Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of
fenpyrazamine

EC Number: not assigned
CAS Number: 473798-59-3

ECHA/RAC/CLH-O-0000003187-73-01/F

Adopted
30 November 2012

30 November 2012
CLH-O-0000003187-73-01/F

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

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

Chemical Name: **fenpyrazamine**

EC Number: **not assigned**

CAS Number: **473798-59-3**

The proposal was submitted by **Austria** and received by the RAC on **25/01/2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification is:

	CLP	**DSD**
Current entry in Annex VI to CLP Regulation	No entry	No entry
Proposal by the dossier submitter for consideration by the RAC	Aquatic Chronic 2 (H411)	N, R51-53
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) as proposed by the dossier submitter	Aquatic Chronic 2 (H411)	N, R51-53

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **25/01/2012**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12/03/2012**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Stephen Dungey**
Co-rapporteur, appointed by RAC: **Urs Schlüter** (supported by **Norbert Rupprich**)

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **30 November 2012,** and the comments received are compiled in Annex 2.

The opinion of the RAC was adopted by **consensus**.

OPINION OF THE RAC

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

Classification and labelling in accordance with the CLP

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 statement Code(s)		
613-318-00-5	fenpyrazamine (ISO); S-allyl 5-amino-2-isopropyl-4-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-1-carbothioate	-	473798-59-3	Aquatic Chronic 2	H411	GHS09	H411			

Classification and labelling in accordance with the criteria of DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
613-318-00-5	fenpyrazamine (ISO); S-allyl 5-amino-2-isopropyl-4-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-1-carbothioate	-	473798-59-3	N; R51/53	N R: 51/53 S: 60-61		

SCIENTIFIC GROUNDS FOR THE OPINION

Human health hazard assessment

Acute toxicity

Summary of the Dossier submitter's proposal
The dossier submitter did not propose a classification for acute toxicity (oral, dermal, by inhalation). The proposal was based on oral, dermal and inhalation studies in rats.

Comments received during public consultation
There were no specific comments received during public consultation regarding acute toxicity.

Assessment and comparison with the classification criteria
Fenpyrazamine was tested for acute oral toxicity in female rats. There was no lethality at 2000 mg/kg (the only dose level tested). Classification for acute oral toxicity is only indicated for substances with oral LD_{50} values less than 2000 mg/kg (CLP and DSD).

Fenpyrazamine was tested for acute dermal toxicity in male and female rats. There was no lethality at 2000 mg/kg (the only dose level tested). Classification for acute dermal toxicity is only indicated for substances with dermal LD50 values less than 2000 mg/kg (CLP and DSD).

Fenpyrazamine was tested for acute inhalation toxicity in male and female rats. The test concentration of 4.84 mg/l air was reported to be the highest air-borne concentration that could technically be administered. At this air-borne concentration of 4.84 mg/l there was no mortality in exposed rats. LC50 values need to be lower than 5 mg/l air in order to classify a substance (dust) for acute inhalation toxicity (both CLP and DSD).

Based on the data available for acute toxicity, RAC concluded that for all routes of exposure specified, fenpyrazamine does not require classification for acute toxicity. This conclusion is in agreement with the dossier submitter's proposal.

Specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal
The dossier submitter did not propose a classification for specific target organ toxicity for single exposure. The proposal was based on low toxicity in acute tests in rats.

Comments received during public consultation
There were no specific comments received during public consultation regarding specific target organ toxicity for single exposure.

Assessment and comparison with the classification criteria
Acute toxicity studies by three different routes of application (oral, dermal, inhalation), as already indicated in the chapter on acute toxicity, did not induce lethality at dose levels relevant for classification. Furthermore, there were no clinical signs and no gross abnormalities at necropsy seen in any of the studies. Thus, there were no indications of specific non-lethal target organ toxicity.

In the acute inhalation study no signs of irritation of the respiratory tract were observed.

