that such activity is not observed in isolated human hepatocytes. There is also evidence to propose that human hepatocytes have a low haem demand compared to the mouse. Therefore, these effects in mice, do not support classification with R48 in accordance with Directive 67/548/EEC.

Comparison with criteria under CLP

A substance is classified with STOT RE under CLP when it has produced or has been shown to have the potential to produce significant toxicity in humans or be harmful to human health following repeated exposure by the oral, dermal or inhalation routes. This can be on the basis of human data or evidence from studies in animals that cause such adverse effects at or below given guidance values (≤ 10 mg/kg/day or ≤100 mg/kg/day in a 90 day oral study in the rat).

As noted above, there is no toxicological data available on tralkoxydim in humans relevant to STOT RE.

The main target organ of toxicity for tralkoxydim following oral administration to animals is the liver.

The effects in rats and hamsters occur above the relevant guidance values for classification with STOT RE.

In dogs, toxicologically significant effects (slight to marked fatty changes in the liver) were noted at 50 mg/kg/day in a 90 day study and from 5 mg/kg/day in a 1 year study. Such effects at these dose levels are considered to show that classification with STOT-RE 2 is appropriate.

In the mouse, significant liver effects were observed from 5 mg/kg/day in a number of 28 day studies. These effects included an increase in porphyrin, necrosis and hyperplasia and fibrosis of the bile ducts. Additional mechanistic studies have been conducted and it is proposed that the porphyrinogenic activity in mice following treatment with tralkoxydim is due to a species specific metabolic pathway which results in the formation of N-methyl protoporphyrin IX. This has not been seen to occur in rats or in hamsters and guinea pigs at significant levels or at low doses. In addition, *in vitro* investigations show that such activity is not observed in isolated human hepatocytes. There is also evidence to propose that human hepatocytes have a low haem demand. Therefore, these effects in mice, do not support classification with STOT-RE.

Dossier submitter's conclusion

CLP classification: STOT RE 2 – H373, 'May cause damage to organs through prolonged exposure' (DSD: Xn; R48/22)

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter to classify tralkoxydim for repeated dose toxicity (target organ liver, oral route). During public consultation, this proposal was supported by several member states but questioned by Industry. Industry considers the liver changes observed in the 90-day and 1-year dog studies not to be of sufficient adversity to warrant classification, based on the following reasoning: *"The liver effects do not appear to have any impact upon the well being of the animal and do not increase notably in magnitude when the duration of dosing is increased from 90 days to 1 year. In addition, the incidence of fatty change in the liver of male dogs at 5 mg/kg/day (moderate in 1/4 males) is of no toxicological relevance as it is not accompanied by any correlating changes in clinical chemistry, haematology or macroscopic findings and is accompanied by only a marginal increase in liver weight of <10%. Furthermore, these liver findings are confined to the dog and are not seen in the rat or hamster and those liver effects identified in the mouse are shown to be species-specific and therefore not relevant for human health hazard or risk assessment."*

RAC supports the conclusion of the dossier submitter that in the 90-day studies with rats and hamsters, (severe) effects occur only above the relevant guidance values for classification of 100 and 50 mg/kg bw/day for CLP and DSD, respectively. The same is true for the chronic studies with rats (2-year) and hamsters (79- and 80-week) where severe effects occur at 117.9–162.8 mg/kg bw/day and 700.3–672.2 mg/kg bw/day, respectively, i.e. dose levels clearly above the extrapolated guidance values of 12.5 and 6.25 mg/kg bw/day for CLP and DSD, respectively.

RAC also concluded that there is sufficient evidence that the hepatic effects observed in mice can be explained by porphyrin accumulation which is not relevant for humans; this is in line with the justification provided by the dossier submitter. No other effects relevant for classification for repeated dose toxicity were observed in the mouse.

In dogs, the liver was one of the organs affected in the 90-day and 1-year study. The hepatic effects observed in the 90-day study included increased liver weights, vacuolation of hepatocytes and fatty changes. Vacuolation of hepatocytes is considered to be directly related to the fatty changes. Fatty changes were slight (7/8 animals) to marked (1/8 animals) at 50 mg/kg/day in the 90-day dogs study.

According to CLP Annex I chapter 3.9.2.7.3 and DSD chapter 3.2.4, morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver), should be taken into consideration in the classification process.

The fatty changes observed at 50 mg/kg bw/day (the guidance value for DSD, assuming that this value for rats is also applicable to dogs) were slight to marked, so not severe. It is not likely that severe effects would have been observed at 100 mg/kg bw/day (the guidance value for CLP). Compared to the 90-day study, the effects only increased slightly in the 1-year study, where microscopic effects on the liver included fatty changes at 5 (moderate, in 1 out of 4 males) and 50 mg/kg bw/day (moderate in 1/4 females and 2/4 males, and marked in 1/4 females and 2/4 males). It is unlikely that the effects at the extrapolated guidance values for CLP and DSD (25 and 12.5 mg/kg bw/day, respectively) should be considered as severe. So, in itself, the fatty changes as observed in the liver following tralkoxydim treatment do not meet the criteria for classification.

