Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of
Tebufenpyrad

EC Number: n.a.

CAS Number: 119168-77-3

ECHA/RAC/CLH-O-0000001794-68-03/F

Adopted

9 March 2012

9 March 2012
ECHA/RAC/CLH-O-0000001794-68-03/F

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: **Tebufenpyrad**

EC Number: **n.a.**

CAS Number: **119168-77-3**

The proposal was submitted by **Germany**
and received by RAC on **29 July 2011**

The proposed harmonised classification

	CLP 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	Acute Tox. 3 (H301) Acute Tox. 4 (H332) Skin Sens. 1B (H317) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410) M (acute) = 10 M (chronic) = 10	Xn, R20/22 R43 N R50/53 N; R50/53: C ≥ 2.5 % N; R51/53: 0.25 % ≤ C < 2.5 % R52/53: 0.025 % ≤ C < 0.25 %
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Acute Tox. 3 (H301) Acute Tox. 4 (H332) Skin Sens. 1B (H317) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410) M (acute) = 10 M (chronic) = 10	Xn, R20/22 R43 N, R50/53 N; R50/53: C ≥ 2.5 % N; R51/53: 0.25 % ≤ C < 2.5 % R52/53: 0.025 % ≤ C < 0.25 %

PROCESS FOR ADOPTION OF THE OPINION

Germany 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on **29 July 2011**. Parties concerned and MSCAs were invited to submit comments and contributions by **12 September 2011.**

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Andrew Smith**
Co-rapporteur, appointed by RAC: **Stephen Dungey**

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 **9 March 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 opinion of RAC was adopted by **consensus*.***

OPINION OF RAC

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

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

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
n/a	Tebufenpyrad (ISO); N-(4-tert-butylbenzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide	-	119168-77-3	Acute Tox. 3 Acute Tox. 4 Skin Sens. 1B STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H301 H332 H317 H372 (Gastro-intestinal tract, Oral) H400 H410	GHS06 GHS09 Dgr.	H301 H332 H317 H372 (Gastro-intestinal tract, Oral) H410	-	M (acute) = 10 M (chronic) = 10	-

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
n/a	Tebufenpyrad (ISO); N-(4-tert-butylbenzyl)-4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide	-	119168-77-3	Xn; R20/22 R43 N; R50/53	Xn, N R: 20/22-43-50/53 S: (2)- 24-37-46-60-61	N; R50/53: C ≥ 2.5 % N; R51/53: 0.25 % ≤ C < 2.5 % R52/53: 0.025 % ≤ C < 0.25 %	-

SCIENTIFIC GROUNDS FOR THE OPINION

This opinion on harmonised classification and labelling relates to all hazard classes. Unless otherwise specified, the following endpoint evaluations by RAC relate specifically to the proposal of the Dossier Submitter.

HUMAN HEALTH HAZARD ASSESSMENT

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

Summary of Dossier Submitter's proposal

The Dossier Submitter proposed classification as Acute Tox 3 (H301) (Toxic if swallowed) and Acute Tox. 4 (H332) (Harmful if inhaled) according to the CLP Regulation. The classification proposed according to DSD is Xn; R20/22 (Harmful by inhalation and if swallowed). No classification was proposed for dermal exposure or STOT SE.

The dossier presented data from four acute toxicity studies in rat: two oral, one dermal and one inhalation.

Comments received during public consultation

Two Member State competent authorities responded during the public consultation, both indicating that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

RAC agrees with the Dossier Submitter that classification is required both for acute oral and inhalational toxicity. The available data show that the lowest LD50 values were for male F344 and male Sprague-Dawley rats, falling in the range 200-320 mg/kg/day. These findings support classification with Acute Tox 3 (H301) and Xn; R22, in accordance with the relevant criteria. The LC_{50} of 2.7 mg/l, in male "CD" rats, supports classification with Acute Tox 4 (H332) and Xn; R20. As there was no mortality observed in a rat dermal study at the limit dose, no classification for this route of exposure is required.

