Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Fluazinam

EC Number: -

CAS Number: 79622-59-6

ECHA/RAC/CLH-O-0000002667-66-01/F

Adopted

15 June 2012

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

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

Substance Name: **Fluazinam**

EC Number: **-**

CAS Number: **79622-59-6**

The proposal was submitted by **Austria** and received by RAC on **20 May 2011.**

The proposed harmonised classification is

	Regulation (EC) No 1272/2008	**Directive 67/548/EEC**
Current entry in Annex VI to CLP Regulation	-	-
Proposal by the dossier submitter for consideration by the RAC	Skin Irrit. 2 (H315) Skin Sens. 1 (H317) Eye Dam. 1 (H318) Acute Tox. 4 (H332) STOT SE 3 (H335) Repr. 2 (H361) Aquatic Acute 1 (H400) Acute M-factor = 10 Aquatic Chronic 1 (H410)	Xn; R20 Xi; R37/38 Xi; R41 R43 Repr. Cat. 3, R63 N; R50/53
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) as proposed by the dossier submitter	Skin Irrit. 2 (H315) Skin Sens. 1 (H317) Eye Dam. 1 (H318) Acute Tox. 4 (H332) STOT SE 3 (H335) Repr. 2 (H361) Aquatic Acute 1 (H400) Acute M-factor = 10 Aquatic Chronic 1 (H410)	Xn; R20 Xi; R37/38 Xi; R41 R43 Repr. Cat. 3, R63 N; R50/53

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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on **20 May 2011**. Parties concerned and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 4 July 2011.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Annick Pichard**
Co-rapporteur, appointed by RAC: **José Luis Tadeo**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **15 June 2012,** in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

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

OPINION OF RAC

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

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

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
612-287-00-5	Fluazinam	-	79622-59-6	Acute Tox. 4 Eye Dam. 1 Skin Sens. 1A Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H332 H318 H317 H361d H400 H410	GHS05 GHS07 GHS08 GHS09 Dgr	H332 H318 H317 H361d H410		Acute: M=10 Chronic: M=10	

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

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
612-287-00-5	Fluazinam	-	79622-59-6	Xn; R20 Xi; R41 R43 Repr. Cat. 3; R63 N; R50/53	Xn; N R: 20-41-43-50/53-63 S: (2-)26-36/37-39-46-60-61	N; R50/53: C ≥ 2,5 % N; R51/53: 0,25 % ≤ C < 2,5 % R52/53: 0,025 % ≤ C < 0,25 %	

SCIENTIFIC GROUNDS FOR THE OPINION

Fluazinam is a pyridine fungicide. In 2008 it was approved for Annex I listing under Council Directive 91/414/EEC, with Austria as Rapporteur Member State. In accordance with Article 36(2) of the CLP Regulation, fluazinam should now be considered for harmonised classification and labelling. Therefore, this proposal considers all physical and chemical properties as well as human health and environmental endpoints.
Fluazinam is currently not listed in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).

General comment

For various endpoints (carcinogenicity, acute inhalation, irritation), the dossier submitter pointed to an impurity called "impurity 5" and argued that the adverse effects observed were due to this impurity.
However, the dossier submitter did not provide any information (either toxicological or an entry in Annex VI to CLP) to support this argument. RAC considered that effects caused by an impurity should be included as part of the properties of a substance; the effects of a regular impurity such as impurity 5 of fluazinam should therefore be included in determining the classification.
This comment is in accordance with previous RAC recommendations.

Human health hazard assessment

Acute toxicity

Summary of the Dossier Submitter's proposal

After oral application to mice and rats of both sexes, fluazinam is of low acute toxicity with LD_{50} values $\geq$ 4100 mg/kg bw.
After acute dermal application of fluazinam to rats of both sexes, the acute dermal LD_{50} was > 2000 mg/kg bw.
Where the inhalation LC_{50} of fluazinam in rats is concerned, the original study design consisted of whole body exposure (which might include oral, dermal and inhalation route) and the inhalation LC_{50} of fluazinam was 0.46 mg/l. In the repeat dose study, snout only exposure was used. Furthermore, polyethylene glycol 400 was used as a solvent control in the original study. As fluazinam is completely soluble in polyethylene glycol 400, the exposure results might differ from that of a more representative exposure. In the repeat study, fluazinam was administered as *a dust aerosol* which is more representative of the potential exposure. The inhalation LC_{50} of fluazinam in rats (nose only exposure) was > 1.1 mg/l.
According to the classification criteria in Directive 67/548/EEC, fluazinam should therefore be classified as harmful by inhalation with Acute Tox. 4 (H332; "Harmful if inhaled") according to the CLP Regulation (Xn; R20 according to Directive 67/548/EEC) since the LC_{50} in rats is reported to be > 1.1 mg/l.

Comments received during public consultation

Four MSCAs made comments. Three MSCAs agreed with the proposal. One MSCA disagreed because it could not be concluded from the study that the exact LC_{50} would be below 5 mg/l.