Based on the data available for acute toxicity RAC concluded that fenpyrazamine does not require classification for specific target organ toxicity (single exposure). This conclusion is in agreement with the dossier submitter's proposal.

Eye irritation skin corrosion/irritation

Summary of the Dossier submitter's proposal

The dossier submitter proposed not to classify fenpyrazamine for irritation (skin, eye) or corrosivity. The proposal was based on a skin and an eye irritation study in rabbits.

Comments received during public consultation

There were no specific comments received during public consultation regarding irritation/corrosivity.

Assessment and comparison with the classification criteria

Fenpyrazamine was tested for skin irritation in rabbits. No skin irritation reactions were observed in any animal during the observation period of 72 hours after the removal of the patches.

Fenpyrazamine was tested for eye irritation in rabbits. No effects on cornea or iris were observed. With respect to conjunctiva, the only finding was a score of 1 for redness of the conjunctiva in one animal after 24 hours. Thus, for the redness of conjunctivae, the individual mean score (based on the 24-, 48- and 72-hour values) for this animal was 0.3. The minimum individual score for conjunctival effects that triggers classification is a score of 2 under both CLP and DSD. Therefore these data do not require a classification for eye irritation.

Based on the data available, RAC concluded that fenpyrazamine does not require a classification for skin, eye, or respiratory tract corrosion/irritation. This conclusion is in agreement with the dossier submitter's proposal.

Respiratory and skin sensitisation

Summary of the Dossier submitter's proposal

The dossier submitter did not propose a classification for sensitisation (skin, respiratory). The dossier submitter's conclusion not to propose classification for sensitisation was based on a skin sensitisation study in Guinea pigs (OECD 406).

Comments received during public consultation

There were no specific comments received during public consultation regarding skin sensitisation. With regard to respiratory sensitisation there were no comments questioning the proposal not to classify fenpyrazamine for respiratory sensitisation. Some explicitly supported non-classification for respiratory sensitisation.

Assessment and comparison with the classification criteria

In a valid Guinea pig maximisation test (GPMT), 2 of the 20 test animals showed grade 1 irritation (challenge phase, both observation times). In the control group, skin reactions were not observed in any of the 10 animals. These findings are equivalent to a sensitisation rate of 10%.
Because test results from a GPMT need to exceed a 30% level of incidence, RAC concluded not to classify fenpyrazamine for skin sensitisation (CLP and DSD). This conclusion is in agreement with the dossier submitter's proposal. No data are available on respiratory sensitisation.

Based on the data available for skin and respiratory sensitisation RAC concluded that fenpyrazamine does not require a classification for the hazard class "sensitisation" (CLP and DSD). This conclusion is in agreement with the dossier submitter's proposal and the comments received during public consultation.

Specific target organ toxicity (CLP) and repeated dose toxicity (DSD) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The dossier submitter did not propose a classification for repeated dose toxicity. The proposal was based on repeated dose toxicity studies: two rat studies (90 days and 2 years), two mouse studies (90 days and 78 weeks), and two dog studies (90 days and 1 year).

Comments received during public consultation

There were no specific comments received during public consultation regarding repeated dose toxicity.

Assessment and comparison with the classification criteria

Data reporting of repeated dose toxicity (RDT) findings in the CLH dossier is essentially restricted to NOAELs and LOAELs and to a qualitative description of the adverse effects at the LOAELs (e.g. "reduced level of haemoglobin"). As a rule, there is no dose-related information on the incidence and severity of lesions. This is usually needed in order to differentiate between LOAELs and "effective doses". For classification purposes effective doses rather than LOAELs are compared with guidance values. Nevertheless, the RAC concluded that reporting of the RDT data for fenpyrazamine ialloweda conclusion to be reached on the need, or not to classify fenpyrazamine for targeted organ toxicity for repeated exposure.

