Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Penthiopyrad (ISO); (*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide

EC Number: N.A.
CAS Number: 183675-82-3

CLH-O-0000001412-86-78/F

Adopted

4 December 2015

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4 December 2015

CLH-O-0000001412-86-78/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 Regulation (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: **Penthiopyrad (ISO); (*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl] -1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide**

EC Number: **-**

CAS Number: **183675-82-3**

The proposal was submitted by the **United Kingdom** and received by RAC on **20 April 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

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/harmonised-classification-and-labelling-consultation*** on **2 June 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **17 July 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Pietro Paris**

Co-rapporteur, appointed by RAC: **Christine Bjørge**

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

The RAC opinion on the proposed harmonised classification and labelling of penthiopyrad was adopted on **4 December 2015** by **consensus**.

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

Annex VI	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Entry	No current entry in Annex VI										
Dossier submitter proposal	TBD	Penthiopyrad (ISO); (RS)-N-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide	-	183675-82-3	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=1	
RAC opinion	TBD	Penthiopyrad (ISO); (RS)-N-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide	-	183675-82-3	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=1	
Resulting Entry	TBD	Penthiopyrad (ISO); (RS)-N-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide	-	183675-82-3	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=1	

GROUNDS FOR ADOPTION OF THE OPINION

PHYSICAL HAZARD ASSESSMENT

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

No classification was proposed by the Dossier Submitter (DS) for physical hazards based on the negative results obtained in standard EEC tests. Additionally, it was mentioned that penthioyrad does not liberate any flammable gases in contact with water, does not exhibit any pyrophoric properties and does not show self-heating properties (no self-ignition according to the EEC-method A16).

The DS stated that according to its chemical structure, penthiopyrad is considered to have no oxidizing properties: it does not contain chemical groups typical for oxidizing agents and it is regarded as incapable in reacting exothermically with a combustible material.

Comments received during public consultation

One Member State (MS) submitted general comments on the reporting of physical hazard properties in the IUCLID file and in the CLH report including the most appropriate IUPAC name for penthiopyrad.

Assessment and comparison with the classification criteria

RAC is in agreement with the DS proposal that penthiopyrad does not meet the criteria for a classification as a flammable substance. Penthiopyrad is not pyrophoric and does not react with water to liberate flammable gases. When penthiopyrad was tested in a standard self-ignition temperature study, no spontaneous ignition was reported below 400 ^{0}C.
Penthiopyrad does not contain chemical groups associated with explosive properties and the structure of the substance indicates that penthiopyrad will not have oxidative properties.

In conclusion, RAC agrees with the DS that **no classification** is required for physico-chemical properties of penthiopyrad.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The DS proposed not to classify penthiopyrad for acute toxicity via the oral, inhalation or dermal route since no mortality was observed at the maximum tested doses in studies performed in compliance with Good Laboratory Practice (GLP) and in accordance with OECD Test Guidelines (TG).

Comments received during public consultation

One MS supported not classifying penthiopyrad for acute toxicity.

Assessment and comparison with the classification criteria

Acute toxicity: oral

One acute oral toxicity study in rats, performed according to OECD TG 423 and GLP, was included by the DS in the CLH report. The LD_{50} value was more than 2000 mg/kg bw in both male and female rats. According to the CLP criteria, no classification for oral acute toxicity is justified above 2000 mg/kg bw.

In conclusion, in agreement with the DS proposal and the CLP criteria, the available data provide the basis for RAC's conclusion **not to classify** penthiopyrad for acute toxicity following oral exposure.

Acute toxicity: inhalation

One acute inhalation toxicity study in rats, performed according to OECD TG 403 and GLP, was included in the CLH report by the DS. The LC_{50} values in both male and female rats was > 5.59 mg/L (dust aerosol). According to the CLP criteria no classification for inhalation acute toxicity is justified above 5.0 mg/L (dust and mists).

In conclusion, in agreement with the DS proposal and the CLP criteria the available data provide the basis for RAC's conclusion **not to classify** penthiopyrad for acute toxicity following inhalation exposure.

Acute toxicity: dermal

One acute dermal toxicity study in rats, performed according to OECD TG 402 and GLP, was included in the CLH report by the DS. The LD_{50} values in both male and female rats were > 2000 mg/kg bw. According to the CLP criteria no classification for dermal acute toxicity is justified above 2000 mg/kg bw.

In conclusion, in agreement with the DS proposal and the CLP criteria the available data provide the basis for RAC's conclusion **not to classify** penthiopyrad for acute toxicity following dermal exposure.

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

Summary of the Dossier Submitter's proposal

No classification for STOT SE was proposed by the DS since there was neither human data to provide information on this end point nor any clear evidence of any specific toxic effects on any target organs or tissues from the available animal data.
Clinical signs of toxicity observed after single exposures to penthiopyrad were transient in nature and considered to be non-specific signs of general acute toxicity.

In the acute inhalation study, clinical signs were considered to be unspecific and insufficient by the DS to regard the substance as a respiratory irritant.

Comments received during public consultation

One MS provided supported not classifying penthiopyrad for STOT SE.

Assessment and comparison with the classification criteria

From the acute toxicity studies following oral, inhalation or dermal exposure there was no clear evidence of effects on a target organ or tissues. Clinical signs were reported after single inhalation exposure to penthiopyrad, but they were considered to be transient and related to unspecific signs of general acute toxicity. STOT SE 3 covers 'transient effects' occurring after single exposure, specifically respiratory tract irritation and narcotic effects. Classification in Category 3 is primarily based on human data which was not available for penthiopyrad. Narcotic effects were not observed in animal studies with penthiopyrad. RAC therefore agrees with the DS that penthiopyrad does not fulfil the criteria for STOT SE 3.
Penthiopyrad was also tested in an acute and in a subchronic neurotoxicity study in rats. Both studies were GLP-compliant and performed according to OECD TG 424. After acute exposure, dose-dependent clinical signs associated with effects on the nervous system were reported including abnormal gait, hunched posture and decreased/reduced motility and activity. These effects occurred on day 1 only and concurrently with other signs of toxicity (e.g. bradypnea, hypothermia). In the sub-chronic study, there were no treatment-related deaths or clinical signs, despite a treatment-related decrease in bodyweight gain greater than 10% in both sexes. In both studies, the macroscopic examination performed at termination revealed no treatment-related

lesions at any dose level. Brain weight and dimensions were also unaffected by treatment at all dose levels. There were no treatment-related histopathological findings in any of the central and peripheral nerve tissues. According to the CLP criteria, transient functional changes are not considered relevant for classification for STOT SE.