RAC assessment - comparison with the classification criteria and justification

Comparison with the classification criteria:

According to the CLP criteria for oral and dermal acute toxicity, if the LD_{50} values are above 2000 mg/kg bw, no classification and labelling is required.
Hence, when comparing the values observed for fluazinam in the acute oral and dermal toxicity studies with the criteria, no classification and labelling is necessary.
For dust, category 4 is defined to be for a range of exposure estimates between 1 and 4.5 mg/l.
Hence, as the inhalation LC_{50} in rats following nose only exposure to fluazinam dust was > 1.1 mg/l, Acute Tox. 4 (H332; "Harmful if inhaled") is therefore justified.

During the opinion making process, a RAC member while agreeing with the proposed classification indicated to add the additional labeling for corrosive effects to the respiratory tract (EUH071), based on destruction of the respiratory tract tissue observed in the third study and supported by the corrosive effects on eyes. In relation to EUH071 the RAC considered that this would not be warranted because there were no signs of corrosivity in the acute toxicity inhalation study.

Conclusion:

When comparing the available data with the classification criteria, RAC concluded that classification of fluazinam as Acute Tox. 4 (H332) according to the CLP Regulation and as Xn; R20 according to Directive 67/548/EEC was justified.

Eye corrosion / irritation

Summary of the Dossier Submitter's proposal

In the study by Shults (1992), significant corneal epithelial effects involving up to approximately 25 % of the corneal surface in 3 rabbits were observed at 72 hours. The effect persisted through day 7 of the study in 2 rabbits.
Iridal effects were observed in four rabbits and persisted in one animal until termination of the study on day 21. Conjunctival irritation was observed in all six rabbits at the 1 hour interval and persisted in one animal until day 21. Hence, fluazinam has been shown to be severely irritating to the eyes of New Zealand White rabbits.
On the other hand, when comparing the criteria for classification and labelling according to Directive 67/548/EEC and the CLP Regulation with the effects seen in the eye irritation study by Leuschner (2006), fluazinam would not be considered irritating to the eyes.

Considering the criteria for classification and labelling according to Directive 67/548/EEC and to the CLP Regulation, fluazinam has to be classified as severely irritating to the eyes (Xi; R41, Risk of serious damage to eyes) and Eye Dam. 1 (H318), respectively, since corneal, iridal and conjunctival effects which persisted partly through day 21 of the study are reported in the Shults (1992) study.

Comments received during public consultation

Four MSCAs agreed with the dossier submitter's proposal

RAC assessment - comparison with the classification criteria and justification

Comparison with the classification criteria:

The classification is justified considering that "at least in one animal effects on cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days" are observed.

Conclusion:
When comparing the available data with the classification criteria, RAC concluded that classification as Eye Dam. 1 (H318) according to the CLP Regulation (Xi; R41 according to Directive 67/548/EEC) is justified.

Sensitisation

Skin Sensitisation

Summary of the Dossier Submitter's proposal

In the Magnusson and Kligman dermal maximization study by Cummins (1984), and in the Buehler test by Pritchard (1986), fluazinam caused evidence of delayed contact hypersensitivity (redness) in guinea pigs. In the Magnusson and Kligman dermal maximization study by Chevalier (2006), none of the test group animals showed a dermal reaction after challenge.

Considering the criteria for classification and labelling, fluazinam should be classified as Skin Sens. 1A (H317) according to the CLP Regulation (R43 according to Directive 67/548/EEC) since in skin sensitization studies (Buehler) delayed contact hypersensitivity (redness) in guinea pigs was observed in 35 % of the tested animals.

Comments received during public consultation

Four MSCAs made comments. Three agreed with the dossier submitter's proposal, one MSCA requested more information about the tests.

RAC assessment - comparison with the classification criteria and justification

Comparison with the classification criteria:

The intradermal induction was 0.2 % and redness was observed in > 15 % of the tested animals which justifies a classification as Skin Sens. 1A (H317) according to the CLP Regulation (R43 according to Directive 67/548/EEC).

Conclusion:

When comparing the available data with the classification criteria, RAC concluded that classification as Skin Sens. 1A (H317) according to the CLP Regulation (R43 according to Directive 67/548/EEC) is justified.

Reproductive Toxicity

Summary of the Dossier Submitter's proposal

Five relevant reproductive toxicity studies were presented:

- A two generation reproduction study (Tesh *et al*, 1987) for effects on fertility
- Two teratology studies in rabbits (Tesh *et al*, 1985, 1988) for developmental toxicity
- Two teratology studies in rats (Willoughby *et al*, 1984 and Beck, 2006) for developmental toxicity

Sexual function and fertility

Two generation reproduction study in rats (Tesh et al, 1987)

F1 and F2 male and female rats received diets containing 0, 20, 100 or 500 ppm of fluazinam.

Body weights were recorded weekly through mating and on gestation days 0, 6, 13 and 20 and lactation days 1, 4, 7, 14 and 21 in females. The oestrus cycle, mating performance and fertility were recorded. Offspring were observed for clinical signs and mortality and body weights were recorded on days 1, 4, 7, 11, 14 and 21 after birth. Physical development was assessed on a litter basis based on pinna unfolding, hair growth, tooth eruption and eye opening.