For the time being, there is no agreed EU position on how to apply the guidance values for classification of tested species other than rats. The current practice of RAC is to apply the guidance values for rats to other species as well. The guidance values are based on 90-day studies. The adjustment when using studies with different exposure duration usually follows the rule that doubling of duration of exposure results in halving of the guidance values, and vice versa. For the ease of discussion RAC introduced a table containing the study-specific cut-off levels and the available relevant RDT data (especially NOAELs and LOAELs; see supplemental information – in depth analysis by RAC in the BD).

In addition to the repeated dose toxicity studies in mice, rats and dogs, here is an additional 90-day neurotoxicity study in rats. The common toxicological profile seems to be an increase in liver weight and hepatocellular hypertrophy; such effects (without any further evidence of cytotoxicity) are not considered to support RDT classification. There are some changes in blood parameters as well for which however there is only limited quantitative information. When the longer-duration studies in rats (2-years), mice (78-weeks) and dogs (52-weeks) are examined, there is no LOAEL lower than the highest guidance value calculated. For the rat and the dog, the corresponding NOAELs are equivalent to the highest guidance values; for the mice the NOAEL (78-weeks) is very much higher than the highest guidance value calculated (for details see table supplemental information – in depth analysis by RAC in the BD).

Fenpyrazamine was additionally tested for dermal toxicity (rat, 28-day study). The LOAEL of 1000 mg/kg/d which is not considered to be an effective dose (see table) is higher than the highest guidance value calculated (600 mg/kg/d).

Thus RAC concluded that the reported data from repeated dose studies do not support a RDT classification for fenpyrazamine (both CLP and DSD). This conclusion is in agreement with the dossier submitter's proposal.

Germ cell mutagenicity

Summary of the Dossier submitter's proposal

The dossier submitter did not propose a classification for mutagenicity. Three in vitro studies and one in vivo study were available and were used for assessing mutagenicity of fenpyrazamine.

Comments received during public consultation

Commenting parties, including three industry representatives and several individuals, fully agreed with the mutagenicity evaluation in the CLH report.

Assessment and comparison with the classification criteria

Fenpyrazamine was tested in the following set of mutagenicity assays:

- Bacterial assay for gene mutation (OECD 471)
- In vitro mammalian chromosome aberration test in Chinese hamster lung cells (CHL/IU) (OECD 473)
- In vitro Chinese hamster V79/HPRT locus gene mutation assay (OECD 476)
- Mouse micronucleus test (CD mice) (OECD 474)

The results of all these in vitro and in vivo mutagenicity tests have been evaluated to be negative. Thus there is no experimental evidence of a genotoxic potential of fenpyrazamine. RAC concluded that these data do not justify a classification of fenpyrazamine for mutagenicity (both CLP and DSD). This conclusion is in agreement with the dossier submitter's proposal and the comments received during public consultation.

Carcinogenicity

Summary of the Dossier submitter's proposal

The dossier submitter did not propose a classification. The evaluation is based on the results of the oral carcinogenicity studies in rodents (CD-1 mice and Wistar rats) and on Mode of Action (MoA) considerations.
Carcinogenic effects in the liver and the thyroid gland were observed in male rats, but not in female rats or female and male mice.

There was a small increase of carcinomas in male rats in follicular tissue of the thyroid gland. This increase was only observed at the highest dose level tested (3/49 versus a highest incidence of 1/50 at lower dose levels). The incidence observed was above the relevant historical control data (ranging from 0 to 4%). The dossier submitter concluded that the experimental data indicated that fenpyrazamine increased catabolism of thyroid hormones driven by increased hepatic UGT activity leading to increased TSH levels, hypertrophy and thyroid gland tumours. Referring to an agreed EU position (ECB, 1999), that was also cited in the ECHA CLP guidance p 400, version 3.0 on the (limited) human relevance of this MoA in combination with a low experimental carcinogenic potency, the dossier submitter evaluated the observed thyroid gland tumours as not relevant for classification.