Other effects observed in the 90-day and 1-year dog studies included reductions in red blood cell parameters and increased white blood cell counts at 50 mg/kg bw/day and increases in adrenal weights combined with multifocal vacuolation of cells in the zona fasciculate (minimal to slight in 90-day study, moderate to marked in 1-year study). In the 1-year study, the effect on the adrenals was also observed in some animals at 5 mg/kg bw/day (minimal degree). Further, changes in clinical chemistry were observed at 50 mg/kg bw/day in both studies, including reductions in albumin, total protein, cholesterol and triglyceride concentrations and increases in alkaline phosphatase and alanine transaminase activity. At 5 mg/kg bw/day, these effects were absent or much smaller.

The effects observed seem to indicate that there is an increase in fat storage in the liver with a reduction in transport of triglycerides and proteins through the blood to other organs. The increase in adrenal weight and vacuolation may be related to the decrease in cholesterol, since cholesterol is used in the adrenal cortex for the synthesis of hormones. Tralkoxydim is known to inhibit acetyl-co-carboxylase which has a function in the synthesis of fatty acids and cholesterol.

Overall, in dogs there seems to be a dysfunction of the liver with possible secondary effects on other organs like the adrenals. The effects at 5 mg/kg bw/day are not severe enough to warrant classification. The effects at 50 mg/kg bw/day constitute a borderline case for classification: in the 90-day study, this level is at or below the maximum guidance levels for CLP and DSD, but the severity of the effects is less than in the 1-year study, where 50 mg/kg bw/day is above the extrapolated maximum guidance levels for both CLP and DSD.

RAC concluded that the case is not strong enough for classification, and therefore the proposal by the dossier submitter to classify tralkoxydim with STOT RE 2 – H373 (liver)/Xn; R48/22 is not supported.

RAC conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Mutagenicity

Summary of Dossier submitter's proposal

Negative results were obtained in the available *in vitro* and *in vivo* studies. The increase in chromosome aberrations in the *in vitro* cytogenetic assay and the increase in PCE containing micronuclei in the *in vivo* bone marrow micronucleus study were small, could not be reproduced in repeated studies and were only seen at a dose level causing mortality.

Comparison with criteria
Substances known to induce heritable mutations or which are regarded as if they induce heritable mutations in the germ cells of humans are classified in Category 1A or 1B accordingly. This is based on human data or positive result from *in vivo* studies. As there are no human data classification in Cat 1A is not appropriate. As the *in vivo* studies produced negative results classification in Cat 1B is not appropriate.

Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans are classified in Category 2. This is based on positive evidence obtained from experiments in mammals and/or in some

cases from *in vitro* experiments. Tralkoxydim produced negative results in three *in vitro* and two *in vivo* studies therefore classification in Category 2 is not appropriate.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data.
Directive 67/548/EEC: No classification is justified based on available data.

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter not to classify tralkoxydim for mutagenicity. This proposal/endpoint was not specifically commented on during public consultation.

Given that, overall, tralkoxydim tested negative in three *in vitro* studies (a bacterial mutation assay, and a mammalian gene mutation and chromosomal aberration assay) and two *in vivo* studies (an UDS and micronucleus assay), RAC supported the conclusion of the dossier submitter that tralkoxydim should not be classified for mutagenicity.

RAC conclusion

CLP: No classification is justified based on the available data
Directive 67/548/EEC: No classification is justified based on the available data

Carcinogenicity

Summary of Dossier submitter's proposal

The carcinogenic potential of tralkoxydim has been investigated in rats and hamsters.

In a two year carcinogenicity study in rat, a dose related increased incidence of Leydig cell tumours was noted in male rats reaching 28.8% at 2500 ppm (corresponding to 117.9 mg/kg bw/d in males and 162.8 mg/kg bw/d in females) compared to 5.8% in controls. This was above the range seen in contemporary historical controls and no mechanistic data are available to dismiss the relevance to humans. In addition, the strain of rat used (Alpk) is not known to have a high background incidence of Leydig cell tumours. These tumours are therefore considered treatment related.

An increased incidence of brain and spinal cord astrocytoma was noted in males at 2500 ppm. These tumours are rare and, as the incidence was at the upper level observed in contemporary historical control data, it is prudent to consider that they are treatment related. However, the increase in such tumours was observed at the top dose and in male rats only.

In hamsters, a dose related increased incidence of combined benign and malignant sex cord stromal tumours in the ovaries was observed. High dose levels were used in the hamster study and there was no increase in any individual histological tumour type. However, the combined incidence is above the level seen in historical controls at the same and another UK laboratory and in published data. These tumours are therefore considered treatment related.