In conclusion, in agreement with the DS and the CLP criteria the available data provide the basis for RAC's decision **not to classify** penthiopyrad for STOT SE.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The skin irritation potential of penthiopyrad (99.8% purity) had been tested in three female New Zealand White rabbits in accordance with the OECD TG 404 and GLP. Penthiopyrad caused no clinical signs or skin irritation and hence the CLP criteria for classification as a skin irritant were not met. Therefore the DS did not propose any classification for this hazard class.

Comments received during public consultation

One MS supported not classifying penthiopyrad for skin corrosion/irritation.

Assessment and comparison with the classification criteria

In the absence of any signs of skin corrosion/irritation in a well conducted study in rabbits performed according to OECD TG 404 and GLP, the data available for penthiopyrad did not fulfil the criteria for skin corrosion/irritation under CLP neither in terms of severity of scores nor in terms of irreversibility.

In conclusion and in agreement with the DS proposal the available data provide the basis for RACs recommendation **not to classify** penthiopyrad for skin corrosion/irritation.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS did not propose classification of penthiopyrad for eye corrosion or irritation. Penthiopyrad (99.8% purity) had been tested in three female New Zealand White rabbits per group in accordance with OECD TG 405 and GLP. In one of the two groups, the eyes of the rabbits were irrigated with luke-warm water for 30-60 seconds 30 seconds after test substance instillation. In both groups, no corneal or iridial lesions were evident. Slight and transient conjunctival redness and chemosis were reported in rabbits, in those animals with non-irrigated eyes, as expected.

According to the DS, none of the individual scores at any time point were considered relevant for classification and the overall response did not meet the criteria for classification under the CLP Regulation. The DS therefore did not propose to classify penthiopyrad for serious eye damage/eye irritation.

Comments received during public consultation

One MS supported not classifying penthiopyrad for this hazard class.

Assessment and comparison with the classification criteria

One study in rabbits performed according to the OECD TG 405 and in compliance with GLP was included in the CLH report by the DS. In this study non-irrigated animals showed mild conjunctival redness (0.33, 0, 0.33) and conjunctival chemosis (0.33, 0, 0.33) at 24-48h for each animal. The animals were free of all ocular reactions at 48h and 72h after installation. In irrigated animals the conjunctival redness was 0, 0, 0.33 and conjunctival chemosis 0, 0, 0 (at 24h for each animal). The animals were free of all ocular reactions at 24h, 48h and 72h after installation. No corneal or iridial lesions were reported in the non-irrigated or irrigated animals.

In conclusion, penthiopyrad induced transient mild eye irritation in rabbits shown as conjunctival redness and chemosis. None of the individual scores at 24, 48 and 72h were greater than 1, and therefore, not relevant for classification according to the CLP criteria where in at least two out of three animals a positive response of corneal opacity ≥ 1, and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or chemosis ≥ 2 calculated as mean scores at 24, 48 and 72h after installation and which fully reverse after 21 days.

In conclusion and in agreement with the DS proposal, the available data provide a basis for RACs recommendation **not to classify** penthiopyrad for eye corrosion/irritation.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

No data were reported by the DS in the CLH report and not classification proposal was made.

Comments received during public consultation

No specific comments were received during public consultation.

Assessment and comparison with the classification criteria

No data regarding respiratory sensitisation was provided by the DS. Therefore, **no conclusion** regarding the classification on respiratory sensitisation following exposure to penthiopyrad could be drawn by RAC.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS did not propose to classify penthiopyrad as a skin sensitiser based on a negative Guinea pig maximisation test (GPMT) performed according to OECD TG 406 and GLP.

Comments received during public consultation

One MS supported not classifying penthiopyrad for skin sensitisation.

Assessment and comparison with the classification criteria

The skin sensitising potential of penthiopyrad was assessed in a Guinea pig maximisation test (GPMT) performed according to OECD TG 406 and GLP. Penthiopyrad did not induce skin sensitisation in the GPMT with induction doses of 5% intradermal and 50% topical and a challenge dose of 50%. Appropriate responses were obtained in the positive and negative control groups. According to the CLP criteria, classification as a skin sensitiser is warranted if at > 1% intradermal induction dose ≥ 30% of animals give a positive response in a GPMT. As none of the animals were positive in the well-conducted test, the classification criteria were not met.

In conclusion and in agreement with the DS proposal, RAC concludes that **classifying penthiopyrad for skin sensitisation is not warranted**.

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

Summary of the Dossier Submitter's proposal

The DS did not propose to classify penthiopyrad for STOT RE. The DS summarised information on nine repeated dose toxicity studies, grouping the results per tested species. Further to this, the

DS also reported information on repeated dose toxicity from other relevant studies (carcinogenicity, reproductive toxicity, neurotoxicity and immunotoxicity). With the exception of the 28-day oral study in Beagle dogs, all other studies were conducted under GLP and in accordance with OECD guidelines. The rat and mouse studies were performed using the same strains (Wistar rats and CD-1 mice, respectively)

In the Wistar rat, adverse effects were noted in the liver of both sexes at doses relevant for classification i.e., 100 mg/kg bw/d in the 90 day study. Effects were also noted on some clinical chemistry and haematological parameters at this dose level. The effects seen in the liver included fatty changes, hepatocellular hypertrophy, hepatocellular degeneration and Kupffer cell proliferation. According to the DS, due to the low severity of these effects at this dose level, they do not warrant classification for STOT-RE under the CLP Regulation. At higher doses (i.e., doses not relevant for classification), the DS noted adverse effects in the thyroid, adrenal gland and ovaries.