The liver proved to be a second target organ for carcinogenicity in male rats. There was a small increase of liver carcinomas at the highest dose level tested (2/50 versus 0/50 at the lower dose levels). There was no increase in the incidence of adenomas (1/50 in controls and at all dose levels). The corresponding historical control incidences for liver carcinomas range between 0 and 2.8%. Based on fenpyrazamine MoA data the dossier submitter recognised evidence of a phenobarbital-like mode of action (activation of the nuclear receptor CAR) and indicated that the experimental carcinogenic potency of fenpyrazamine appeared to be lower than the corresponding potency of phenobarbital. Significantly, the dossier submitter did not consider this CAR-mediated MoA to be relevant for humans andased on this weight-of-evidence approach proposed not to classify fenpyrazamine for liver carcinogenicity.

Comments received during public consultation

Comments received during public consultation supported the dossier submitter's proposal not to classify fenpyrazamine based on the increased incidence of thyroid gland tumours in male rats. There was no comment indicating the need for classifying fenpyrazamine for carcinogenicity based on the thyroid gland tumours.
Although there was no comment received during public consultation directly requiring a carcinogenicity classification for liver tumours there were nevertheless recommendations to have a more in depth discussion on the relevance of the liver tumours observed. These comments and questions can be summarised as follows:

- Can the liver tumours (2/50) be considered a chance finding?
- Is the carcinogenic profile of fenpyrazamine similar to the corresponding profile of phenobarbital?
- Is there sufficient information to conclude that a phenobarbital-like mode of action is not relevant for humans and thus to conclude that a carcinogenicity classification for this type of tumour development is not warranted?
- What might be the role of the pregnane X receptor?

Assessment and comparison with the classification criteria

RAC considered the key data and arguments that are relevant to the proposal not to classify fenpyrazamine for carcinogenicity.

It is one of the central classification criteria (in both the CLP and DSD regulation) that the relevance of substance-related tumours observed in animal studies to humans should be considered. If there is sufficiently reliable information that a specific MoA for tumour development in rodents does not sufficiently affect humans, then a corresponding classification is not warranted. Human relevance is therefore discussed below both for the thyroid gland and liver tumours observed in male rats.

Thyroid gland tumours

RAC supports the dossier submitter's proposal that there is no justification to classify fenpyrazamine for carcinogenicity based on the thyroid gland tumours. There was only a small increase in thyroid tumours in male rats, not in female rats or mice. The thyroid gland related carcinogenicity in male rats is considered of low potency. Fenpyrazamine MoA data sufficiently indicate that there is a substance-related enhancement of thyroid hormone metabolism. Referring to a corresponding specialised expert recommendation (ECB, 1999), that was also cited in the ECHA CLP guidance (p 400, version 3.0) on the limited human relevance of specific MoA's for thyroid gland tumour development RAC supports the dossier submitter's recommendation and agrees no classification for carcinogenicity is warranted for fenpyrazamine based on the thyroid gland tumours.

Liver tumours

The RAC discussion on the carcinogenicity of fenpyrazamine focused on the putative 'phenobarbital-like' MoA and lack of relevance for humans and the dossier submitter's weight-of-evidence approach (see above).

RAC considered whether the comparison of fenpyrazamine and phenobarbital MoA for tumour formation is an acceptable approach for assessing whether fenpyrazamine should be classified for carcinogenicity: phenobarbital is an established rodent liver carcinogen while fenpyrazamine obviously is not. When comparing both substances and indicating a possibly similar mode of action (phenobarbital-like) the dossier submitter ultimately assumed that the 2 liver tumours observed in male rats had been triggered by that phenobarbital mode of action. RAC considers this comparative approach to be too uncertain and speculative to provide adequate evidence. Furthermore, RAC recognises that there is still no agreed EU position on the relevance of the phenobarbital mode of action for humans. To decide on such arguments, RAC would require an in-depth discussion of phenobarbital data (epidemiology, rodent data and mode of action). Such a discussion could not be based on the summaries in the fenpyrazamine CLH dossier. Thus RAC decided to reject the comparison of fenpyrazamine with phenobarbital and to focus the assessment on the actual fenpyrazamine carcinogenicity data instead.