Findings:

Body weights

For both generations and both sexes, mean food consumption of treated animals of the low (20 ppm) and intermediate groups (100ppm) was not different compared to controls.

F_0 females and both sexes in the F_1 generation of the high dose group (500 ppm) showed a slight reduction in food intake during maturation. Mean body weight of F_0 females of the 500 ppm group was reduced during maturation (9.4 %) and early gestation periods (6 to 7 %). Throughout the lactation period, mean body weight was similar to that of controls.

Mean body weight was significantly reduced for females of the F_1 generation receiving 500 ppm of fluazinam during the maturation (4.5 to 12.2 %) and gestation periods (12 to 13 %). Mean body weight of females of the intermediate group (100 ppm) was slightly reduced (2 to 4 %) during the gestation period when compared to controls. Reduced mean body weight was also recorded in F_1 females of the 500 ppm group during the gestation and lactation period (10 to 11 %)

Mating performance

Mating performance, pregnancy rate and gestation index of the F_0 generation were not adversely affected by treatment at any dose level. Gestation length was very slightly increased (23 days versus 22.5) in the high dose group. Implantation sites and mean litter sizes were within the laboratory background control ranges.

In the F_1 generation, conception rate and fertility index were slightly reduced (75 % versus 91 % and 75 % vs. 87 %, respectively) in the 500 ppm group compared to the control group. Gestation length was slightly increased (23 days versus 22.5) in the high (500 ppm) and intermediate (100 ppm) dose groups. Numbers of implantation sites (12.2 versus 15.3) and mean litter sizes up to day 4 post partum (9.8 versus 12.4) were slightly reduced for F_1 animals of the high dose group (500 ppm) and the intermediate group (100 ppm; 13.1 and 11.3 versus 15.3 and 12.4, respectively), but not statistically significant. In both generations, survival and lactation indices and sex ratios were unaffected by treatment.

Offspring

Birth weight of F_1 pups was similar in all groups but the mean body weight gain of pups during lactation period was significantly lower in the 500 ppm group compared to the control group at weaning (44.5 g versus 50.8 g) despite the culling that occurred on day 4 post partum. The rate of physical development (pinna unfolding, hair growth, tooth

eruption and eye opening) of F_1 offspring was similar in all dose groups, although completion of these developmental landmarks was slightly earlier in the 500 ppm group (statistically significant for pinna unfolding, hair growth and eye opening).

Pathology

Necropsy of adults and offspring in both generations revealed no adverse treatment related effects.

Increased absolute liver weights, although not statistically significant, were seen in F_0 females of all treated groups and in F_0 males (23.3 g versus 22.3g) and females (14.0 g versus 13.5 g) receiving 500 ppm. Relative liver weights were significantly increased in both sexes in the highest dose groups (7.6 % for males and 12.1 % for females when compared to controls), as well as in females in the intermediate (5 %) and low dose (5.2 %) group, but a clear dose response was not observed.

Histopathology

Histopathological examination of the reproductive organs of controls and high dose group males and females of F_0 and F_1 adults revealed no changes considered to be of toxicological importance. *Livers* of F_0 and F_1 males of the 500 ppm group and also of F_1 males of the 100 ppm group showed a statistically significant increase of periacinar hepatocytic fatty changes. Livers of F_1 females of the 500 ppm group showed a statistically significant decrease of centriacinar fatty changes.

The **NOAEL for systemic toxicity** was considered to be **20 ppm**, equivalent to approximately **1.5 mg/kg bw/d for males** and **1.7 mg/kg bw/d for females**.
Therefore, the **reproductive NOAEL** can be set at **100 ppm**, equivalent to approximately **7.26 mg/kg bw/d for males and 8.43 mg/kg bw/d for females**.

Developmental toxicity

Two teratology studies in rabbits (Tesh et al, 1985, 1988)

In the **first study** (1985) results should be cautiously considered since several animals were affected by a Pasteurella infection. In this study, rabbits were exposed at dose levels of 0.3, 1 and 3 mg/kg bw fluazinam from day 6 to 19 of gestation.

There was no evidence of a teratogenic potential up to the highest dose tested (3 mg/kg bw/d). As the mean food consumption of animals treated with 3 mg/kg bw/d fluazinam was slightly, but not statistically significantly reduced, the **maternal NOAEL** can be set at **3 mg/kg bw/d**.

Based on incomplete ossification in the high dose group (incidence twice as high compared to the control group), the **NOAEL for foetal toxicity** is **1 mg/kg bw/d**.

In the **second study** (1988), the general condition of the treated white rabbits females exposed at 2, 4, 7 and 12 mg/kg was similar to that of the controls throughout the study.