In the CD-1 mouse, the DS also reported the liver as a target organ at a dose relevant for classification, i.e., 300 mg/kg bw/d in a 28 day repeated dose study. However, the DS concluded that this effect was not sufficiently severe to warrant classification for STOT-RE under the CLP Regulation. At higher doses (i.e., not relevant for classification), adverse effects were also noted in the thyroid (as in Wistar rats), and on some haematological and clinical chemistry parameters.

In the Beagle dog, the toxicological profile was similar to that seen in rats and mice, and the target organs were the liver and thyroid. Adverse effects were also noted in the gallbladder. In the non-guideline 28 day study which used only 1 dog/sex/dose, effects were noted in the thyroid from ~27 mg/kg bw/d, and in the liver from 80 mg/kg bw/d. However, in the guideline 90 day and 52 week studies, effects in the liver were only noted at very high doses (from ~811 and ~445 mg/kg bw/d, respectively). Effects in the thyroid were only noted at high doses in females in the guideline 90 day study (~811 mg/kg bw/d), and were not observed at all in the guideline 52 week study.

The effects in the gallbladder consisted of slight mucosal oedema of the lamina (at doses ≥ 79.6 mg/kg bw/d in a 28 day study), cholecystitis (at doses 811 mg/kg bw/d in the 90 day study, and at doses 445 mg/kg bw/d in the 52 week study) and mucosal epithelial hyperplasia (at doses 445 mg/kg bw/d in the 52 week study).

In addition, the adrenal gland was a target organ in rats and dogs after 52 weeks of treatment at high doses. However, since the effects were slight and at doses above guidance values, classification was not further considered.

In conclusion, the DS demonstrated using a weight of evidence approach that the severity of gallbladder effects, the long-term adverse effects in the liver and the thyroid do not warrant classification for STOT-RE under the CLP Regulation.

Comments received during public consultation

No specific comments were received during public consultation.

Assessment and comparison with the classification criteria

According to the CLP criteria, substances have to be classified for repeated dose toxicity Category 2 if the significant adverse effects, which indicate functional impairment, occur at oral dose levels ≤ 100 mg/kg bw/d in a 90-day rodent study. The cut-off guidance value is 200 mg/kg bw/d for dermal exposure. These values may be adjusted according to Haber´s rule to take into account studies of different duration.

Significant adverse effects may include, but are not limited to, mortality, significant functional changes in various organ systems, significant adverse changes in clinical biochemistry, haematology, or urinalysis parameters, significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination; multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs; morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction and/or evidence of appreciable cell death in vital organs incapable of regeneration.

Nine repeated dose toxicity studies are available for penthiopyrad: three 28 day oral studies (in the rat, mouse and dog); one 28 day dermal study in rat, three 90 day oral studies (in the rat, mouse and dog), and two 1 year oral studies (in the rat and dog).

In the 28 day oral study in rats the target doses were 0, 25, 65, 160, 400 and 1000 mg/kg bw/d, and the NOAEL was 160 mg/kg bw/d based on clinical chemistry changes and decreased body weight at the next dose level. At the highest dose level, increased liver weight and histopathological alterations in the liver were found. Adjusting to the duration of a 90-day study, the LOAEL of 400 mg/kg bw/d in this study exceeds the STOT RE guidance value.

In the 28 day oral study in mice with doses of 0, 30, 100, 300 and 1000 mg/kg bw/d, the NOAEL was 100 mg/kg bw/d in males, and 300 mg/kg bw/d in females. The target organ was the liver. Effects on clinical chemistry and haematology were also seen at $\geq$ 300 mg/kg bw/d, increasing in a dose-related manner. The LOAEL at 300 mg/kg/d matches the cut-off value for classification for STOT-RE, if adjusted to duration of exposure.

The 28-day range-finding study in dogs was not conducted according to the relevant test guideline and included only 1 animal/sex/dose group. The NOAEL was 27.1 in males and 29.1 in females with a LOAEL of 79.6 in males and 94.1 in females. The liver and thyroid were the target organs, with slight diffuse hepatocellular hypertrophy at the top dose of 920 mg/kg bw/d in the male dog and from 316 mg/kg bw/d in the female dog. Even though the LOAEL is lower than the guidance value for STOT RE if adjusted to 90 days by applying Haber´s rule, RAC considers that this study should be given limited weight when evaluating the STOT RE hazard category in a weight of evidence approach. This is because the results from the study are considered not to be consistent with the results from the other dog studies with longer duration (90 days and 1 year). Additionally, the study is not carried out according to test guideline and there was only 1 animal/sex/dose group.

In the 90 day oral study in rats dosed with 0, 40, 100, 250, and 625 mg/kg/d, no effects were observed at 40 mg/kg/d. The liver was the target organ at doses ≥ 100 mg/kg bw/d, and dose-related responses were observed included increased liver weights, minimal to slight histopathological changes in the liver, and mild haematological changes and clinical chemistry perturbations. None of these findings were severe enough to be considered by RAC as relevant for classification as STOT RE. In the 90 day study in mice receiving 0, 30, 100, 300 and 1000 mg/kg bw/d, the NOAEL was 100 mg/kg/d and increased liver weights were seen at 300 mg/kg/d. Mild haematological perturbations and histopathological alterations in the liver and the thyroid were seen in the top dose group. Also in the 90 day study in dogs the liver and thyroid were the target organs, but effects were only seen at the top dose, which was > 800 mg/kg/d.

In the 1 year oral study in dogs the target organ was again confirmed to be the liver, but only at very high doses (from 445 mg/kg bw/d), and the thyroid effects were absent. In the 1 year study in the rat no adverse effects were observed at 25 mg/kg bw/d, equaling the guidance (cut-off) value for STOT RE when adjusted for the duration of the study. At higher doses the liver and the thyroid were the target organs.