For the RAC discussion of potential liver carcinogenicity, the non-neoplastic and neoplastic findings in livers of rats and mice (carcinogenicity studies) are summarised below:

Rats, male

	Control	**100 ppm**	**300 ppm**	**1200 ppm**	**2400 ppm**
Relative liver weight in %	2.34	2.38	2.38	2.44	2.85**
Hepatocyte hypertrophy minimal	-	2/50	2/50	7/50##	6/50#
Fatty change	30/50	14/50	21/50	34/50	38/50
Vacuolated foci	6/50	13/50	7/50	7/50	38/50#
Adenoma	1/50	1/50	1/50	1/50	1/50
Carcinoma	-	-	-	-	**2/50**

Historical control data for liver carcinoma range from 0 to 2.8%
Rats, female

	Control	100 ppm	300 ppm	1200 ppm	2400 ppm
Relative liver weight in %	2.64	2.59	2.58	2.55	2.90**
Hepatocyte hypertrophy minimal	1/50	2/50	1/50	7/50#	5/50
Fatty change	13/50	12/50	10/50	16/50	26/50**
Vacuolated foci	6/50	1/50	1/50	3/50	3/50
Adenoma	2/50	-	-	-	-
Carcinoma	-	-	-	-	-

Mice, male

	Control	100 ppm	1500 ppm	3000 ppm	
Relative liver weight in %	4.78	5.19	5.36	6.17**	
Hepatocyte hypertrophy	3/52	4/52	5/52	7/52	
Adenoma	4/52	5/52	9/52	5/52	
Carcinoma	-	1/52	2/52	2/52	

Historical control data for liver carcinoma range from 0 to 5.8%

Mice, female

	Control	100 ppm	2000 ppm	4000 ppm	
Relative liver weight in %	4.92	4.69	5.54	7.52**	
Hepatocyte hypertrophy	0/52	1/51	2/51	9/52##	
Adenoma	1/52	-	-	1/52	
Carcinoma	-	-	-	-	

"-" means 0/50
* P<0.05 different from control by Dunnett's test
** P<0.01 different from control by Dunnett's test
# P<0.05 different from control according to Fisher's Exact Test
P<0.01 different from control according to Fisher's Exact Test

RAC recognised the following key findings on potential liver carcinogenicity of fenpyrazamine:

- There was an increase of relative liver weight / hepatocyte hypertrophy in rats and mice (males and females) at the high doses.
- There was no toxicologically significant increase in the incidences of liver adenomas in the carcinogenicity studies in rats and mice.
- 2/50 male rats given the high dose had liver carcinomasat the high dose level. No liver carcinomas were seen in the other male rat groups or in female rats. The historical control incidences for liver carcinomas in male rats were up to 2.8%. The 4% incidence in male rats is thus just above the upper range of HCD.
- In male mice there is no dose related increase of liver adenomas or carcinomas. The highest incidence of liver carcinomas in male mice (2/52) is within the range of historical control incidences (0 to 5.8%).

The increases in relative liver weight / hepatocyte hypertrophy in the high dose groups of female rats and male and female mice were not associated with an increased incidence of liver adenomas and carcinomas. Taking this into account the slightly elevated incidence of liver carcinomas in male rats could be considered a chance finding.

Overall conclusion for carcinogenicity

RAC concluded that the slightly increased incidence of thyroid tumours in male rats should be considered species-specific and not relevant for humans. The small increase of liver carcinomas in male rats is assessed to be a chance finding. Additionally recognising that fenpyrazamine can be considered a non-genotoxic substance RAC finally concluded that the available data did not warrant a carcinogenicity classification for fenpyrazamine.

Reproductive toxicity

Summary of the Dossier submitter's proposal

The dossier submitter proposed not to classify fenpyrazamine for reproductive toxicity based on two reproductive toxicity studies in rats and one in rabbits.