Based on the available data, tebufenpyrad does not meet the criteria for STOT-SE classification.

In conclusion, RAC proposes the following classification:

- Acute Tox. 3 (H301; "Toxic if swallowed") according to the CLP Regulation
- Acute Tox. 4 (H332; "Harmful if inhaled") according to the CLP Regulation
- Xn; R20/22 ("Harmful by inhalation and if swallowed") according to DSD

Irritation/Corrosion

Summary of Dossier Submitter's proposal

No classification was proposed for corrosion or irritation. Tebufenpyrad proved non-irritant in one rabbit skin irritation study (OECD 404) and there is no evidence of skin irritation in humans. Tebufenpyrad proved mildly irritant to the eye in a rabbit eye

irritation study (OECD 405). However, there were only very slight eye reactions and all alterations proved reversible within 72 hours after application. No adverse findings were reported in man. No clear macroscopical signs of respiratory irritation were observed in the acute inhalation study.

Comments received during public consultation

Two Member State competent authorities responded during the public consultation, both indicating that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

RAC agrees that the results of the available skin and eye irritation tests, and from all the other available toxicity studies, indicate no classification is required for irritation or corrosion.

Sensitisation

Summary of Dossier Submitter's proposal

The Dossier Submitter reported two studies for skin sensitisation in Guinea pigs. One positive Magnusson and Kligman maximisation test (OECD 406) and one negative Buehler test (OECD 407). The positive findings in the more rigorous maximisation test should overwhelm the negative outcome of the Buehler test, according to the Dossier Submitter. The classification proposed was therefore Skin Sens. 1B (H317) (May cause an allergic reaction) (CLP) and R43 (May cause skin sensitisation by skin contact) (DSD).

No relevant data were available for respiratory sensitisation.

Comments received during public consultation

Two member state competent authorities responded during the public consultation, both indicating simply that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

RAC agrees that the maximisation test is the more rigorous of the two studies available and that the positive results found justify classification.

The Dossier Submitter has reported that an intradermal dose of 1% tebufenpyrad in the maximisation test produced positive responses in 53% (10/19) and 74% (14/19) of animals challenged at concentrations of 10% and 50% tebufenpyrad, respectively. This provides an indication of potency that can be used to classify tebufenpyrad according to the revised criteria in the 2nd Adaptation to technical and scientific progress of the CLP Regulation (Regulation 286/2011).

For an intradermal induction with 1% test substance: a positive result in ≥ 60% of animals in a maximisation test leads to a category 1A classification, whereas a positive result in ≥ 30% (but less than 60%) of animals leads to category 1B. Since these criteria set no limits for the challenge dose applied in a maximisation test, it could be argued strictly that the observation of 74% sensitised animals at a challenge concentration of

50% tebufenpyrad indicates classification in 1A. However, the criteria further describe a weight of evidence approach for this sub-categorisation. Given the finding of moderate potency at a 10% challenge concentration in the maximisation test, and a clear negative result at 10% and 50% challenge in the Buehler test reported by the Dossier Submitter, the overall weight of evidence favours classification in 1B.

In conclusion, RAC agrees with the Dossier Submitter that classification for skin sensitisation is required. RAC further agrees that

- According to the CLP Regulation and taking into account the 2nd ATP, a category 1B classification and the hazard statement H317 ("May cause an allergic skin reaction") are appropriate, and that
- According to DSD, R43 ("May cause sensitisation by skin contact") is appropriate.

Specific Target Organ Toxicity (STOT-RE)/Repeated dose toxicity

Summary of Dossier Submitter's proposal

The dossier reported several repeated dose studies conducted with tebufenpyrad in rats, mice, rabbits and dogs. Effects on bodyweight and food consumption were observed after oral administration in rat, dog and mouse and after dermal administration in rabbits. While in rats and mice the liver was the main target organ, gastrointestinal effects and lesions were predominant in dogs. The lowest NOAEL was obtained in rats (0.7 mg/kg bw/day) whereas in dogs an overall NOAEL of 2 mg/kg bw/day was derived. Thus, toxicity was in the same magnitude in rats and dogs. Mice appeared less vulnerable.