In short-term hamster studies tralkoxydim was shown to induce liver enzymes at high doses (17000 ppm in a 28 day study and 4000 ppm (corresponding to 240 mg/kg bw/day in males and females) in a 90 day study). At such high doses, and in the presence of liver enzyme induction, testosterone hydroxylase was also induced. Such

increases are indicative of a hormonal disturbance (induction of specific enzymes responsible for the metabolism of steroid hormones).

Comparison with criteria

In accordance with the criteria in CLP, classification in category 1A for carcinogenicity is not justified given that there is no evidence of tralkoxydim having caused cancer in humans.

On consideration of all available data, there are a number of factors which indicate that classification in Category 2 would be appropriate based on the overall level of concern. Considering the results of *in vitro* and *in vivo* studies, tralkoxydim is not considered to be genotoxic. In the hamster, the tumours are predominantly benign in nature, are predominantly unilateral (only 1 bilateral), and manifest as a wide variety of histological subtypes. The increase in brain and spinal cord astrocytomas was only observed at the top dose and in male rats only. In addition, the incidence was at the upper level observed in historical controls.

Dossier submitters conclusion

CLP: Carc. 2 – H351, Suspected of causing cancer
Directive 67/548/EEC: Carc. Cat. 3; R40

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter to classify tralkoxydim for carcinogenicity under CLP as Carc. 2 – H351 (DSD, Carc. Cat. 3; R40), based on Leydig cell tumours and brain and spinal cord astrocytomas in rats and ovarian sex cord stromal tumours in hamsters. During public consultation, this proposal was supported by several Member States and questioned by industry. Industry argued that the brain and spinal cord astrocytomas in male rats at the highest dose are unrelated to treatment, because the incidence was not significantly increased and within the historical range, known/suspected neurocarcinogens in the rat tend to be mutagenic (whereas tralkoxydim is not) and no brain or spinal cord tumours were detected in the 80-week hamster study (whereas hamsters are susceptible to neurocarcinogens).

The increased tumour incidences to be considered for classification are presented in Table 1.

Table 1.Increased tumour incidences of potential relevance for classification

	Dose (ppm **)				**Historical control incidences**
RAT 2-yr study	**0**	**50**	**500**	**2500**	
♂ Leydig cell tumours (B) - unilateral - bilateral - total	 3/52 0 3/52 (5.8%)	 4/53 1/53 5/53 (9.4%)	 6/52 0/52 6/52 (11.5%)	 9/52 6/52 15/52 (28.8%)$	 3.8-19.2%
♀ Uterine adeno-carcinoma (M)	1/51	1/52	0/53	3/52 (5.8%)	0-5.8%
♂ Astrocytoma (M) - brain	 2/52	 1/53	 2/52	 3/52	 0-5.8%

- spinal cord - total	0/52 2/52	0/53 1/53	0/52 2/52	(5.8%) 1/52 (1.9%) 4/52 (7.7%)	0-1.9% 0-7.7%
HAMSTER 80-week study	**0**	**500**	**2500**	**12000**	
♀ Sex cord stromal tumours* - B - M - total	1/49 (2%) 1/49 (2%) 2/49 (4.1%)	2/50 (4%) 2/50 (4%) 4/50 (8%)	4/48 (8.3%) 2/48 (4.2%) 6/48 (12.5%)	5/51 (9.8%) 2/51 (3.9%) 7/51 (13.7%)$^{\$}$	# 1.9-2% 0-2% 1.9-3.9%

B = benign, M = malignant; * comprising of thecal cell, granulosa cell and interstitial cell tumours; all unilateral, except for one benign tumour at 2500 ppm that was bilateral; ** corresponding to 0, 2.3, 23.1 or 117.9 mg/kg/day in males and 0, 3.0, 30.1 or 162.8 mg/kg/day in females; # from two contemporary studies from the same laboratory only; $ statistically significant.

In agreement with the dossier submitter, RAC concluded that the uterine adenocarcinomas observed in female rats at the highest dose are not to be considered related to treatment, due to their low incidence (within, yet at the upper level of the historical control range) and the lack of a dose-response relationship.

A small increase in rare brain and spinal cord astrocytomas was observed in male rats at the highest dose only. Given that this increase was not statistically significant, the incidences were within (yet at the upper level of) the historical control range and no such increase was observed in female rats or in hamsters, RAC concluded that the astrocytomas are not to be considered treatment-related (in contrast to the dossier submitter). This conclusion was also drawn by EFSA in their peer review of tralkoxydim in 2008.

The increase in Leydig cell tumours observed in male rats was dose-dependent and reached statistical significance at the highest dose, at which level the incidence was above the historical control range for the strain of rats used in the study (Alpk). Although the relevance of this type of tumours for humans is limited for certain rat strains with a high spontaneous background (such as the F344 strain), this is not the case for the Alpk strain (background incidence only 3.8-19.2%). Also, certain mechanisms of inducing Leydig cell tumours have proven to be of no relevance to humans: gonadotropin-releasing hormone (GnRH) agonists and dopamine agonists. Mechanistic information on tralkoxydim is however not available, so it is not clear whether the induction of Leydig cell tumours by tralkoxydim occurs through one of these mechanisms, or via other mechanisms that are of potential relevance to humans. RAC therefore supports the conclusion by the dossier submitter that these tumours should be considered treatment-related. This conclusion is in line with the EFSA conclusion in their peer review of tralkoxydim in 2008.