Comments received during public consultation

Interested parties fully agreed with the reproductive toxicity evaluation in the CLH report.

Assessment and comparison with the classification criteria

Fenpyrazamine was tested for reproductive toxicity according to the following study guidelines:

- Two-generation reproduction toxicity study rat (OECD 416)
- Developmental toxicity study (rat) (OECD 414)
- Developmental toxicity study (rabbit) (OECD 414)

Two-generation reproduction toxicity study rat

In the 2-generation reproduction study, fenpyrazamine was administered continuously in the feed of rats. The main toxicological response in F0 and F1 adults was characterised by an increase in relative liver and thyroid weight and decreased body weight gain; these adverse effects are essentially limited to the highest dose level tested. Depending on the specific period of exposure, the reduction of body weight gain of female rats ranges from about 10 to 30%.

In the opinion of RAC there are a few reproductive effects to be specifically looked at; all these adverse effects are limited to the highest dose tested. There is some pre-implantation loss in F1 females, but not in F0 : The mean number of implantations per dam is significantly reduced from 12.6 (control) to 10.6 (highest dose) (-16%). This is the only adverse effect in the 2-gen study with relevance in the context of fertility impairment. However, this reduction of implantations is considered small, is limited to F1 females and is confined to the highest dose used where general systemic toxicity was also observed. RAC agrees with the opinion of the dossier submitter that this degree of effect at the highest dose level does not warrant classification for fertility impairment.

Post-implantation loss is increased from 9.9% in controls to 19.3% at the highest dose level (only in F1 females, not in F0 ones). RAC noted that the dossier submitter had reported that this increased incidence of post-implantation loss was within the historical control incidences; however, the corresponding historical control data were not included in the CLH report.
Pup viability was slightly reduced for F1 pups, but not for F2 pups. Body weight development of pups (of both generations) was reduced in the highest dose group in which there is a decrease of body weight gain in parental animals as well.

Developmental toxicity study in rats

Fenpyrazamine was tested in rats at dose levels of up to 500 mg/kg/d. All females survived until the scheduled sacrifice and did not show any adverse clinical signs. The corrected body weight gain was significantly reduced at the highest dose level (7.8 g versus 30.4 g of controls). The mean foetal weight was reduced from 4.9 g (controls) to 4.2 g (high dose). No visceral or skeletal malformations were observed in the study. There was an increase of visceral and skeletal

variations and delayed ossifications at the high dose level; these incidences were above historical control incidences (for details of findings see Background Document). Because of the nature of these effects (variations and delayed ossifications) and the fact that they only occur at the high dose level where also maternal toxicity is seen, these findings are not considered relevant for classification.

Developmental toxicity study in rabbits
Fenpyrazamine was tested in rabbits at dose levels up to 90 mg/kg/d. There was a high proportion of abortions/early deliveries especially at the high dose level. They are attributed to severely reduced food consumption and markedly reduced body weight in these does. Reporting of foetal findings of the rabbit developmental study is limited to summary data (foetuses with external malformation, with skeletal malformations, skeletal variations and visceral malformations). These summary data do not indicate any developmental toxicity of fenpyrazamine in rabbits.

Summary
Based on the reported data (negative results in the two developmental toxicity studies and only weak evidence of post-implantation loss in the 2-generation study), RAC concluded that there is no sufficiently convincing evidence of developmental toxicity in rats or rabbits. Based on the data of the 2-generation study in rats RAC concluded that there is no specific evidence of impaired fertility.

Thus RAC recommends not classifying fenpyrazamine for either developmental toxicity or for adverse effects on sexual function and fertility (CLP and DSD). This is in agreement with the dossier submitter's proposal and the comments received during public consultation.