In dogs, findings at LOAELs of 6 or 10 mg/kg bw/day were rather unspecific and in mice, effects were generally weak and confined to rather high dose levels.

Although the NOAELs/LOAELs in the short-term toxicity studies in rats and dogs (duration between 28 days and one year) were rather low, the Dossier Submitter concluded that the effects do not support any classification. Liver weight increase was more likely an adaptive than a true toxic effect. Following the recovery phase, absolute liver weight in the previously treated male and female groups was virtually the same as in the controls. Alterations in clinical chemistry and haematological parameters were minor and apparently did not result in functional changes. Furthermore, these effects proved reversible. Histopathological liver findings were confined to slight hepatocyte hypertrophy. More severe effects such as necrosis, fibrosis or fatty degeneration were not seen.

The Dossier Submitter concluded that no classification is required for repeated dose toxicity or specific target organ toxicity.

Comments received during public consultation

Two Member State competent authorities responded during the public consultation, both indicating that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

Tebufenpyrad has been tested for repeated dose toxicity by the oral route in rats, mice and dogs, and in a dermal study in rabbits. Following oral dosing, there were changes in a variety of organs in rats, mice and dogs (see background Document). However, the most significant findings related to the liver in rats and mice, and the gastro-intestinal

tract in dogs. The key findings are summarised in the following table (more substantial details provided by the Dossier Submitter are available in the Background Document).

Study design	**Doses mg/kg/d**	**Severe effects at doses relevant for classification**	**Other significant adverse effects at doses relevant for classification**
Studies involving oral exposure			
Rat, developmental toxicity study, gavage	0, 15, 50 and 150 mg/kg/day	Increased mortality at 150 mg/kg	Clinical signs at 150 mg/kg included loose stools (possible indicator of toxicity to gastro-intestinal tract)
Rat, developmental toxicity study, gavage	0, 15, 50 and 90 mg/kg/day	None	Reduced body weight gain at 50 and 90 mg/kg
Rat, 28-day, diet	Approx. 0, 3,11 and 60 mg/kg/day	None	Increased liver weight associated with clinical chemistry (increased albumin, alkaline phosphatise and higher total protein, decreased globulin). Two rats with dark coloured liver (top dose).
Mouse, 28-day, diet	Approx. 0, 5, 15, 40/55, 130/160 or 380/425 mg/kg/day, males/females	None	Increased liver weight and associated clinical chemistry at 130/160 mg/kg.
Dog, 28-day, capsule	0, 6, 20, 60, 200 mg/kg/day	**Gastro-intestinal tract irritation at all doses; Increased mortality and body weight loss at 200 mg/kg only**	None
Rat, 90-day, diet (with 4-week recovery)	Approx. 0, 0.7, 7 and 30 mg/kg/day	None	Increased liver weight at 7 and 30 mg/kg associated with minor clinical chemistry changes and no significant macroscopical or histopathalogical findings. Effects were reversible.
Mouse, 90-day, diet (with 4-week recovery)	Approx. 0, 5, 40/50, or 175/210 mg/kg, male/females	None	Increased liver weight and associated clinical chemistry at 175/210 mg/kg.
Dog, 90-day, capsule	0, 1, 3, 6 mg/kg/day		No treatment-related adverse

			effects in this study
Dog, 90-day, capsule	0, 2, 10, 20 mg/kg/day	Gastro-intestinal tract irritation at 10 and 20 mg/kg	Reduced body weight gain
Dog, 12 month, capsule	0, 1, 6, 20 mg/kg/day	Gastro-intestinal tract irritation at 6 and 20 mg/kg.	Reduced body weight gain
Study involving dermal exposure			
Rabbit, 21-day,	0, 40, 200, 1000 mg/kg/day	None	None

Effects on the liver
Although adverse effects were seen in the livers of rats and mice following repeated oral dosing with tebufenpyrad, they were limited to an increase in liver weight and associated changes in clinical chemistry. These effects were only seen at the higher doses studied and were found to be reversible. RAC agrees with the Dossier Submitter that these were probably adaptive changes in response to tebufenpyrad exposure.