Findings:

Body weights

Absolute maternal body weights in animals dosed at concentrations of 2, 4 and 7 mg/kg/day were comparable to controls. Mean body weights in 12 mg/kg/day dosed animals were lower than concurrent controls from day 10 through day 20 of gestation, reaching statistical significance on day 20 (4.07 kg versus 4.33 kg). The mean body

weights were increased during the post-dosing period and the animals had recovered approximately 50 % of their body weight gain differences with the concurrent control animals by termination (4.25 kg versus 4.40 kg)

Necropsy findings

- *Macroscopic examination* showed respiratory tract infection and areas of discolouration or pallor of livers in animals of the 4, 7 and 12 mg/kg bw/day groups.
- *Microscopic changes* included: hepatocytic hypertrophy at 7 and 12 mg/kg; increased apoptosis (2 animals out of 16); necrosis/degeneration of single hepatocytes (2 and 4 animals out of 16); increased brown pigment within the hepatocytes (3 and 2 animals out of 16); focal hepatocytic necrosis (0 and 2 animals /16); bile plugs (1 animal / 16 at the highest dose); and an increase in the number of binucleate hepatocytes. Statistical significance was reached in the 7 and 12 mg/kg bw/day groups.

So the **maternal NOAEL** can be set at **4 mg/kg/day.**

Reproduction data

Abortion

Two females (out of 17) in each of the 4 and 7 mg/kg bw/day dose groups and one out of 17 animals in the 12 mg/kg bw/day group aborted during the study. Total resorption was observed in one animal out of 17 in the 7 mg/kg bw/day group and in 5 animals out of 16 in the 12 mg/kg bw/day group.

Pre-implantation loss was elevated without dose-response relationship (between 19.8 % and 27.2 %) in all treated groups in comparison to the concurrent controls, but all values fell within the recorded background control range of the laboratory (4.7 – 35.7 % in 92 studies).

Post-implantation loss was increased at 4 mg/kg/day (25.9 %) compared to concurrent controls, however, no increase was observed at the 7 mg/kg/day dose level. A significant post-implantation loss (20 %) was noted for the 12 mg/kg bw/day group.

There were placental anomalies (not described) that exceeded the historical control high values in the 12 mg/kg/day group (18.2 %).

Foetal observations

There were several abnormalities noted in foetuses during the external and visceral examination of all treatment groups, but mainly in the high-dose group.

The incidence of several skeletal abnormalities was clearly increased in the high-dose group compared to both the study control values and the historical control range for the laboratory. Effects that may be treatment related include kinked tail tip (4.5 %), fused (9.1 %) or incompletely (2.3 %) ossified sternebrae and abnormalities of the head bones (6.8 %).

As significance can be reached at a dose level of 12 mg/kg bw/day, **the NOEL for foetal toxicity can be set at 7 mg/kg bw/day.**

Teratology study in rats (Willoughby et al, 1984)

Female rats received oral doses (gavage) containing 10, 50 and 250 mg/kg bw fluazinam from day 6 to 15 of gestation.

Findings:

Body weights

Animals dosed with 250 mg/kg/day showed weight loss between 6 and 8 days post coitum and statistically significant reduced weight gain when compared to controls during the treatment period (-41.2 % less body weight gain than the control group) which persisted until the end of the gestation (-15.5 % less body weight gain than the control group). This effect on the body weight at the top dose was associated with a statistically significant reduction in the mean food consumption during the early dosing period. Weight gain in the 50 mg/kg bw/day group was marginally, but not significantly, reduced. So the **maternal NOAEL** was considered to be **10 mg/kg/day.**

Necropsy findings

Macroscopic examination of dams on day 20 of gestation revealed no changes attributable to treatment.

Reproduction data

- Numbers of implantations, live young and the extent of pre-implantation loss were unaffected by treatment with fluazinam.
- Post-implantation loss was increased (11 % versus 4.2 %) in the 250 mg/kg/day group compared to concurrent controls, however, not statistically significant and within the range of the historical controls of the laboratory.
- Foetal and placental weights were significantly reduced in the high dose group (250 mg/kg) (2.81 g versus 3.19 g and 0.47 g versus 054 g, respectively) These reductions were also seen at the intermediate dose level (50 mg/kg bw/day) but without statistical significance (3.11 g and 0.49 g respectively). The 10 mg/kg/day dose group was unaffected by treatment with fluazinam.
- Abnormalities were noted in the litters of four high-dose animals and included facial/palatal cleft and/or diaphragmatic hernia. Three litters had just one foetus with one of the abnormalities and the remaining litter with up to 8 foetuses with facial/palatal cleft.
- The skeletal examination showed a reduction in the degree of ossification of cranial bones (54.3 % versus 22.9 %), sternebrae, caudal vertebrae (13 % versus 6.4 %), metacarpals/metatarsals (10.1 % versus 7.1 %) and pubic bones in high-dose foetuses (22.5 % versus 10.7 %). They were outside of the historical control.
- An increased incidence of gross morphological foetal abnormalities (diaphragmatic hernia (3.1 %) and facial/palatal cleft (2.3 %) was recorded at the top dose, values were outside the range of the concurrent controls and the recorded background controls of the laboratory.

In this study, fluazinam showed a teratogenic potential at a maternally toxic dose of 250 mg/kg bw/day after oral application. The **NOAEL** for developmental effects was considered to be **10 mg/kg bw/day**.

Teratology studies in rats (Beck, 2006)

Mated females rats received oral doses (gavage) containing 10, 50 and 300 mg/kg bw fluazinam from day 6 to 19 of gestation.