In female hamsters, a dose-related increased incidence of combined benign and malignant sex cord stromal tumours in the ovaries was observed. When looking at the individual cell types, no increase in tumour incidence was observed, and the individual incidences were within the (limited) historical control data from either the same laboratory, or another laboratory or published data. The combined incidences at 2500 and 12000 ppm (corresponding to 138.9 and 672.2 mg/kg bw/d), however, were above the level seen in historical controls, and RAC considered them to be related to treatment,

in line with the dossier submitter. In their peer review of tralkoxydim in 2008, EFSA also did not dismiss the ovarian tumours, despite industry arguing at that time that there is no basis for a treatment-related aetiology for these tumours.

The two tumour types that are considered treatment-related are mostly benign and unilateral, and occur each in one species only, at relatively high doses (especially in hamsters). Further, tralkoxydim was shown not to be mutagenic. RAC therefore considers the evidence for carcinogenicity as limited, and agrees with the proposal of the dossier submitter to classify tralkoxydim under CLP criteria as **Carc. 2 – H351** (DSD, **Carc. Cat. 3; R40**). Route specificity has not been shown.

RAC conclusion

CLP classification: Carc. 2 – H351, 'Suspected of causing cancer' (DSD, Carc. Cat. 3; R40)

Reproductive toxicity

Summary of Dossier submitter's proposal

Fertility

In a multi-generation study in rats, minor signs of parental toxicity were observed including reductions in body weight gain and food consumption. In addition, the body weight gains of the offspring were also persistently lower but overall there were no treatment related effects on the reproductive parameters.

Whilst effects in the male reproductive organs were observed in rats, hamsters and dogs in the repeated dose studies, such effects were not observed in the multigeneration study in rats and no adverse effects on fertility were noted at doses of up to 91 mg/kg/day.

In addition, whilst repeat dose studies have shown that tralkoxydim caused minor perturbations in hormone levels, no adverse effects on fertility were observed in the multigeneration study in the rat at doses of up to 91 mg/kg/day.

Development

A number of developmental toxicity studies have been conducted in both rats and rabbits. In both of the rat studies severe maternal toxicity was evident (at 200 and 300 mg/kg/day) and was accompanied by severe foetal toxicity. There was an increase in external/visceral defects including a number of foetuses with anasarca (massive body oedema) and one foetus with cleft palate in the 1st study at 300 mg/kg/day. These effects were not observed in the second study at 200 mg/kg/day. An increase in major skeletal defects were noted in both studies at 300 mg/kg/day and 200 mg/kg/day including misshapen and fused vertebrae along with a high incidence of minor skeletal variations. The effects seen at 200 and 300 mg/kg/day can be considered to have occurred due to the toxicity of the substance at these levels and are not a developmental effect. There was a single incidence of misshapen sacral vertebrae (2nd and 3rd vertebrae) at 30 mg/kg/day in the 1st study and at 3 mg/kg/day in the 2nd study. This is a rare effect, as demonstrated by the historical control data. However, there are inconsistent results in the two studies (the effect was observed at 30 mg/kg/day but not at 3 mg/kg/day in the 1st study whereas in the 2nd study it was found to occur at 3 mg/kg/day) and there is some evidence of foetal toxicity at 30 mg/kg/day (evidenced by reduced ossification and the increased incidence of short ribs).

In the rabbit severe maternal toxicity was evident at 100 mg/kg/day. There was no clear evidence of any developmental effects.

Comparison with criteria

Fertility

As no human data are available classification in Category 1A is not appropriate. Classification in Category 1B is based on clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. Classification in Category 2 is appropriate when the evidence is not sufficiently convincing to place the substance in Category 1.

Whilst effects on the male reproductive organs were observed in repeat dose studies such effects were not noted in a multigeneration study and there was no effect on any of the fertility parameters. Therefore, no classification for fertility is proposed.

Development

The effects seen at 200 and 300 mg/kg/day can be considered to have occurred due to the toxicity of the substance at these levels and are not a developmental effect. There was a single incidence of misshapen sacral vertebrae (2nd and 3rd vertebrae) at 30 mg/kg/day in the 1st study and at 3 mg/kg/day in the 2nd study. This is a rare effect, as demonstrated by the historical control data. However, there are inconsistent results in the two studies (the effect was observed at 30 mg/kg/day but not at 3 mg/kg/day in the 1st study whereas in the 2nd study it was found to occur at 3 mg/kg/day) and there is some evidence of foetal toxicity at 30 mg/kg/day (evidenced by reduced ossification and the increased incidence of short ribs). In conclusion, this effect observed in one foetus, at different dose levels in different studies, is not considered to support classification for developmental toxicity in accordance with the criteria.