Effects on the gastro-intestinal tract
In dogs only, signs of gastro-intestinal tract irritation were observed at relatively low doses of tebufenpyrad (6 mg/kg/day and above after 28 days; 10 and 20 mg/kg after 90 days; 6 and 20 mg/kg after 1 year). According to the summary provided by the Dossier Submitter, the findings appear to have been most severe in the 28-day study, at the highest dose of 200 mg/kg, where increased mortality and "stomach erosion" were evident. There was focal mucosal congestion in the stomach and intestines after 90 days at lower doses. Clinical observations included increased incidences of vomiting and loose/stool/diarrhoea amongst treated dogs.

In rats, there were no similar observations of an effect on the gastro-intestinal tract. However, at the highest dose for which data are available (150 mg/kg/day, dosing of pregnant dams by gavage in a developmental toxicity study), there was increased mortality together with clinical signs that included loose stools. No such findings were seen in other studies, but these were conducted with lower doses of tebufenpyrad

Comparison with criteria

The findings in rats and mice were not sufficiently severe to justify classification, the liver effects being indicative of an adaptive response to tebufenpyrad. However, in contrast to the view of the Dossier Submitter, RAC can see an argument for classification based on the findings in dogs.

The increased mortality, body weight loss and severe effects on the gastro-intestinal tract seen in dogs after oral dosing for 28-days with 200 mg/kg/day tebufenpyrad justify classification in Category 2 for specific target organ toxicity (STOT RE; CLP). Tebufenpyrad does appear to be irritant to the skin or eyes (see above) and therefore the effects seen in the dog can be regarded as being specific to the gastro-intestinal tract. They could occur in humans. According to the criteria, classification is possible when increased morbidity or death and significant organ damage are seen below 300 mg/kg in such a study. The less severe findings seen at 10 and 20 mg/kg following 90 days of treatment with tebufenpyrad further support this classification (criteria: 90 day study; severe effects in the dose range 10-100 mg/kg can justify classification).

Under DSD, the equivalent classification cut-off recommended for effects in a 28-day study is 150 mg/kg; the severe effects reported in the 28-day dog study were seen above this cut-off value. There were less severe effects, with no increased mortality, in

both the 28-day and 90-day studies. RAC agrees with the Dossier Submitter that these observations do not justify classification.

Given the nature of the gastro-intestinal effects seen after oral treatment, RAC anticipates that they would not occur following either repeated inhalational or dermal exposure.

The observation of increased maternal mortality and clinical signs including loose stools at 150 mg/kg tebufenpyrad in a rat developmental toxicity study adds support to this case for classification for effects on the gastro-intestinal tract.

There were no data available to indicate a classification for repeated dose toxicity after either dermal or inhalation exposure. The treatment-related changes seen in the 21-day dermal study in rabbits were not sufficiently severe to justify classification.

In conclusion, RAC proposes the following classification:
STOT RE 2 (H373; "May cause damage to the gastro-intestinal tract through prolonged or repeated oral exposure").

Mutagenicity

Summary of Dossier Submitter's proposal

Tebufenpyrad proved negative for gene mutations in bacteria and mammalian cells *in vitro*. The substance did not interact with the DNA in rat hepatocytes as demonstrated by negative UDS assays both *in vitro* and *in vivo*. These findings are of particular importance because they suggest a non-genotoxic mechanism for the liver tumours that were observed in the long-term study in rats (see below). The described weak clastogenic potential *in vitro* was considered to be of no toxicological relevance because it was not confirmed in the *in vivo* micronucleus test that is generally considered a suitable study type to further investigate chromosome aberrations found *in vitro*. Although there was no evidence of bone marrow toxicity in this assay (such as a skewed numeric ratio between polychromatic and normochromatic cells), it can be reasonably assumed that the bone marrow was actually reached by the test substance because residual concentrations of tebufenpyrad or its metabolites were found in bone in the ADME study (Hallifax, 1992, TOX93-00414). Thus, based on the weight of evidence, the Dossier Submitter concluded that tebufenpyrad is devoid of a genotoxic potential *in vivo* that could involve a risk for humans.