Findings:

Body weights

Pregnant females of the 300 mg/kg bw/day group lost weight between day 6 and 9 of pregnancy (-1.8 %), and the mean body weight of this group remained statistically

significantly inferior compared to the control group from day 9 to day 20 of pregnancy (4.4 % on day 9 of gestation to 8.9 % on day 20 of gestation). Due to decreased mean gravid uterine weights, reduced mean foetal weights and decreased mean numbers of viable foetuses, a statistically significant reduced mean body weight gain during gestation days 15 – 20 was observed in animals of the high dose group. The mean net body weight gain of the high dose group was therefore 30.1 % below the value of the control group. At 50 mg/ kg/day, the terminal net mean body weight of females was also reduced when compared to control (11.2 %) but without statistical significance.

The **NOAEL** for maternal toxicity was considered to be **10 mg/kg bw/day**.

Reproduction data

Mean litter data for the different treatment groups showed that the percentage of viable foetuses in the litters in the 300 mg/kg bw/day group were statistically significantly lower (85.8 versus 96.4 %) than controls due to an increase in the mean litter proportion of post-implantation loss (early resorptions) (14.2 % versus 3.6 %; statistically significant). Mean foetal body weights (3.4 and 3.0 g versus 3.6 g) were statistically significantly reduced in the 50 and 300 mg/kg bw/day groups. Mean placental weights, number of corpora lutea, implantation sites and mean litter proportion of pre-implantation loss were similar to controls in all dose groups.

External malformations

External malformations were noted in the control, 10, 50 and 300 mg/kg bw/day groups, respectively. Due to the low mean litter proportions of these findings, the lack of statistical significance and the fact that the occurrence of the findings were within historical control data range, all external malformations in the 50 and 300 mg/kg bw/day groups were considered unrelated to treatment.

Visceral malformations and variations

Mean litter proportions of renal papillae not developed and/or distended ureter(s) in the 50 and 300 mg/kg bw/day groups (1.6 % and 2.5 % per litter, respectively) were increased compared to concurrent controls (0.8 % per litter). Although the differences were not statistically significant compared to the concurrent controls, the values exceed the maximum mean value in the historical control data (0.8 % per litter). A dose-related increase of renal papillae not fully developed were observed in 2(1) and 5(4) foetuses(litters) in the 50 and 300 mg/kg bw/day groups, respectively.

Skeletal malformations and variations

Treatment related differences in mean litter proportions of skeletal developmental variations (unossified sternebrae, reduced ossification of the skull, cervical centrum and vertebral arches) were noted in the 50 and 300 mg/kg bw/day groups, although not statistically significant compared to concurrent controls. However, these developmental variations were considered treatment related because they corresponded to the reduced mean foetal body weights in the 50 and 300 mg/kg bw/day groups, indicating a developmental delay and/or were outside the historical control data range.
Mean litter proportion of 27 pre-sacral vertebrae in the 300 mg/kg bw/day group (3.2 % per litter) was higher than concurrent controls (0.0 % per litter) and outside the historical control data range (1.8 % per litter), although not statistically significant.

The **NOAEL for developmental effects** can be set at **10 mg/kg bw/day**.

Dossier submitter's classification proposal:

Considering the criteria for classification and labelling according to Dir 67/548/EEC and the CLP Regulation, fluazinam should be classified as Repr. 2 (H361) under the CLP Regulation and labelled with the signal word "Warning" (Repr. Cat. 3; R63, Possible risk of harm to the unborn child, Directive 67/548/EEC) respectively, for the following reasons:

In a teratology study in rabbits, increased incidences of foetal abnormalities (placental abnormalities, kinked tail tip, fused or incompletely ossified sternebrae and abnormalities of the head bones) were observed.

In a teratology study in rats, foetal and placental weights were significantly reduced, foetal immaturity and gross morphological foetal abnormalities were reported. In a second study in rats, post-implantation loss, resulting in a statistically significant decrease of viable foetuses was reported. Decreased foetal weight, not developed renal papillae, distended ureter(s), reduced ossification of the skull and vertebral arches and unossified sternebrae were observed.

Comments received during public consultation

- Five MSCAs supported the classification proposed by the dossier submitter.

- One MSCA considered that the occurrence of palatal clefts and diaphragmatic hernia in rat foetuses at a dose level of 250 mg/kg bw (Willoughby *et al*. 1984), significant signs of foetal growth retardation in rats at a dose level of 300 mg/kg bw (Beck *et al.* 2006), and high resorption rates in rats at a dose level of 300 mg/kg bw (Beck *et al.* 2006), would justify a classification for **Repr. 1B (H360D)** under the CLP Regulation (**Repr. Cat. 2; R61;** Directive 67/548/EEC). On the other hand, cleft palates and diaphragmatic hernia were not observed in the study by Beck *et al*. (2006) up to a dose level of 300 mg/kg bw/d and the observed findings in foetuses need to be balanced against maternal toxicity.

- One notifier commented on the classification and disagreed with the dossier submitter's proposal. The notifier provided the study of Beck, 2006, which was assessed by the dossier submitter. The notifier's rationale for no classification is based on the two teratogenicity studies in rat. The first study conducted in 1985 used corn oil as vehicle. The quality was not described and it is suggested that the difference of results compared to the second study could be linked to the vehicle.