No adverse effects/target organs were identified in the 28 day dermal study in rats.

In conclusion, the main target organs of penthiopyrad are the liver and the thyroid, with accompanying histopathological effects and mild changes in clinical chemistry. In the studies given most weight in a weight of evidence approach, the effects arise at doses above the guidance values for STOT RE. Thus, in agreement with the DS, RAC is of the opinion that **no classification is warranted for repeated dose toxicity** for penthiopyrad.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The DS did not propose to classify penthiopyrad for germ cell mutagenicity based on a weight of evidence approach. The database included in the CLH report covered *in vitro* (four studies) and *in vivo* (two studies) mutagenicity studies. Except for an unscheduled DNA synthesis (UDS) assay, all studies were conducted under GLP and in accordance with OECD test guidelines.

In vitro, penthiopyrad was negative in a bacterial gene mutation assay, in a bacterial DNA damage/repair test and in a mouse lymphoma assay with or without metabolic activation. In an *in vitro* mammalian chromosome aberration test, penthiopyrad caused an increase in the incidence of structurally aberrant cells in the presence of S9. Based on the results of this last study, the DS considered penthiopyrad to induce chromosomal aberrations in cultured mammalian cells in the presence of S9.

An *in vivo* micronucleus assay conducted in mice was considered negative. In addition, a non-guideline *in vivo*/*in vitro* UDS assay in male CD (SD) rats showed that penthiopyrad did not induce DNA repair, as assessed by NNG counts and the proportion of cells in repair, at doses up to and including the limit dose of 2000 mg/kg.

The DS concluded that, although penthiopyrad induces chromosal aberrations *in vitro*, the negative *in vivo* studies show that penthiopyrad does not fulfil the CLP criteria for mutagenicity and does not warrant classification for germ cell mutagenicity.

Comments received during public consultation

One MS provided support to not classify penthiopyrad for skin sensitisation.

Assessment and comparison with the classification criteria

Penthiopyrad was tested in four well conducted *in vitro* tests (bacterial gene mutation test, bacterial DNA damage or repair test, mammalian chromosome aberration test and a mutation test in mouse lymphoma cells) and in two well conducted *in vivo* tests (micronucleus assay and unscheduled DNA Synthesis assay). From the *in vitro* studies only the mammalian chromosomal aberration test with S9 showed a positive response, however, the *in vivo* micronucleus test was negative. All the other *in vitro* and *in vivo* tests were negative.
In conclusion and in agreement with the DS, RAC concludes that penthiopyrad is not considered mutagenic, and **no classification for mutagenicity** is proposed.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

The DS did not propose to classify penthiopyrad for carcinogenicity. The CLH report summarised two GLP-compliant guideline carcinogenicity studies by the oral route, one in rats, and one in mice. In addition, two non-guideline mode of action (MoA) studies were also available, investigating the effects of penthiopyrad on hepatic drug metabolising enzyme induction, cell proliferation and thyroid function in rats following dietary administration for 2 weeks.
Two tumour types were assessed and compared with the CLP criteria. In summary, the apparent increase in the incidence of liver tumours in male mice was considered by the DS to be an artefact of the very low concurrent control value, and not an effect of treatment. The follicular cell adenomas seen in male rats was evaluated in a weight of evidence approach, in light of the ECHA Guidance on the Application of the CLP Criteria (2009), the Specialised Experts guidance on non-genotoxic thyroid carcinogens (ECBI, 1999), IARC (2001) and EPA (1998).

In the carcinogenicity study in rats, the incidence of thyroid follicular adenoma in males at the top dose (18.4% at 250 mg/kg bw/d) exceeded the concurrent control incidence of 6.0%, and slightly exceeded the historical control range high value of 14.29% (range 0 – 14.29%). The total

incidence of follicular adenoma in males at this dose level was not statistically significant (Fisher's exact test), but the incidence in survivors sacrificed at the end of the treatment period (9/34) was statistically significantly higher than the control incidence of 6/37 (p = 0.0395). No excessive toxicity was noted at this dose level.

Based on the results of the MoA study, the DS postulated that penthiopyrad is a phenobarbital-type hepatic UDP-glucuronosyl transferase (UDPGT) inducer with a potential to enhance biliary excretion of T4, thereby lowering circulating T4 levels, which results in an increase in circulating TSH through negative feedback leading to thyroid follicular cell hypertrophy and subsequently thyroid adenomas. The DS further stated that inhibition of T4 release was listed as one of the clearly established mechanisms for perturbation of the pituitary-thyroid axis (ECBI, 1999) and the proposed MOA for penthiopyrad is consistent with this mechanism. In addition, the DS argued that penthiopyrad is a thyroid carcinogen of low potency.

Overall, the DS concluded that penthiopyrad **does not meet the criteria for carcinogenicity classification** according to CLP.

Comments received during public consultation

One MS submitted a comment in disagreement with the DS proposal, arguing in favour of a classification of penthiopyrad as Carc. 2 (H351). The MS considered that based on the increased incidence of hepatocellular adenoma and carcinoma in male mice at 200 and 600 mg/kg bw/d compared to the concurrent control, the study provides sufficient evidence for carcinogenic properties of penthiopyrad. The MS further referred to the recommendation of EFSA's Pesticides Peer Review Experts' Meeting 95 on mammalian toxicology and the conclusion of EFSA's peer review where a slight majority of the experts suggested to classify penthiopyrad. The DS responded to this comment by referring to the rationale for not classifying penthiopyrad provided into the CLH report.