Comments received during public consultation

Two member state competent authorities responded during the public consultation, both indicating simply that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

Although tebufenpyrad induced chromosome aberrations in cultures of human lymphocytes, both a mouse bone marrow micronucleus test and a rat liver UDS test gave clearly negative results. Accordingly, RAC agrees with the Dossier Submitter that no classification for mutagenicity is required.

Carcinogenicity

Summary of Dossier Submitter's proposal

The CLH report contains two carcinogenicity studies, a 2-year feeding study in rat and an 18-month feeding study in mice. A possible carcinogenic effect of tebufenpyrad was confined to male rats. Benign liver tumours were observed in old rats after long-lasting dietary exposure at dose levels close to or clearly above the maximum tolerated dose (MTD). Interpretation of these findings is difficult because the tumour rate was still inside the historical control range. Even if a true carcinogenic effect at high doses is assumed, there is rather convincing evidence that the tumours were due to peroxisome proliferation. In female rats, incidences of uterus adenocarcinomas were slightly increased and pituitary adenoma were increased in the high dose group, when compared to concurrent controls. However, the incidences were within the historical control range of the testing facility. Hence these two findings were not considered an indication for a carcinogenic hazard.

The Dossier Submitter argued that a clear-cut carcinogenic effect had not been demonstrated. The incidence of liver cell adenoma in male rats was still in the historical control range and according to CLP criteria, no classification should be made for substances that cause liver tumours in rodents and of which peroxisome proliferation is the mode of action. No classification was proposed.

Comments received during public consultation

Two member state competent authorities responded during the public consultation, both indicating that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

Repeated dietary exposure of mice to tebufenpyrad for 18-months produced no evidence of carcinogenicity. In rats, in the only available study, there were slightly increased incidences of several tumour types compared to concurrent controls. However, as discussed below, RAC is of the view that these findings are not indicative of a carcinogenic response to tebufenpyrad and therefore agrees with the Dossier Submitter that no classification is justified.

Benign liver tumours in male F344 rats
The Dossier Submitter has indicated that a slight increase in liver cell adenoma was seen at dietary exposures that also caused an increased liver weight and hepatocellular hypertophy, along with a marked reduction in overall body weight gain (by 8-12% compared to controls). The incidence of adenoma in males was 0/55, 0/55, 0/55, 4/54 and 10/55 at doses equivalent to 0, 0.2, 5, 20, 150 and 300 mg/kg/day tebufenpyrad, respectively. There were 4 unscheduled deaths at the top dose, occurring late in the study. The incidence of about 18% at the top dose was comparable to the historical control range for this tumour type of 20%.

There were also small increases in benign liver cell tumours in females, but there was no clear dose-response: 0/55, 2/55, 0/55, 5/5 and 3/55 at approx. 0, 0.3, 1.0, 8.1 and 17 mg/kg/day tebufenpyrad.

Mechanistic studies have shown that short-term dietary exposure to doses of tebufenpyrad similar to those associated with the increased liver tumours in males produced increased palmitoyl CoA oxidase activity in female F344 rats (males were not investigated, but there is no reason to anticipate a sex-specific response). At these

doses, there were increases in liver weight and hepatocellular hypertrophy, together with a marked proliferation of cytoplasmic peroxisomes.

In another mechanistic study, repeated dietary exposure of N-nitrosodiethylamine-dosed male rats to tebufenpyrad did not produce an increase in hepatic glutathione S-transferase positive foci after partial hepatectomy. In contrast, there was an increased incidence of these foci in similar rats exposed to the rat liver tumour promoter, phenobarbital. The authors of this study suggested that the findings show tebufenpyrad to be devoid of promoting activity in the liver.