RAC assessment - comparison with the classification criteria and justification

Comparison with the criteria:

Considering the criteria for classification and labelling, fluazinam should be classified as Repr. 2 (H361d) according to the CLP Regulation (Repr. Cat. 3; R63, according to Directive 67/548/EEC) for the following reasons:
In a teratology study in rabbits, increased incidences of foetal abnormalities (placental abnormalities, kinked tail tip, fused or incompletely ossified sternebrae and abnormalities of the head bones) were observed at the top dose (12 mg/kg). The effects were seen in presence of maternal toxicity and were outside the range of historical of control values.
In a teratology study in rats, foetal and placental weights were significantly reduced, foetal immaturity and gross morphological foetal abnormalities were reported at maternally toxic doses. In this study, impact on the foetal development of the vehicle used (corn oil) cannot be dismissed.
In a second study in rats, post-implantation loss, resulting in a statistically significant decrease of viable foetuses, was reported. Decreased foetal weight, not developed renal papillae, distended ureter(s), reduced ossification of the skull and vertebral arches and unossified sternebrae were observed at 300 mg/kg in presence of maternal toxicity.
There is no reason to increase the classification to Repr. 1B according to the CLP Regulation (Repr. Cat 2; R61 according to Dir 67/548/EEC), since the adverse effects on

development were seen in both species only at dose levels where maternal toxicity was also seen and since the effect of the vehicle on the occurrence of severe abnormalities cannot be dismissed in one rat study.

To complete the analysis of the studies, the two generation study on rats shows that there is no effect on fertility and no effects on the postnatal development of the pups related to fluazinam toxicity.

Reproductive toxicity category 2 in the CLP Regulation is dedicated to substances which are "suspected human reproductive toxicants". "*Substances are classified in category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in category 1*."

The incidence of abnormalities, their type and distribution among litters and species do not provide strong enough evidence of "known" teratogenicity to fulfil the CLP category 1B criteria as quoted below:

Reproductive toxicity category 1 in the CLP Regulation is dedicated to "substances which are known or presumed human reproductive toxicant". *Substances are classified in category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility or on development in humans or when there is evidence from animal studies possibly supplemented with other information, to provide as strong presumption that the substance has the capacity to interfere with reproduction with humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (category 1A) or from animal data (category 1B).*

Conclusion:

When comparing the available data with the classification criteria, RAC concluded that Repr. 2 (H361d) according to the CLP Regulation (Repr. Cat. 3; R63 according to Directive 67/548/EEC) is justified.

Environmental hazards

Summary of the Dossier Submitter's proposal

The dossier submitter proposed Aquatic Acute 1 (H400) with an M-factor of 10 and Aquatic Chronic 1 (H410) (no M-factor proposed) according to CLP. The proposed classification according to Directive 67/548/EEC was N; R50/53 without specific concentration limits.

Degradation and bioaccumulation

Hydrolysis

Fluazinam is hydrolytically stable in acidic conditions, while under neutral conditions it is rapidly hydrolysed with DT_{50} values in the range 2.7 – 4.5 d. Its major metabolite CAPA is steadily hydrolyzed to DCPA with a DT_{50} value of about 32 days. DCPA is resistant to further degradation.

Photolysis

Fluazinam undergoes rapid aquatic photolytic degradation with DT_{50} = 2.5 d. The multitude of photolytic degradation products result from a complex degradation pathway with reduction and hydrolysis of NO_2, Cl and CF_3 substituents, the cleavage between the ring systems, ring opening and oxidative fragmentation with CO_2 production. The only major metabolite is G-504 (max. 17.1 % after 10 days). CO_2 production was 17.7 % after 30 days of exposure to simulated sunlight, indicating low ultimate photodegradation.

Biotic degradation

The substance is not readily degradable under test conditions. In a "28-Day-Manometric Respirometry Test" after 28 days the BOD in the test flasks was 12 and 14 mg O_2/l (arithmetic mean 13 mg O_2/l). The biodegradation rate was 1 %, based on $ThOD_{NH4,}$ and 0 %, based on $ThOD_{NO3}$.

In water-sediment study fluazinam was rapidly degraded with a DT_{50} in the whole system in the range from 3.1 to 5.7 d. The metabolite AMPA was reported as the major metabolite in sediment and was degraded with DT_{50} value of 33.9 days ("Emperor" sediment). The mineralization to CO_2 was low with maximal amounts of 2.2 % at day 100 indicating very low ultimate degradation.

Aquatic bioaccumulation

At 25ºC, the log K_{ow} of fluazinam is 4.19 (pH 4 to 7), indicating a potential for bioaccumulation.
In addition, a bioaccumulation test showed moderate bioaccumulation in fish, with a BCF of 960 - 1090 (whole fish). BCF was determined only for viscera and fillet, but was not corrected for lipid content.