No classification is proposed in accordance with Directive 67/548/EEC following the same reasoning.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data.
DSD: No classification is justified based on the available data.

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter not to classify tralkoxydim for reproductive toxicity (nor for fertility, nor for developmental toxicity). During public consultation, this proposal was supported by some MSCAs and by Industry, but some other MSCAs suggested that classification of tralkoxydim under CLP as Repr. 2 – H361fd (DSD, Repr. Cat. 3; R62-63) should be considered, in line with the EFSA proposal in their peer review of tralkoxydim in 2008. EFSA proposed Repr. Cat. 3; R62, based on adverse effects on gonads observed in hamster, dog and rat in subchronic and chronic studies. EFSA's proposal for Repr. Cat. 3; R63 was based on post-implantation loss and malformations observed in rats and abortions and reduced litters in rabbits.

Fertility

No treatment-related effects on fertility were observed in a 3-generation study in rats at dose levels up to and including the highest dose tested of 1000 ppm (corresponding to 91 mg/kg bw/day). Microscopic examination of the reproductive organs of the small number of infertile animals revealed no histopathological findings.

In the subchronic 90-day study with rats, no effects on the reproductive organs (weights, histopathology) were observed at dose levels up to and including the highest dose tested of 2500 ppm (corresponding to 205 – 219 mg/kg bw/day). In the chronic 2-year study with rats, there was an increase in large testes with white areas at the highest dose of 2500 ppm (corresponding to 117.9 mg/kg bw/day), without accompanying effect on testicular weight. Microscopically, effects on the testes and epididymes were observed, according to table 19 of the CLH report. As this table did not present sufficient detail for evaluation, the dossier submitter upon request of RAC provided after public consultation more detailed individual data and analyses on incidences and severity of the testicular and epididymal lesions. Increased incidences of minimal to slight Leydig cell hyperplasia, minimal to marked tubular atrophy, minimal to marked reduction in numbers of spermatozoa and minimal to moderate nucleated cells in the lumen were mainly observed at 2500 ppm (see also table 2). No information was available regarding the statistical significance of these effects.

Table 2. Histopathology findings on male reproductive organs in 2-year rat study

RAT 2-yr study	0 ppm (0 mg/kg bw/day)	50 ppm (2.3 mg/kg bw/day)	500 ppm (23.1 mg/kg bw/day)	2500 ppm (117.9 mg/kg bw/day)
Total animals (intercurrent deaths and terminal kills)	52	53	52	52
EPIDIDYMES				
Reduced spermatozoa	15 (29%)	7 (13%)	13 (25%)	27 (52%)
Nucleated cells in lumen	18 (35%)	13 (25%)	11 (21%)	31 (60%)
Microcystic degeneration Epithelium	8 (15%)	5 (9%)	13 (25%)	11 (21%)
TESTIS				
Tubular atrophy	22 (42%)	15 (28%)	22 (42%)	29 (56%)
Leydig cell hyperplasia	4 (8%)	5 (9%)	4 (8%)	14 (27%)
Leydig cell tumours	3 (6%)	5 (9%)	6 (12%)	15 (29%)

The effects on testes and epididymes were observed in the presence of some systemic toxicity (in the form of effects on red and white blood cell parameters and reduced plasma cholesterol and increased total protein concentrations) and in the presence of Leydig cell tumours. Leydig cell tumours were only observed in the group with intercurrent deaths and terminal kills (i.e., after 82 weeks), increased incidences in testicular tubular atrophy or reduced spermatozoa were only apparent in animals surviving the full treatment period. Separate consideration of males with and males without Leydig cell tumours showed associations with increased incidences of reduced spermatozoa and testicular tubular atrophy in males with tumours. Males without tumours displayed a high incidence of histological effects in both control and treated males, with only a marginally increased incidence in the high dose group. It is remarked that the distinction between Leydig cell hyperplasia and tumours is difficult as the transition from hyperplasia to tumour is part of a continuous spectrum of change. The available data indicate that the increase in histological changes in the high dose group may, at least partially, be secondary to the Leydig cell hyperplasia and/or tumours, for example due to blockage of tubules. Additionally, an increase in survival of the male high dose group was observed, which might explain slight increases of (age-related) histopathological effects.

Given that treatment-related effects on male reproductive organs in rats were observed in the chronic study (at 117.9 mg/kg bw/day) in the presence of Leydig cell tumours and hyperplasia and at a time point in life at which such effects also occurred in untreated rats, that no such effects were observed in the 13-week study (up to and including 205 mg/kg bw/day) and the 3-generation study (up to and including 91 mg/kg bw/day), and that fertility was not affected in the 3-generation study, the evidence in rats is considered insufficient for classification.