In conclusion, RAC concludes it to be unlikely the slightly increased incidence of liver cell adenomas in male rats was associated with exposure to tebufenpyrad; it was within the historical control incidence range. Furthermore, these benign tumours only occurred significantly at the highest dose, along with significantly reduced body weight gain, increased liver weight and hepatocellular hypertrophy, and there was no such increase in females. Given the negative findings in standard *in vivo* tests for mutagenicity/genotoxicity, RAC concludes that the liver tumours must have occurred by a non-genotoxic mode of action. Overall, RAC considers the weight of evidence to be insufficient to justify classification.

The Dossier Submitter argued that if tebufenpyrad treatment of rats had induced any of the benign liver tumours, this would most likely have been a consequence of peroxisome proliferation (and would therefore be of no relevance to humans). Whilst such a mechanism of action is a possibility, it remains unproven in this instance, and RAC considers the available data to be insufficient to conclude that tebufenpyrad is carcinogenic to the rodent liver.

Pituitary tumours in female F344 rats
An increased incidence of pituitary adenoma was seen in the highest dose group of female rats (23/55, compared to 15/53, 16/54, 10/53 and 11/54 in the other dose groups). There were also a small number of pituitary carcinomas seen, but these were not dose-related (1/53, 0/54, 3/53, 2/54 and 2/54). As the historical control range for the benign tumours was 22.9-61.7% in females, these tumour findings appear unrelated to tebufenpyrad.

Uterine tumours in female F344 rats
An increased incidence of uterine adenocarcinoma was seen in the highest dose group of female rats (4/55, compared to 0/55, 2/55, 1/55 and 0/55 in the other dose groups). The isolated tumour findings at the lower two doses of tebufenpyrad suggest this finding was not treatment-related. The historical control incidence for female rat uterine adenocarcinoma at the testing facility was 0-9.1%, providing further evidence that the findings do not justify classification of tebufenpyrad for carcinogenicity.

In conclusion, RAC agrees with the Dossier Submitter that no classification for carcinogenicity is required.

Reproductive toxicity

Summary of Dossier Submitter's proposal

The dossier reports two fertility studies, a 2-generation rat study (OECD 416) and a 1-generation range finding study (EPA-83-4) Fertility and reproductive performance in rats were not affected by treatment with tebufenpyrad up to the highest dose levels tested. Three additional developmental studies (OECD 414 and EPA 83-3 in rats and OECD 414 in rabbits) indicated for a teratogenic potential. No classification was proposed.

Comments received during public consultation

Two member state competent authorities responded during the public consultation, both indicating that they agreed with the classification proposal. There were no other comments on the human health hazard assessment.

RAC assessment and comparison with criteria

Fertility

RAC agrees with the assessment of the Dossier Submitter. As there was no evidence of an adverse effect on fertility or reproductive performance in the available studies, no classification is justified for this endpoint.

Developmental toxicity

RAC undertook a more detailed analysis of the available data (as presented in Annex 2, section 4.11) than that provided by the Dossier Submitter.

The Appendix to Annex 1 of this document contains tabulated data from two rat developmental toxicity studies and a further study in rabbits.

In the first rat study (EPA 83-3), tebufenpyrad was administered by gavage at doses of 0, 15, 50 and 150 mg/kg/day. There were clinical signs of marked general toxicity at the highest dose, including increased mortality (4/50 dams died, compared to 0/50 in the other dose groups) and significantly reduced body weight during days 6-8 and body weight gain during days 6-16 of gestation. One dam at the highest dose presented with total resorptions, and 16 with viable foetuses. There were no total resorptions in the other dose groups. At the highest dose, there was increased post-implantation loss (especially significant as increased late resorptions: total/mean per dam: 1/0.05, 2/0.9, 1/0.05 and 11/0.65 in the respective dose groups), mean foetal body weight (significantly reduced at the highest dose: 3.28g against 3.54 g in controls) accompanied by slightly delayed ossification.