Environmental hazards

Summary of the Dossier submitter's proposal
The Dossier Submitter proposed to classify the substance as Aquatic chronic 2 (CLP H411, DSD N; R51/53). The proposal is based on a long-term algal toxicity result (72-h NOEC of 0.22 mg/L) (CLP),an acute fish toxicity result (96-h LC_{50} of 5.2 mg/L) (DSD) as well as a screening test and two simulation tests concluding that the substance is not rapidly biodegradable according to CLP or readily biodegradable according to DSD..

The dossier submitter reported that the notifier Under Council Directive 91/414/EEC self-classifies the substance with R50/53 according to DSD, but provided no information about the scientific basis for this conclusion.

Comments received during public consultation
A large number of comments in support of the proposed environmental classification were made during the public consultation. The only critical comment on the proposed environmental classification concerned a suggestion to classify the substance with Aquatic acute 1, based on the biomass end point for algae and rapid photolysis leading to a possible lower effect concentration in that test. In the post public consultation response the dossier submitter did not agree with this comment since the algal NOEC based on the growth rate should be used according to CLP. RAC agrees with the dossier submitter's view since also the CLP Guidance indicates that growth rate (reproduction) is preferred to biomass as an end point. Since the results are expressed in terms of mean measured concentrations (which were in the range of 83 – 90% of nominal concentrations over the whole test duration), photolysis is not an issue. The addition of Aquatic acute 1 is therefore not appropriate on these grounds.

Assessment and comparison with the classification criteria
Degradability: Fenpyrazamine is hydrolytically stable under standard conditions at pH 4 and 7, but hydrolyses under alkaline conditions, with a half-life of 24 days at pH 9. Aqueous photolysis is rapid, with extensive breakdown after 30 days' incubation and an estimated half-life of about 1.7 days under natural summer sunlight conditions at pH 7. While photolysis is not relevant for classification purposes, it might be a factor in the interpretation of aquatic toxicity tests. Fenpyrazamine failed a test for ready biodegradation (achieving 1% mineralisation in 28 days). Simulation tests in two aerobic water-sediment systems using radio-labelled substance indicated

primary degradation and formation of non-extractable residues, with first order degradation DT_{50} values for the whole system of 18 – 68 days (geometric mean 35.5 days), and relatively little mineralisation over 100 days (3.1 – 8.5 % of applied radioactivity (AR)). Aerobic degradation in soils follows a similar pattern, with limited mineralisation after 120 days (5.2 – 8.5 % of AR) and DT_{50} values of 24 – 40 days. Based on the lack of ready biodegradation, limited mineralisation and primary degradation half-lives exceeding 16 days in an aquatic simulation study, fenpyrazamine does not meet the criteria for being rapidly degradable or readily biodegradable in the environment.

Bioaccumulation: The log n-octanol-water partition coefficient (K_{ow}) of fenpyrazamine is 3.5 at pH 7.2. The experimentally derived steady state bioconcentration factor (BCF) for the parent substance was between 8 and 9 L/kg wet weight (ww) for fish with an average lipid content of about 1.9% (w/w). This is equivalent to a BCF of up to 24 L/kg ww after normalization to a 5% lipid content.

The parent substance was extensively metabolized in fish, and the steady-state BCF based on total radio-active residues (TRR) was 283 – 289 L/kg ww (equivalent to a BCF of up to 760 L/kg ww after normalization to a 5% lipid content). The major residues were the metabolite S-2188-DC and its glucuronic acid conjugate (at concentrations in whole fish of 8.0 – 18.8% and 16.1 – 33.3 % TRR, respectively). More than 95% of the ^{14}C residues were eliminated during the depuration phase (within 14 days), and the depuration half-life was less than one day.