In hamsters, subchronic and chronic toxicity studies showed some effects on the male reproductive organs. In the 28-day study an increase in relative testes weight (21%) was observed without histopathological changes at a very high dose of 17000 ppm. At this dose level testosterone 16α and 16β hydroxylation were also increased, an effect that was also observed in one of the two 90-day studies from 4000 ppm (corresponding to 240 mg/kg bw/day) onwards. Such an effect in itself, however, is not an effect on sexual function and fertility and therefore does not warrant classification.

In the first chronic study of 79 weeks, an increase in relative testes weight (13%) was observed together with small male reproductive organs but without microscopic changes at 7500 ppm (corresponding to 438.6 mg/kg bw/day). In the second chronic study of 80 weeks, also a small increase in testes weight (absolute 6%, relative 11%) was found (at 12000 ppm, corresponding to 700.3 mg/kg bw/d), together with an increase in testicular tubular degeneration. The latter increase was also small (21/51, as compared to an already high incidence in the control group of 16/51) and not statistically significant. Also the severity of the degeneration did not clearly increase with dose. Therefore, this effect is not considered to be induced by tralkoxydim. Given further that an increase in testes weight without microscopic changes is not considered an adverse effect on sexual function (as normally a reduction in testes weight is associated with effects on fertility), none of the effects observed on the gonads in hamsters support classification for fertility.

Also in dogs some effects on the male gonads were observed in repeated dose toxicity studies. In the 90-day study there was a significant decrease in epididymides weight (-21%) at the highest dose level of 50 mg/kg bw/day, but without histopathological changes. The testes weight was not affected at this dose, but there was a single case of slight unilateral testis seminiferous tubule atrophy. The effects were observed in the presence of more general toxicity. Testes atrophy was not seen in the 1-year study, where only minimal unilateral or bilateral tubular degeneration was observed in 0/4, 2/4, 1/4 and 1/4 dogs at 0, 0.5, 5 and 50 mg/kg bw/day, respectively. As the tubular degeneration was only minimal and without apparent dose-response relationship, it is doubtful whether this effect was induced by tralkoxydim.

In the DAR on tralkoxydim there is also a very short summary of a preliminary 6-week study in dogs, using 1 dog/sex/group at dose levels of 0, 10, 50 and 170 mg/kg bw/day. The high dose male dog showed degeneration of testicular tubular cells and absence of sperm in the epididymides. The effects were observed in the presence of more general toxicity in the form of clinical effects, effects on red blood cells, clinical chemistry changes, increased liver weights, adrenal vacuolation, accumulation of fat in the liver and other histopathological changes in the liver. As the finding is limited to one animal, this is not sufficient for classification.

Overall, RAC concluded that the effects observed on the male gonads in the available subchronic and chronic studies with rats, hamsters and dogs provide insufficient evidence for an effect of tralkoxydim on sexual function and fertility at the doses tested. Given further the absence of fertility effects in the 3-generation study in rats, RAC supported the conclusion of the dossier submitter that tralkoxydim should not be classified for fertility.

RAC conclusion

CLP: No classification is justified based on the available data.
DSD: No classification is justified based on the available data.

Developmental toxicity

For evaluation of developmental toxicity, three studies were available (two in rats, one in rabbits).

In the rat studies, the highest dose group in both studies (300 and 200 mg/kg bw/day in study 1 and 2, respectively) was clearly maternally toxic (>10% mortality, marked weight loss and poor clinical condition; at 300 also total resorption of litters, increased post-implantation loss and a reduced number of live foetuses were seen) and foetotoxic (reduced mean foetal and mean litter weights, and increased number of foetuses with external and visceral defects (at 300 only), major skeletal defects (mainly misshapen and fused vertebrae), and minor skeletal defects and variants). Based on the excessive maternal toxicity these dose levels are not further considered for evaluation for classification, as indicated by the criteria (CLP Annex I chapter 3.7.2.4.4).

Minor skeletal effects and variations were also observed at the lower (non-maternally toxic) dose levels as well as in the controls (to a lesser degree). They are considered indicative for a delayed development, but do not provide sufficient evidence for treatment-related developmental toxicity (CLP Annex I chapter 3.7.2.3.3). Major skeletal defects were also observed at non-maternally toxic dose levels, but were confined to one single incidence of misshapen centra from the 2nd and 3rd sacral vertebrae in each study (in study 1 at 30 mg/kg bw/day, in study 2 at 3 mg/kg bw/day). Whereas the misshapen and fused vertebrae at the maternally toxic doses of 200 and 300 mg/kg bw/day occurred with a clear dose-response relationship, at incidences that were clearly outside the (sporadic) historical control incidence, this is not the case at the lower dose levels of 30 and 3 mg/kg bw/day. Given further that the incidence of one foetus (with 2 vertebrae affected) at each of these doses is consistent with the (sporadic) historical control incidence, the effect is considered not treatment-related and thus not supportive of classification.