The main foetal observations in this first study were as tabulated below:

	0 mg/kg	**15 mg/kg**	**50 mg/kg**	**150 mg/kg**	**Historical control**
Foetuses/litters examined (skeletal)	***137/22***	***133/21***	***143/22***	***103/16***	***21,268***
Incomplete ossification of 3 sternabrae	15%	9%	15%	44%	1.1-23.3%
Incomplete ossification of 4 sternabrae	2%	9%	2%	20%	0-17.5%
Metacarpals/metatarsals incompletely ossified/unossified	5%	0%	2%	18%	0-14.6%
Cleft palate	0%	0%	0%	1% (n=1)	0-0.5%
Fetuses/litters examined (visceral)	***278/22***	***281/22***	***286/22***	***209/16***	***44,562***
Microphthalmia	0%	0%	0.7% (n=1)	1.9% (n=2)	0-1.3%
Diaphragmatic hernia	0	0.7	0.7	0	0-1.9%

		(n=1)	(n=1)		
Gross cardiovascular abnormality	0.7% (n=1)	0%	0%	0%	-
Retro-oesophageal oriented aortic arch	0%	0%	0%	0.9% (n=1)	0-1.0%
Subclavian artery (retro-oesophageal and hairline septal defect)	0%	0%	0%	0.9% (n=1)	0-1.2%
Kidneys displaced	0%	0%	0.7% (n=1)	1.9% (n-2)	0-1.7%

RAC considers that the increased resorption rate and the delayed development seen at 150 mg/kg tebufenpyrad to have been related to the maternal toxicity seen in this study. The study authors did not consider the small numbers of several different structural abnormalities to have been indicative of a developmental effect. Generally, the incidences were within or very close to the historical control values and, in some instances, the findings were not dose-related. Noting also the high level of maternal toxicity seen at the highest dose in this study, RAC agrees with the Dossier Submitter that the findings in this study are not indicative of developmental toxicity.

In the second rat study (OECD 414), tebufenpyrad was administered at doses of 0, 15, 50 and 90 mg/kg/day by gavage. There were no treatment-related maternal deaths in this study. However, maternal toxicity was seen at 50 and 90 mg/kg, evident as reduced body weight gain and food consumption between days 6-8 of gestation. The Dossier Submitter concluded that this study indicated a treatment-related increased incidence of the 14th pair of ribs at these maternally toxic doses. Reassuringly, there were no other signs of developmental toxicity in this study.

RAC agrees with the summary of the rabbit developmental toxicity study provided by the Dossier Submitter. There were two incidences of abortion in animals at the highest dose tested, 40 mg/kg/day. Maternal toxicity was evident from 15 mg/kg/day (no deaths; clinical signs, reduced body weight gain and food consumption). It seems most likely the maternal toxicity led to the increased abortion rate.

With this profile of findings, RAC considers that all of the findings in the 3 developmental toxicity studies were either incidental or related to maternal toxicity. As there are no other grounds for concern, RAC is of the view that any reproductive toxicity classification would be inappropriate for tebufenpyrad.

HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The public consultation produced no comments in relation to these endpoints, and RAC agreed with the conclusions presented by the Dossier Submitter: no classification was required for explosivity, flammability or oxidising potential.

ENVIRONMENTAL HAZARD ASSESSEMNT

Summary of Dossier Submitter's proposal

In accordance with the CLP Regulation, the proposal from the Dossier Submitter was to classify the substance as Aquatic acute 1 (H400) based on acute data for fish and Aquatic chronic 1 (H410) based on chronic data for Daphnia. The substance is not rapidly degradable so the proposed M-factor is 10 for both. The corresponding classification according to the DSD is N; R50-53 with SCLs of N; R50/53: C ≥ 2.5 % , N; R51/53: 0.25 % ≤ C < 2.5 %, R52/53: 0.025 % ≤ C < 0.25 % .