Assessment and comparison with the classification criteria

There were two oral carcinogenicity studies available conducted according to the relevant test guideline, one in rats and one in mice. In addition a 52 week study in rats was available.
In the rat carcinogenicity study the animals received penthiopyrad at target doses of 0, 9, 27, 83 or 250 mg/kg bw/d in the feed for two years. Adverse treatment-related, non-neoplastic lesions occurred in the liver, kidneys, lungs, and adrenal glands in animals in the two highest dose groups. There were no treatment-related clinical signs in either sex at any dose level. The NOAEL for non-neoplastic effects was set to 27 mg/kg bw/d. The only neoplastic finding was a treatment-related increase in **thyroid follicular adenoma** in 9 of 49 **males** (18.37 %) in the top dose group, vs. 3/50, 1/50, 6/48 or 2/49 cases/animals in the control and increasing dose groups, respectively. The incidence in the top dose group of males was slightly above the historical control range which was 0-14.29 %.

In the mouse carcinogenicity study the animals received as a target dose 0, 20, 60, 200 and 600 mg/kg bw/d for 78 weeks. Treatment-related non-neoplastic histopathological alterations occurred in the thyroid of both sexes in the two highest dose groups, and in the lungs of females at the top dose. A NOAEL for these effects was established at 60 mg/kg bw/d. There was a late development of **hepatocellular adenomas**, and adenomas and carcinomas together (but not carcinomas alone) in **males** in the two highest dose groups. The incidence of hepatocellular adenomas were 14/52 (27%) in the group receiving 20 mg/kg bw/d, 11/52 (21%) in the group receiving 60 mg/kg bw/d, 13/52 (25 %) in the group receiving 200 mg/kg bw/d and 15/52 (29 %, statistically significant) in the group receiving 600 mg/kg bw/d, vs. 7/52 (13 %) in the control group. These findings were within the historical control range for hepatocellular adenomas (17.31-34.62 %). The incidence of hepatocellular carcinomas alone were not significantly increased in any group. In male mice the number of carcinomas were 1/52 (2%) in the group receiving 60 mg/kg bw/d, 5/52 (9.6%) in the group receiving 200 mg/kg bw/d and in the group receiving 600 mg/kg bw/d 6/52 (11.5%) vs. 2/52 (3.8%) in the control group. The incidence of 2/52 for hepatocellular carcinomas in the contemporary control group is considered the reason why the high dose groups did not reach statistical significance. However, the incidence in the contemporary control group was within the range of the historical controls.

In the 52 week study in rats, the liver, adrenal, thyroid gland and ovary were the target organs, but no increase in tumour incidence was observed in dosed animals. Doses were up to 400 mg/kg bw/d.

Additional factors taken into consideration to assess the overall level of concern were the following:

a) Tumour type and background incidence: The incidence of thyroid follicular adenomas in male rats was only slightly above the historical control range. The hepatocellular adenomas in male mice were within the historical control range, and the incidence in the control group was remarkably low.

b) Multi-site responses: In both rats and mice there was a response in only one organ, so no multi-site response was observed. However a low potency carcinogenic response was observed in both species.

c) Progression of lesions to malignancy: In rats only benign tumours were observed. In mice carcinomas were found, but they were only statistically significant if considered together with the adenomas, and not by themselves.

d) Reduced tumour latency: this was not observed as the tumours in mice occurred at a late life stage. This would be in accordance with a non-genotoxic mode of action, see under k). In rats the latency was not investigated.

e) Whether responses are in a single or in both sexes: Only males were affected in both strains.

f) Whether responses are in single species or several species: A weak tumourigenic response was seen in rats and mice.

g) Structural similarity or not to a chemical for which there is good evidence of carcinogenicity: Not known to RAC.

h) Routes of exposure: The route was oral and considered to be directly relevant to humans.

i) Comparison of ADME (toxicokinetics) between test animals and humans: see under k).

j) The possibility of a confounding effect of excessive toxicity at test doses: Excessive toxicity was not observed at the test doses.

k) Mode of action (MoA) and its relevance for humans: Penthiopyrad was non-genotoxic in tests. Two studies of the MoA in rats were available. In a two-week non-guideline hepatic enzyme induction study in rats, penthiopyrad produced enhanced hepatic cell proliferation at early stages. Hepatic POD, UDPGT, and cytochrome P450 isozymes (among them CYP2B1, indicating a CAR receptor mediated MoA) activities were increased, but with a considerably weaker effect than resulting from dosing with phenobarbitone. Centrilobular hepatocellular hypertrophy and proliferation of smooth endoplasmic reticulum occurred, as well as enlarged liver in some animals and increased microsomal CYP4A1 activity. Gap junction communication was not disturbed.

   In another two-week non-guideline investigation the thyroid function in rats was studied, and the results support a theory that penthiopyrad is a phenobarbital-type hepatic UDPGT inducer with a potential to enhance biliary excretion of T4 resulting in a negative feedback increase of TSH leading to thyroid follicular cell hypertrophy and subsequently thyroid adenomas. Humans appear to be less sensitive to this MoA where the pituitary-thyroid hormone axis is disturbed, and the MoA of formation of certain thyroid tumours in rodents mediated by UDPGT is considered to be not relevant for humans.

In conclusion, RAC agrees with the DS that penthiopyrad **does not warrant a classification for carcinogenicity** according to CLP.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The DS did not propose to classify penthiopyrad for reproductive toxicity.
For effects on fertility and the sexual function, a two generation reproductive toxicity study was reported in Wistar rats (GLP, OECD TG 416). According to the DS, no adverse effects were noted at doses of up to 5000 ppm (278-480 mg/kg bw/d). Therefore no classification for fertility was proposed by the DS.

For developmental toxicity, the DS presented data from two studies conducted under GLP and in accordance with OECD TG 414, one in the Wistar rat and one in the NZW rabbit , both by oral exposure (gavage). According to the DS, no toxicologically significant effects on development were noted at doses of up to 1000 mg/kg bw/d in the rat, or up to 225 mg/kg bw/d in the rabbit. The DS reported some effects in rats that were not considered to be toxicologically significant including increased number of early resorptions and post-implantation losses, decreased live litter size and decreased in the number of implants and the number of viable foetuses at the top dose. Similarly, the DS noted slightly reduced foetal and litter weights at the top dose of 225 mg/kg bw/d in rabbits at which maternal toxicity was observed. The DS could not exclude a treatment-related effect of penthiopyrad in one top dose female that was killed prematurely because of evidence of abortion on day 26. Overall, the DS concluded that mild developmental toxicity was seen in the rabbit only in the presence of maternal toxicity.