In rabbits, abortions and a reduced litter size were observed at the highest dose tested of 100 mg/kg bw/day, in the presence of marked maternal toxicity (in the form of 9 intercurrent deaths out of 18 dams). These effects are therefore considered to be secondary to the (excessive) maternal toxicity. At doses that were not maternally toxic, there was no evidence of teratogenicity. The male sex ratio was significantly decreased at 20 mg/kg bw/day compared to the control group, but was still within the historical control range. Pre-implantation loss was significantly increased at 2.5 and 20 (and 100) mg/kg bw/day (13.0 and 10.3 (and 20.9)%, respectively), but the increase was not dose-related at the lower doses and still within the historical control range (0–24.6%; the controls in the study (3.6%) were at the lower end of this range). These effects therefore do not warrant classification.

Overall, RAC concluded that the effects observed in the rat and rabbit developmental toxicity studies do not warrant classification, and thus supported the conclusion of the dossier submitter that tralkoxydim should not be classified for developmental toxicity.

RAC conclusion
CLP: No classification is justified based on the available data.
DSD: No classification is justified based on the available data.

HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Summary of Dossier submitter's proposal

Tralkoxydim is not highly flammable and does not liberate gases in hazardous amounts in contact with water or air. It does not contain any groups indicative of explosive properties.
Examination of the chemical structure indicates that it does not contain any chemical groups typical of oxidising agents. Thus the substance can be regarded as incapable of reacting exothermically with a combustible material.

Tralkoxydim does not meet the criteria for classification for physico-chemical properties.

Dossier submitter's conclusion

CLP: No classification is justified based on the available data.
DSD: No classification is justified based on the available data.

RAC assessment

RAC supports the non-classification for physico-chemical properties, as proposed by the dossier submitter. This proposal/these properties was/were not specifically commented on during public consultation.

RAC conclusion

CLP: No classification is justified based on the available data.
DSD: No classification is justified based on the available data.

ENVIRONMENTAL HAZARD ASSESSMENT

Hazard to the aquatic environment

Summary of Dossier submitter's proposal

Comparison with criteria

Tralkoxydim is susceptible to hydrolysis under acidic conditions but hydrolytically stable under alkaline conditions. Under neutral to alkaline conditions, considered representative of the majority of European aquatic systems, and an environmentally relevant temperature (12°C), tralkoxydim is considered to have a DT_{50} of 396 days. This means tralkoxydim is considered hydrolytically stable for the purpose of classification.

Tralkoxydim is susceptible to direct photodegradation in pure water under acidic conditions. However, under conditions most closely representative of European conditions, at pH 7 a DT_{50} of 490 days was calculated. This means tralkoxydim is not considered to meet the criteria of 70 % degradation within 28 days.
The simulation study shows that tralkoxydim dissipates in the aquatic environment and undergoes primary degradation to a certain extent. However, the study DT_{50} values mean that tralkoxydim does not meet the criteria of 70 % degradation in the aquatic environment within 28 days.

Based on the above information, tralkoxydim is not considered to undergo rapid and ultimate degradation under environmental conditions and is considered not rapidly degradable for the purpose of classification and labelling (>70 % mineralisation in the aquatic environment within 28 days).

The log K_{ow} of tralkoxydim is anticipated to decrease with increasing pH. This mirrors the increase in water solubility with increased pH given that the dissociated form of tralkoxydim will increase with increasing pH. The highest measured log K_{ow} value of 2.1 at an assumed pH of 7 is less than 3 indicating a limited bioaccumulation potential. Based on a fish bioconcentration study the following BCF_{fish} values were determined: whole fish BCF_{fish} 32; muscle BCF_{fish} 13; and, viscera BCF_{fish} 185. Considering the whole fish BCF_{fish} value for the purpose of classification and labelling, tralkoxydim is not considered bioaccumulative under the Directive 67/548/EEC criteria of >100, and not bioaccumulative under Regulation EC No. 1272/2008 criteria of >500.

Tralkoxydim is used as a herbicide to control weeds. Reflecting this, the most sensitive trophic level appears to be aquatic plants. In a 14-day growth inhibition study using *Lemna gibba* the 14-day EC_{50} based on frond number was 2.6 mg a.s./l (95 % C. I. 2.3 – 2.9 mg a.s./l). The 14-day $NOE_{frond\ no}C$ was 0.58 mg a.s./l. This means the lowest $L(E)C_{50}$ for tralkoxydim is considered to be 1 mg/l $<L(E)C_{50} \leq 10$ mg/l.

Following the recent 2nd ATP in Commission Regulation (EU) No 286/2011 the lowest available NOEC for consideration of chronic toxicity is 0.58 mg active substance/l and therefore in the range >0.1 to ≤1mg/l.