Comments received during public consultation

No objection to the proposed environmental classification was made during the public consultation, but two additional ecotoxicity studies were submitted by Industry (considered below), and two editorial comments were made.

RAC assessment and comparison with criteria

Degradability: Tebufenpyrad is hydrolytically stable under standard conditions at pH 5, 7 and 9. Aqueous photolysis is not expected to be significant (the experimental half-life was 180 days), and is not relevant to classification or interpretation of the ecotoxicity studies. Tebufenpyrad failed a test for ready biodegradation (0% mineralisation). Simulation tests in two aerobic water-sediment systems using radiolabelled substance indicated primary degradation and formation of non-extractable residues (reaching a maximum of 33 % applied radioactivity) over ~100 days but negligible mineralisation. Simulation and field studies with soils also failed to show significant mineralisation over a 28-day period. On this basis, tebufenpyrad does not meet the criteria for being rapidly degradable or readily biodegradable in the environment.

Bioaccumulation: The log n-octanol-water partition coefficient of tebufenpyrad is 4.93 at pH 7. An experimentally derived steady state fish bioconcentration factor (BCF) of between 750 and 800 l/kg ww was obtained after normalization to 5% lipid content. This is a worst case value, since it was based on radio-activity measurements only and will include contributions from metabolites. The BCF based on parent compound analysis was 29 – 61 l/kg ww (after normalization to 5% lipid content). This BCF does not meet the two classification criteria of 100 and 500 for purposes of classification and labelling.

Ecotoxicity: The lowest reliable ecotoxicity results were as follows (the key studies are highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	*Oncorhynchus mykiss*	96-h LC_{50} = 30 µg/l	94-d NOEC = 2.45 µg/l
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} = 46 µg/l	**21-d NOEC = 2.4 µg/l**
	Americamysis bahia	**96-h LC_{50} = 22.0 µg/l**	-
Aquatic algae and plants	*Pseudokirchneriella subcapitata*	72-h E_rC_{50} = 5200 µg/l	72-h NOEC = 54 µg/l

With the exception of the acute *Daphnia* result, all values were based on mean measured concentrations. The purity profile of the key studies complies with the specified composition in section 1, part B of the Background Document.

Classification according to CLP

Acute aquatic hazard: The lowest reliable short-term aquatic toxicity result is a 96-h LC_{50} of 0.02 mg/l for *A. bahia* based on mean measured concentrations (supported by data on fish and other invertebrates in the same range). This concentration is below the threshold value of 1 mg/l. Tebufenpyrad is therefore classifiable as Aquatic Acute 1 (H400). Since this toxicity value is in the range 0.01 – 0.1 mg/l, the M-factor (Acute) is 10.

Chronic aquatic hazard: Tebufenpyrad is considered to be neither rapidly degradable nor readily biodegradable. The lowest reliable long-term aquatic toxicity result is a 21-d NOEC of 0.0024 mg/l for *D. magna* based on mean measured concentrations. This concentration is below the threshold value of 0.1 mg/l for non-rapidly degradable substances. Tebufenpyrad is therefore classifiable as Aquatic Chronic 1 (H410). Since this toxicity value is in the range 0.001 – 0.01 mg/l, the M-factor (Chronic) is 10.

Classification according to DSD

The lack of rapid degradation or ready biodegradation and 96-h LC_{50} of 0.02 mg/l for *A. bahia* mean that tebufenpyrad fulfils the criteria for classification with N; R50-53. The following specific concentration limits are applicable:

Concentration of tebufenpyrad in the mixture, C (w/w)	**Classification of the mixture**
C ≥ 2.5%	N; R50-53
0.25% ≤ C < 2.5%	N; R51-53
0.025% ≤ C < 0.25%	R52-53

In summary, RAC agrees with the original proposal of the Dossier Submitter, although the data leading to the acute (and DSD) classification conclusion are slightly different.

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 (excl. confidential information). A revised version of the CLH report, submitted after PC, is included in Annex 2, section 2.

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