Therefore no classification was proposed for toxicity to reproduction by the DS based on the results of these studies.

Comments received during public consultation

One MS supported not classifying penthiopyrad for reproductive toxicity.

Assessment and comparison with the classification criteria

Fertility:
A 2-generation reproductive toxicity study conducted according to OECD TG 416 in rats with oral exposure to penthiopyrad via diet was included by the DS. In this study no effects on fertility or sexual function was reported up to the highest dose of 5000 ppm corresponding to 278, 340, 439 and 480 mg/kg bw/d in P_{males}, $F1_{males}$, $P_{females}$ and $F1_{females}$, respectively.

Systemic toxicity was reported from the mid dose, 1000 ppm corresponding to 54, 64.2, 90.5 and 95.6 mg/kg bw/d in P_{males}, $F1_{males}$, $P_{females}$ and $F1_{females}$, respectively. The effects reported were (i) increases in relative liver weight in P/F1 females and in F1 females and (ii) increase in the relative adrenal weight. Histopathology showed adrenal cortical hypertrophy (10/24) in F1 females. At the highest dose (5000 ppm) more severe effects were reported in the liver, adrenal and thyroid in males and females in both generations including histopathological changes in thyroid and liver and relative organ weight changes in the liver, adrenal and thyroid.

In a 2-generation reproductive toxicity study penthiopyrad did not induce effects on sexual function and fertility up to doses showing systemic toxicity. Significant fertility parameters, such as mating, fertility and pregnancy indices, as well as sperm parameters were not altered by the administration of penthiopyrad. In the absence of effects on sexual function and fertility RAC concludes that penthiopyrad **should not be classified** for these effects.

Development:
Two developmental toxicity studies were available for penthiopyrad performed according to OECD TG 414, one in Wistar rats and one in NZW rabbits, both by oral exposure (gavage). Furthermore, one postnatal developmental neurotoxicity study according to OECD TG 426 in SD rats by oral (gavage) exposure was included.

In the rat developmental toxicity study, a slight but statistically significant increase in post-implantation losses and resorptions was reported at 1000 mg/kg bw/d. The results are detailed in the table below.

Dose mg/kg bw/d	Corpora Lutea	Implantations	Resorptions			Live young			Implantation loss (%)	
			Early	Late	Total	Male	Female	Total	Pre-	Post-
0	13.3	12.1	0.5	0.0	0.5	5.4	6.2	11.6	10.5	4.0
62.5	13.8	12.4	0.8	0.0	0.8	5.7	5.8	11.5	11.1	7.0
250	12.5	11.3	0.5	0.0	0.5	4.9	5.9	10.8	9.2	5.3
1000	13.1	11.7	1.4*	0.0	1.5*	5.3	4.9*	10.2	10.8	13.0**

*, $p < 0.05$; ** $p < 0.01$

The average litter weight was also reported to be 12% lower than control animals in the high dose group. In the 2-generation reproductive toxicity study a decrease in F1 male bw gain from postnatal day (PND) 4 and in F2 males and females from PND 14 in the high dose group (5000 ppm) was also reported.

The incidence of major abnormalities, minor visceral and skeletal abnormalities and skeletal variants in treated and control animals did not indicate effects related to treatment since the foetal and litter incidence of major abnormalities at 250 and 1000 mg/kg bw/d were lower than the control incidences. At 62.5 mg/kg bw/d a higher incidence of foetuses with major abnormalities was reported, but were not statistically significant ($p>0.05$). Major abnormalities were also reported in the concurrent control animals, and were regularly found in the laboratory historical control data.

The maternal toxicity reported included a decrease in body weight and food consumption at 1000 mg/kg bw/d on gestation day (GD) 6-9 (37.5% and 9.5%, respectively). However, subsequently food consumption and body weight were similar to the controls. At GD 20 there were no statistically significant differences in body weight between the control animals and the treated animals. In a study by Fleeman et al. (2005) it has been shown that a reduced body weight gain of 50% and more up to body weight reduction did not cause an increased number of resorptions or post-implantation losses. Therefore, the increase in post-implantation losses is not considered to be a secondary consequence of maternal toxicity. At 1000 mg/kg bw/d a statistically significant decrease in uterine weight was reported (57 g vs 66 g in control animals) which was consistent with the higher number of resorptions and post-implantation losses in the high dose group.

In the postnatal developmental neurotoxicity study SD rats were exposed to penthiopyrad at doses of 0, 100, 250 and 500 mg/kg bw/d from GD6 to lactation day (LD) 6 followed by an exposure of offspring from PND 7 to PND 21. No effects on post-implantation losses or early resorptions were reported, however, lower doses were used in this study compared to the rat developmental toxicity study. In the offspring a statistically significantly decreased pup body weight was reported up to LD 6 from 250 mg/kg bw/d. After PND 7 and up to PND 21 the decrease in pup bw was evident from 100 mg/kg bw/day. No maternal toxicity was reported in this study.

In the rabbit developmental toxicity study a decrease in the foetal weight (7.8% decreased compared to controls) and litter weight (13.5% compared to controls) was reported in the high dose group (225 mg/kg bw/d). The maternal effects included a decrease in the mean uterine weight in the high dose group (225 mg/kg bw/d). No effects of treatment at any dose level on bw gain was reported. One animal aborted on GD 26 in the high dose group in the presence of marked decreased food consumption and a weight loss of 0.69 kg between GD 18-26. The abortion was considered by the DS to be treatment-related due to very low incidences of abortion in this strain of rabbits. A high incidence of abortion was also noted in a dose-range finding study with doses of 0, 250, 500 and 1000 mg/kg bw/day, where abortion incidence of 33% was seen following exposure to 500 or 1000 mg/kg bw/d. However, at these dose levels marked maternal toxicity was observed including poor clinical conditions, statistically significant reduction in body weight, marked inappetence, low water consumption and abnormal faeces.