Based on acute toxicity data, tralkoxydim is not acutely toxic to fish or Daphnia (representative of invertebrates/crustacea). One algal growth inhibition study shows tralkoxydim is not toxic to *Ananaena flos-aquae* (blue green algae). Two algal growth inhibition studies are available for *Pseudokirchneriella subcapitata* (green alga formerly *Selenastrum capricornutum*). The first quotes a 96 hour E_rC_{50} of >5.1 mg/l based on the highest exposure concentration. The second with an extended exposure concentration range (considered within solubility given the likely pH range), quotes a 96 hour E_rC_{50} of 20 mg a.s./l with a LOE_rC above the previous study exposure range. This indicates that at an environmentally relevant pH, with increased solubility due to ionisation, tralkoxydim is toxic to algae within the range 10 mg/l $<L(E)C_{50} \leq 100$ mg/l.

Dossier submitter's conclusion

CLP classification: Aquatic Chronic 2 - H411, Toxic to aquatic life with long lasting effects
As the substance is not considered Aquatic Acute 1 or Aquatic Chronic 1, an M factor of 1 is not applicable. (DSD: N; R51/53)

RAC assessment

The evaluation by RAC relates to the proposal of the dossier submitter to classify tralkoxydim for aquatic chronic toxicity with Aquatic Chronic 2 – H411 (CLP) or N; R51-53 (DSD), based on the results of an aquatic toxicity test with *Lemna gibba* (14-d EC_{50} = 2.6 mg/l and NOEC = 0.58 mg/l, based on frond number) and the substance being not rapidly degradable and having low potential to bioaccumulate (BCF < 500). The classification proposal was supported during public consultation.
Tralkoxydim does not fulfil the criteria for rapid degradability of > 70% degradation in 28 days, given the results of simulation tests using media from two natural water/sediment systems, indicating a DT_{50} of 60.1–161.3 days. Abiotic studies on hydrolysis also support the overall evidence that the substance does not rapidly degrade. Based on this information, RAC agrees with the dossier submitter that tralkoxydim is not considered to

undergo rapid and ultimate degradation under environmental conditions and can be considered not rapidly degradable for the purpose of classification and labelling.

Tralkoxydim does not bioaccumulate significantly, given a log K_{ow} of 2.1 and BCF for whole fish of 32. It does not fulfil the criteria for bioaccumulation (with triggers for BCF of 500 and 100 under CLP and DSD, respectively).

Tralkoxydim is not acutely toxic to invertebrates with a 48h-EC_{50} value of > 175 mg/l. The lowest toxicity values for the remaining species are 96h-LC_{50} of > 6.1 mg/l in fish, 96h-E_rC_{50} of > 5.1 mg/l in algae and a 14-day-EC_{50} of 2.6 mg/l to aquatic plants. The lowest toxicity values in chronic studies were a 21-day NOEC of 2.1 mg/l to *Daphnia,* a 28-d NOEC to fish of 4.6 mg/l, a 96-h NOEC to algae of 5.1 mg/l and 14-day NOE_rC to the aquatic plants *Lemna gibba* of 0.58 mg/l. According to the CLP Regulation the aquatic plant growth tests are normally considered as chronic tests but the EC_{50}s are treated as acute values for classification purposes.

According to OECD guideline 221 (*Lemna* sp. Growth Inhibition Test), a 7-day exposure is recommended for classification purposes in case *Lemna* spp is the most sensitive species. For tralkoxydim, however, only a 14-day EC_{50} and NOEC are available from the *Lemna* study. Since no 7-day EC_{50} and NOEC can be calculated, RAC considers the dossier submitter's proposal to use the 14-day EC_{50} and NOEC values acceptable.

Conclusion - CLP

In aquatic toxicity studies, the lowest EC_{50} values for algae and aquatic plants and LC_{50} value for fish were obtained at concentrations in the range of 1 – 10 mg/l. As these values are above the classification threshold of 1 mg/l for Aquatic Acute 1 – H400, tralkoxydim does not need to be classified for acute aquatic toxicity. The lowest chronic toxicity value of 0.58 mg/l is obtained for aquatic plants. Tralkoxydim is not rapidly degradable. Tralkoxydim therefore fulfils the criteria for classification as **Aquatic Chronic 2 – H411** (for chronic values between 0.1 and 1 mg/l). The assignment of an M-factor is not applicable for this category.

Conclusion - DSD

In aquatic toxicity studies, the lowest EC_{50} values for algae and aquatic plants and LC_{50} value for fish were obtained at concentrations in the range of 1 – 10 mg/l, i.e. the classification range for 'toxic'. Tralkoxydim is not readily degradable. Tralkoxydim therefore fulfils the criteria for classification with **N; R51/53**. The following concentrations limits apply: N; R51/53: C ≥ 25%, R52/53: 2.5% ≤ C < 25%

RAC conclusion

CLP: Aquatic Chronic 2 - H411, Toxic to aquatic life with long lasting effects (no M-factor), (DSD, N; R51/53, SCLs as specified above)

ANNEXES:

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