Acute (short-term) aquatic toxicity

The results of short-term aquatic toxicity data for fish, crustaceae and algae are summarized in the table below. According to these studies, fluazinam is of high toxicity for all taxonomic groups, with a lowest EC_{50} value of 0.036 mg/l for fish (*Oncorhynchus mykiss*), based on measured concentrations. This short-term aquatic toxicity study was conducted at pH 6.8 to 7.1. This implies that the un-dissociated form was dominant (pKa=7.34), and therefore it is likely to be conservative, because fluazinam generally showed lower toxicity at basic pH.

Data element: Acute (short-term) aquatic toxicity of the active substance Fluazinam Generally expressed in terms of LC_{50} or EC_{50} (mg/l)				
	L(E)C_{50} [mg/l]	Test guideline / design	GLP (y/n)	Reliability
Fish (96 hr LC_{50}):				
*Oncorhynchus mykiss***	**0.036***	FIFRA Guideline 72-1	y	y
Crustacea (48 hr EC_{50}):				
*Daphnia magna***	0.220*	OECD 202	y	y
Algae (72 or 96 hr E_rC_{50}):				
*Pseudokirchn. Subcapitata****	> 0.220*	OECD 201	y	y
Conclusion: relevant endpoint for classification is LC/EC_{50} = 0.036 mg/l (measured pH 6.8 – 7.1)				

* Based on the mean measured concentrations.

**Toxicity tests on fish and Daphnia were conducted under flow-through conditions with verification of fluazinam concentration.
***Algae test were conducted under static conditions with verification of fluazinam concentration.

Chronic (long-term) aquatic toxicity

The results of long-term aquatic toxicity data for fish, crustacea and algae, summarized in the table below, show that fluazinam is highly toxic for all taxonomic groups. The relevant endpoint for chronic classification is the NOEC for fish (*Pimephales promelas)*. This value is $NOEC_{F0\ growth}$ = 0.0029 mg/l, based on mean measured concentration. This long-term toxicity study, as well as the short term study, was conducted at pH 6.8 to 7.1 and is considered to be conservative, because fluazinam generally showed lower toxicity at basic pH.

Data element: Chronic (long-term) aquatic toxicity of the active substance Fluazinam Generally expressed in terms of NOEC (mg/l)				
	NOEC [mg/l]	Test guideline / design	GLP (y/n)	Reliability
Fish (34 d $NOEC_{F0\ growth}$)				
*Pimephales promelas***	**0.0029***	FIFRA Guideline 72-5	y	y
Crustacea (21 d $NOEC_{growth,}$):				
*Daphnia magna***	0.0125	OECD 202 (1984)	y	y
Algae (96 h NOEC):				
*Pseudokirchneriella subcapitata****	0.048*	OECD 201	y	y
Conclusion: relevant endpoint for classification is $NOEC_{F0\ growth,\ F1\ survival}$ = 0.0029 mg/l (measured pH 6.7–7.6)				

* Based on the mean measured concentrations.
**Toxicity tests on fish and Daphnia were conducted under flow-through conditions with verification of fluazinam concentration.
***Algae test were conducted under static conditions with verification of fluazinam concentration.

Aquatic toxicity of degradation products

Acute toxicity data are available for AMPA, the major metabolite resulting from biodegradation. This substance is poorly soluble and no acute toxicity is recorded at levels up to the water solubility. AMPA is not rapidly degradable (DT_{50} = 33.9 d ("Emperor" sediment)) and no experimentally determined BCF or log K_{ow} values are available. There are no data on chronic toxicity for this substance.

No data on aquatic toxicity of DCPA (metabolite formed in hydrolysis) and G-504 (metabolite formed in photolysis) are available.

Comments received during public consultation

Several comments were received during public consultation concerning the degradation of fluazinam. The comments proposed the consideration of fluazinam as non-rapidly degradable due to low mineralisation, and the setting of a chronic M-factor of 10.

RAC assessment - comparison with the classification criteria and justification

Endpoint	Classifcation Criteria		Evidence for Fluazinam
	CLP (2nd ATP)	**DSD**	
Degradation Fluazinam	Fluazinam it is rapidly hydrolysed with DT_{50} values in the range 2.7 – 4.5 under environmental relevant conditions. DCPA, the stable main metabolite, was found in amounts of 70.9 % (label I, day 56) and 38 % (label II day 28) of the applied radioactivity. Fluazinam is not readily biodegradable under OECD 301F test conditions within 28 days (pH 7.4). In water/sediment studies Fluazinam was degraded with a DT_{50} in the whole system in the range from 3.1 to 5.7 d. The metabolite AMPA was reported as major metabolite with amounts of max. 26.7 % AR (maximum of phenyl label; system 1, day 14) in sediment and was degraded with DT_{50} value of 33.9 days (average both labels; 24 days (phenyl label) and 43.7 days (pyridyl label; "Emperor" sediment). Although AMPA is the major metabolite, other metabolites are formed for which no data has been provided and thus it has not been demonstrated that they do not meet the criteria for classification. The mineralization to CO_2 was low with maximal amounts of 2.2 % at day 100 indicating very low ultimate degradation.		Fluazinam is **not readily biodegradable** under OECD 301F test conditions within 28 days. Fluazinam indicates primary degradation in abiotic degradation tests and in the water/sediment study, but ultimate degradation is low in any of these degradation studies. Due to -the low ultimate degradation of Fluazinam -missing data on aquatic toxicity of DCPA (metabolite formed in hydrolysis) as well as other metabolites formed in the water/sediment study, **Fluazinam is not rapidly degradable.**
Bioaccumulation Fluazinam	**BCF > 500** (960 – 1090) **log K_{ow} is > 4** (4.19 at pH 4 - 7)	**BCF > 100** (960 – 1090) **log K_{ow} is > 3** (4.19 at pH 4 - 7)	The BCF* and the log K_{ow} exceeds the classification criteria for Directive 67/548/EEC as well as for CLP indicating a **potential for bioaccumulation.** *In the DAR the BCF was determined only for viscera and fillet, but was not corrected by lipid content. The classification as **R53** according to Directive 67/548/EEC is based on the **non rapid degradation** and on the observed potential for bioaccumulation.