In conclusion, following exposure to penthiopyrad, effects were reported in the rat and rabbit developmental toxicity studies that indicate some evidence of adverse effects on development. They consisted in slight but statistically significant increases in post-implantation losses ($p<0.01$) and early resorptions ($p<0.05$) at 1000 mg/kg bw/d in rats. These effects are not considered to be

a secondary consequence of maternal toxicity. In addition, slightly decreased litter size or weight (rat and rabbit) and decreased uterine weight in rats were noted. Finally, abortions were reported in rabbits, but considered by RAC to be secondary to severe maternal toxicity.

RAC therefore concludes that based on the only very slight increase in post-implantation losses and early resorption in rats not considered to be secondary to maternal toxicity, and the abortions seen in the rabbit study in the presence of severe maternal toxicity a classification for developmental toxicity of penthiopyrad is not justified and **no classification for developmental toxicity** is warranted.

In conclusion, **no classification for toxicity to reproduction** is warranted.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier Submitter's proposal

Penthiopyrad is currently not listed on Annex VI to CLP (Regulation (EC) 1272/2008). The DS proposed to classify the substance as Aquatic Acute 1 – H400 (M=1) and Aquatic Chronic 1 – H410 (M=1).

Degradation

A hydrolysis study carried out according to OECD TG 111 and in compliance with GLP (Tognucci, 1999a) indicated that penthiopyrad is hydrolytically stable since less than 10% of the substance was hydrolysed at 50 °C after 5 days at pH 4, 7 and 9. On this basis, the DT_{50} at 25 °C is considered greater than one year.

The photodegradation of penthiopyrad in water was studied according to OECD TG 21 and GLP (Burgener, 1999). No significant photolytic degradation occurred during 15 days of continuous irradiation with artificial sunlight at pH 7.0 and 25 °C, showing that penthiopyrad was photolytically stable.

A ready biodegradation study is available following OECD TG 301F (Manometric Respirometry Test) and GLP (Seyfried, 2007). Test solutions were prepared with 100 mg test item meaning the substance was tested above the water solubility of 1.375 mg/L at pH 7 and 20 °C. Validation criteria for the reference and toxicity controls were met. The biodegradation of the substance after 28 days of incubation was -1%. Therefore penthiopyrad is considered not readily biodegradable and consequently not rapidly degradable for classification and labelling.

An aerobic water/sediment simulation study, carried out according to OECD TG 308 and in compliance with GLP, was run for 185 days in the dark at 20 °C using two systems (Adam, 2008). Likewise, an anaerobic water-sediment study was carried out for 100 days at 20 °C in the dark conducted according to OECD TG 308 and in compliance with GLP (Adam, 2007),
Neither of the two water/sediment simulation test provided sufficient data to show penthiopyrad was ultimately degraded to a level > 70% within 28 days (equivalent to a half-life < 16 days) or transformed to non classifiable products (See the BD for further details).

Bioaccumulation

The log Kow values for penthiopyrad have been calculated based on solubility in n-octanol and water: 4.36 (pH=4), 4.62 (pH=7) and 4.54 (pH=10) (Franke, 2008a and Franke 2008b). These values are based on water solubility in buffered solutions. Moreover, there is a calculated log Kow value of 3.9 (pH=5 and 20° C) (Labano, 2012) based on solubility in distilled water; it is just below the CLP log Kow trigger value of 4 intended to identify substances with a potential to bioaccumulate. Other values were just greater than 4 ((Franke, 2008a and Franke 2008b).

However, an experimental aquatic BCF for penthiopyrad is available following a GLP compliant OECD TG 305 Guideline study (Mitsui Chemicals Agro, Inc., 2008). The bioaccumulation of

[^{14}C]-penthiopyrad in rainbow trout was determined under flow-through conditions over 28 days. During the uptake phase the fish were exposed to the nominal dose levels of 1.0 and 10 µg/L of the substance. Afterwards, the fish were transferred to untreated water for 14 days during the depuration phase. Steady state mean BCF values were 158-186 L/kg (0,1 µg/L nominal exposure concentration) and 155-182 L/kg (10 µg/L nominal exposure concentration) for whole fish tissues of the Total Radioactive Residues (TRR) in fish. The range of BCF values includes values 1-1.18 fold those calculated from study data in order to account for high total organic carbon concentrations. The study report and DAR include BCF values based on the lipid content in control fish and they are not lipid normalised. However, the DS indicated that given the low BCF values (below 200 L/kg) it is unlikely that lipid normalisation would result in BCF values greater than 500 L/kg. Even if there is some uncertainty due to the study limitations, key validity criteria were met and the study was considered reliable.

The DS concluded that based on experimental results bioaccumulation of the substance in fish is not expected.

Aquatic toxicity

Several acute and chronic aquatic toxicity data are available following GLP and standard guidelines; these were reviewed under Directive 91/414/EEC and considered valid. Further details are presented for studies conducted on the active substance penthiopyrad but not for its degradants as these are less toxic and not considered further for classification of penthiopyrad. A summary of available valid information on the aquatic toxicity of penthiopyrad is presented in the following Table:

Method	Test organism	Test system	Endpoint mg/L	Remarks	Reference
Acute toxicity to fish OECD TG 203, GLP	Rainbow Trout *(Oncorhynchus mykiss)*	96 h Static	LC_{50} 0.386*	mm	Mitsui Chemicals Agro , Inc., 2007a
Acute toxicity to fish OECD TG 203, GLP	Common Carp *(Cyprinus carpio)*	96 h Flowthrough	LC_{50} 0.572*	mm	Mitsui Chemicals Agro , Inc., 2005
Acute toxicity to fish OECD TG 203, GLP	Bluegill Sunfish *(Lepomis macrochirus)*	96 h Static	LC_{50} >0.604*	mm	Mitsui Chemicals Agro , Inc., 2007b
Acute toxicity to fish OECD TG 203, GLP	Fathead Minnow *(Pimephales promelas)*	96 h Semi-Static	**LC_{50} 0.290***	mm	Mitsui Chemicals Agro , Inc., 2009a
Acute toxicity to fish OECD TG 203, GLP	Sheepshead Minnow *(Cyprinodon variegates)*	96 h Semi-Static	LC_{50} 1.38*	mm	Mitsui Chemicals Agro , Inc., 2007e
Fish Early Life-Stage (FELS) toxicity OECD TG 210, GLP	*Fathead Minnow (Pimephales promelas)*	33 d Flow-through	**NOEC 0.051** Based on length and wet weight	mm	Mitsui Chemicals Agro , Inc., 2008
Daphnia sp Acute Immobilisation OECD TG, 202 GLP	*Daphnia magna*	48 h Static	EC_{50}>1.375 (experimental water solubility limit)	mm	Maeda, 2005
Daphnia magna Reproduction OECD TG 211, GLP	*Daphnia magna*	21 d Flowthrough	NOEC 0.471	mm	Palmer *et al.*, 2007c
Mysid Acute Toxicity Test OPPTS 850.1035 GLP	Mysid Shrimp *Americamysis bahia*	96 h Semi-Static	LC_{50}>1.7	mm	Palmer *et al.*, 2007d
Oyster Acute Toxicity Test (Shell Deposition) OPPTS 850.1025, GLP	Eastern Oyster *(Crassostrea virginica)*	96 h Flowthrough	EC_{50} 1.2	mm	Palmer, 2008
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Pseudokirchneriella subcapitata*	72 hours Static	ErC_{50} >4.0 NOErC 0.45	twa	Sueta, 2005

Method	Test organism	Test system	Endpoint mg/L	Remarks	Reference
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Pseudokirchneriella subcapitata*	96 hours Static	ErC_{50} >1.5 NOErC 0.788	gmm	Palmer *et al.*, 2009a
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Skeletonema costatum*	96 hours Static	ErC_{50} >1.576 NOErC 0.373	gmm	Palmer *et al.*, 2009b
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Anabaena flosaquae*	96 hours Static	ErC_{50} > 1.240 NOErC 1.240	gmm	Palmer *et al*, 2009c
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Navicula pelliculosa*	96 hours Static	ErC_{50} > 1.429 NOErC 1.429	gmm	Palmer *et al.,* 2009d
Lemna sp. Growth Inhibition Test OECD TG 221, GLP	*Lemna gibba*	7d Static	ErC_{50} > 1.205 NOErC 1.205	mm	Sindermann *et al.,* 2008

mm refers to mean measured
gmm refers to geometric mean measured concentrations
twa refers to time weighted average
*Based on binomial method due to lack of two or more concentrations where mortality (%) was between 0 and 100
Key endpoints used in acute and long-term hazard classification are highlighted in bold.

Aquatic acute toxicity data on penthiopyrad are available for fish, invertebrates, algae and aquatic plants. Fish are the most acutely sensitive trophic group. The lowest result was a semi-static 96h-LC_{50} value of 0.290 mg/L (mean measured) for Fathead Minnow (*Pimephales promelas*), provided with OECD TG 203 compliance.

Adequate chronic toxicity data are available for all three trophic levels. The lowest result (flow-through 33-day NOEC=0.051 mg/L, mean measured) was provided for the fish Fathead Minnow (*Pimephales promelas*) with OECD TG 210 compliance. The DS stated that the original study report considered length and dry weight as the most sensitive endpoints resulting a NOEC of 100 µg/L. Nevertheless, the DS reported the outcome of the review under Directive 91/414/EEC resulting in a revised NOEC of 51 µg/L, from a statistical analysis showing that the 100 µg/L exposure concentration induced significant reductions in fish total length and wet weight compared to control fish. Therefore the revised NOEC of 51 µg/L was agreed and considered valid for the purpose of classification.

Comments received during public consultation

Two Member States contributed during public consultation stating a general agreement with the proposed environmental classification.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS' proposal to consider penthiopyrad as not rapidly degradable. The substance is hydrolytically and photolytically stable. In a ready biodegradation study no degradation was observed over 28 days. Moreover, the degradation information from water/sediment simulation tests did not provide sufficient data to show penthiopyrad was ultimately degraded to a level > 70% within 28 days (equivalent to a half-life < 16 days) or transformed to non classifiable products.

Bioaccumulation

Penthiopyrad has a low potential to bioaccumulate based on steady state mean BCF values of 158-186 L/kg (0,1 µg/L nominal exposure concentration) and 155-182 L/kg (10 µg/L nominal exposure concentration) obtained in the experimental OECD TG 305 which was performed under GLP.

Aquatic toxicity

Acute Toxicity: Fish are the most acutely sensitive trophic group with the lowest LC_{50} of 0.290 mg/L being observed for Fathead Minnow (*Pimephales promelas*);this is within the range 0.1 to 1.0 mg/L.

Chronic Toxicity: Adequate chronic toxicity data are available for all three trophic levels and the lowest value of 0.051 mg/L is a 33-day NOEC for the Fathead Minnow (*Pimephales promelas*) which is within the range 0.01 to 0.1 mg/L.

Conclusion on the classification

Penthiopyrad is considered not rapidly degradable and does not fulfil the criteria for bioaccumulation potential. The lowest acute toxicity value falls in the range 0.1 mg/L < $L(E)C_{50}$ ≤ 1 mg/L and the lowest chronic toxicity value lies in the toxicity range of 0.01 < NOEC ≤ 0.1 mg/L.

RAC concludes that penthiopyrad fulfils the CLP criteria for classification as **Aquatic Acute 1 - H400** with an **M-factor of 1** and **Aquatic Chronic 1 - H410** with an **M-factor of 1**.

ANNEXES:

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

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