S-2188-DC is also one of the main products of photolysis, alkaline hydrolysis and mammalian metabolism. It forms through loss of the *S*-2-propen-1-yl carbothioic-acid ester group from the parent substance. No data are presented about the aquatic degradability of S-2188-DC (too few data were available in the water-sediment study to estimate a DT_{50}). The DAR[2] indicates that its log K_{ow} is 0.23 (estimated using KOWWIN, version not stated). It is not stated whether this substance falls within the applicability domain of the model, but it appears to have a lower bioaccumulation potential than the parent. Aquatic acute toxicity tests for fish, *Daphnia* and algae are summarised in the DAR, and it is an order of magnitude less acutely toxic than the parent substance (all acute $L(E)C_{50}$s were above 82 mg/L; the 72-h NOEC for algae was 2.7 mg/L). Based on this evidence, fish metabolites do not need to be taken into account in defining the BCF for fenpyrazamine.

In summary, the BCF for the parent substance is below the threshold values of CLP(500) and DSD, (100)for the 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} = 5.2 mg/L**	90-d NOEC = 0.37 m/L
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} = 5.5 mg/L	21-d NOEC = 0.34 mg/L
Aquatic algae and plants	*Pseudokirchneriella subcapitata*	72-h E_rC_{50} > 0.9 mg/L	**72-h NOE_rC = 0.22 mg/L**

All values were based on mean measured concentrations. Despite the potential for photolysis, the concentrations in the algal study were well maintained. The purity profile of the key studies complies with the specified composition in Section 1. Although the algal study provides an unbounded E_rC_{50} value, it is likely that 50% inhibition would have been achieved at a concentration of around 1.1 mg/L (for details see graph under the section "supplemental information – in depth analysis by RAC" in the BD). The algal study also gave a 96-h EC_{50} of 0.19 mg/L and 96-h NOEC of 0.053 mg/L based on cell density. The CLP Regulation indicates that the growth rate end point is appropriate for acute classification. Whilst the Regulation does not explicitly state which NOEC is relevant for long-term classification, the guidance indicates that growth rate is preferred to biomass inhibition. In the absence of any further guidance on the use of cell density results, and to remain consistent with other classification proposals, the more sensitive algal end points are not considered to be relevant for the classification of fenpyrazamine.

Classification according to CLP

Acute aquatic hazard: The lowest reliable short-term aquatic toxicity result is a 96-h LC_{50} of 5.2 mg/L for *O. mykiss*. This is supported by acute toxicity data on invertebrates in the same range and an extrapolated 72-h E_rC_{50} of around 1.1 mg/L for the alga *P. subcapitata* (from a study with an unbounded result). These concentrations are above the threshold value of 1 mg/l. Fenpyrazamine is therefore not classifiable as Aquatic acute 1 (H400).

Chronic aquatic hazard: Fenpyrazamine is not considered to be rapidly degradable. The lowest reliable long-term aquatic toxicity result is a 72-h NOEC of 0.22 mg/L for *P. subcapitata*, supported by long-term toxicity data on fish and invertebrates in the same range. This concentration is below the threshold value of 1 mg/L for non-rapidly degradable substances. Fenpyrazamine is therefore classifiable as Aquatic chronic 2 (H411).

Classification according to DSD

The lack of ready biodegradation and 96-h LC_{50} of 5.2 mg/L for fish (with similar values for invertebrates and algae) mean that fenpyrazamine fulfils the criteria for classification with N; R51-53.

Conclusion:

RAC agrees with the original proposal of the Dossier Submitter and concludes that the the environmental classification for fenpyrazamine as, Aquatic Chronic 2 (CLP, H411; DSD N; R50-53) is justified.

REFERENCES:

[1] European Chemicals Bureau (1999). Draft Summary record. Specialised Experts in fields of carcinogenicity, mutagenicity and reprotoxicity meeting of the 1-2 September 1999. ECBI/49/99- Add 1, Rev 2.

[2] DAR public version, risk assessment provided by the rapporteur Member State Austria for the new active substance fenpyrazamine, P 46, Volume 1, February 2011. http://www.efsa.europa.eu/en/efsajournal/pub/2496.htm

ANNEXES:

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

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and RAC (excl. confidential information). The revised CLH report as received after public consultation is included as an appendix to the RCOM for information.