Endpoint	Classifcation Criteria		Evidence for Fluazinam
	CLP (2nd ATP)	**DSD**	
Acute aquatic toxicity Fluazinam	**LC/EC_{50} ≤ 1 mg/l**		Fluazinam is of high acute toxicity to fish (*Oncorhynchus mykiss*) with a LC_{50} = 0.036 mg/l and fulfills the criteria for the proposed classification as **R50** according to Directive 67/548/EEC and the criteria for the proposed classification as **Aquatic Acute 1** (H400) according to Regulation EC 1272/2008. An **M-factor of 10** is applicable based on 0.01 <$L(E)C_{50}$ ≤0.1 mg/l.
	Active substance Fluazinam		
	Oncorhynchus mykiss **LC_{50} = 0.036 mg/**l		
	Daphnia magna EC_{50} = 0.220 mg/l		
	Pseudokirchn. Subcapitata E_rC_{50} = 0.220 mg/l		
Chronic aquatic toxicity Fluazinam	**For non rapidly degradable substances: 0.001 <NOEC ≤0.01 mg/l**		Fluazinam is not rapidly degradable and of high chronic toxicity to fish (*Pimephales promelas*) with $NOEC_{F0\ growth}$ = 0.0029 mg/l. Therefore Fluazinam fulfills the criteria for the proposed classification as **Aquatic Chronic 1** (H410) according to Regulation EC 1272/2008. An **M-factor of 10** is applicable based on 0.001 < NOEC ≤ 0.01 mg/l.
	Pimephales promelas	**$NOEC_{F0\ growth}$= 0.0029mg/l**	
	Daphnia magna	$NOEC_{growth}$ = 0.0125 mg/l	
	Pseudokirchn. Subcapitata	NOEC = > 0.048 mg/l	

Endpoint	CLP (2nd ATP)		Evidence for AMPA
	CLP (2nd ATP)	**DSD**	
Degradation of metabolite AMPA	No studies on photolysis, hydrolysis and ready biodegradability are available. In a water/sediment study AMPA was reported as major metabolite with amounts of max. 26.7 % AR (maximum of phenyl label; system 1, day 14) in sediment and was degraded with DT_{50} value of 33.9days (average both labels; 24 days (phenyl label) and 43.7 days (pyridyl lab el; "Emperor" sediment)		Based on DT_{50} of 33.9 d in a water/sediment system**, AMPA should be considered as not rapidly degradable.**
Bioaccumu-lation of metabolite AMPA	**BCF > 500 log K_{ow} > 4**	**BCF > 100 log K_{ow} > 3**	No experimentally determined BCF or log K_{ow} data available
Acute aquatic toxicity of metabolite AMPA	**$L(E)C_{50}$s are above the water solubility; Water solubility ≤ 1 mg/l**		"**No acute toxicity**" as $L(E)C_{50}$s are above the water solubility. Due to the low solubility of the test substance the tests could not

	Brachydanio rerio	
	Daphnia magna	
	Scenedesmus subspicatus	
Chronic aquatic toxicity of metabolite AMPA	**L(E)C_{50}s are above the water solubility ; Water solubility = <1 mg/l** (no chronic aquatic toxicity studies with fish or daphnia are available)	AMPA was poorly soluble and no acute toxicity is recorded at levels up to the water solubility. AMPA is not rapidly degradable (DT_{50} water/sediment = 33.9 d) and no experimentally determined BCF or log K_{ow} values are available. AMPA (classification is based on acute aquatic toxicity data, no chronic aquatic toxicity studies with fish or daphnia are available) fulfills the criteria for the proposed classification as **R53** according to Directive 67/548/EEC and the criteria for the proposed classification as **Aquatic Chronic 4** (H413) according to Regulation EC 1272/2008.
	Brachydanio rerio	
	Daphnia magna	
	Scenedesmus subspicatus	

Conclusion:

RAC concludes that an environmental classification for fluazinam as, Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) according to the CLP Regulation, with an M-factor of 10 for both acute and chronic categories; and as N; R50/53 according to Directive 67/548/EEC, is justified.

ANNEXES:

Annex 1 Background Document (BD)[1]

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

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