Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of

Flutianil (ISO);
(2*Z*)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}
[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]
acetonitrile

EC Number: -
CAS Number: 958647-10-4

CLH-O-0000001412-86-101/F

Adopted
10 March 2016

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10 March 2010

CLH-O-0000001412-86-101/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: **Flutianil (ISO); (2Z)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile**

EC Number: **-**

CAS Number: **958647-10-4**

The proposal was submitted by the **United Kingdom** and received by RAC on **11 May 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 **16 June 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **31 July 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Boguslaw Baranski**

Co-Rapporteur, appointed by RAC: **Riitta Leinonen**

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 was adopted on **10 March 2016** by **consensus**.

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 state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	xxx-xxx-xx-x	flutianil (ISO); (2Z)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile	Not assigned	958647-10-4	Repr. 2 Aquatic Chronic 1	H361d H410	GHS08 GHS09 Wng	H361d H410		M=100	
RAC opinion	xxx-xxx-xx-x	flutianil (ISO); (2Z)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile	Not assigned	958647-10-4	Aquatic Chronic 1	H410	GHS09 Wng	H410		M=100	
Resulting Annex VI entry if agreed by COM	xxx-xxx-xx-x	flutianil (ISO); (2Z)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile	Not assigned	958647-10-4	Aquatic Chronic 1	H410	GHS09 Wng	H410		M=100	

GROUNDS FOR ADOPTION OF THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

In a standard study (EEC A.10), flutianil did not ignite and consequently does not meet the criteria for classification as a flammable solid. In addition, experience in handling and use indicates that the substance is not pyrophoric and does not emit flammable gases on contact with water.

Following a theoretical consideration of the chemical structure, flutianil is not considered to be explosive. Furthermore, no sharp exothermic reaction was observed by differential scanning calorimetry up to 600°C.

In a standard study (EEC A.17), flutianil did not exhibit oxidising properties. Consequently, it does not meet the criteria for classification as an oxidising solid.

The substance does not contain groups which are indicative of explosive or oxidising properties.

The Dossier Submitter (DS) proposed no classification for physico-chemical properties based on the negative results in standard tests.

Comments received during public consultation

One MSCA supported the DS's proposal not to classify flutianil for physico-chemical properties.

Assessment and comparison with the classification criteria

Since flutianil does not have explosive or oxidising properties and is not (auto-)flammable, RAC supports **no classification** for physico-chemical properties, as proposed by the DS.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral

Flutianil was tested for acute oral toxicity in female Wistar rats, according to OECD test guideline (TG) 423, GLP compliant study. No deaths were observed at the single dose tested, 2000 mg/kg bw/d. No treatment related clinical signs of toxicity or effects on body weight were observed. No abnormalities were recorded at necropsy.

No classification for acute oral is proposed by the DS, as the LD_{50} was >2000 mg/kg bw/d.

Dermal

Flutianil was tested for acute dermal toxicity in Wistar rats, according to OECD TG 402, GLP compliant study. No deaths were observed at the single dose tested, 2000 mg/kg bw/d. No treatment related clinical signs of toxicity or effects on body weight were observed. No abnormalities were recorded at necropsy.

No classification for acute dermal toxicity is proposed by the DS, as the LD_{50} was >2000 mg/kg bw/d for both males and females.

Inhalation

In an OECD TG 403, GLP compliant, acute inhalation study, rats were nose-only exposed to single dose 5.17 mg/L of flutianil for 4 hours. No deaths were observed at dose 5.17 mg/L. No abnormalities were found at necropsy except for slight reddening of the left maxilloturbinate of the nasal cavity in one animal.

No classification for acute inhalation is proposed by the DS, as the LC_{50} was >5.17 mg/L for both males and females.

Comments received during public consultation

Two MSCAs supported the DS's proposal not to classify flutianil for acute dermal or inhalation toxicity.

Assessment and comparison with the classification criteria

Oral

Since the oral LD_{50} value exceed the value for which classification for acute oral toxicity is required (2000 mg/kg bw), RAC concluded that flutianil should **not be classified** for acute oral toxicity according to the CLP criteria.

Dermal

Since the dermal LD_{50} value in male and female rats is above the threshold value for classification (2000 mg/kg bw), RAC concluded that flutianil should **not be classified** for acute dermal toxicity according to the CLP criteria.

Inhalation

Since the inhalation LC_{50} value in male and female rats is above the threshold value for classification (5 mg/L/4h), RAC concluded that flutianil should **not be classified** for acute inhalation toxicity according to the CLP criteria.

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

Summary of the Dossier Submitter's proposal

The information gained from the acute toxicity studies showed no indication that flutianil causes specific organ toxicity to rats after a single exposure; therefore no classification for STOT SE was proposed by the DS.

Comments received during public consultation

Two MSCAs supported the DS's proposal not to classify flutianil for STOT SE.

Assessment and comparison with the classification criteria

According to CLP criteria, substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure are classified in STOT SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect. Classification in STOT SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

In the acute toxicity studies there were no clinical signs of toxicity following oral and dermal exposure to flutianil. Signs following inhalation exposure to flutianil were indicative of non-specific, general toxicity and were observed at concentration of > 5.17 mg/L, which was non-lethal to rats. Slight irritation of the nasal mucosa was seen only in one rat exposed by nose at a non-lethal concentration of 5.17 mg/L and the negative skin and eye irritation studies indicate that flutianil would not be irritating to the respiratory tract.

There was no clear evidence of specific toxic effects on any target organ or tissue and no signs of respiratory tract irritation or narcotic effects were observed, therefore in the opinion of RAC **no classification for specific target organ toxicity (single exposure)** is warranted.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The skin irritation potential of flutianil was assessed in a standard skin irritation GLP compliant study (OECD TG 404) in three female Japanese White rabbits. Neither erythema nor oedema was seen in any of the animals; the average individual scores over 24, 48 and 72 hours were zero. The DS proposed no classification for skin corrosion/irritation.

Comments received during public consultation

Two MSCAs supported the DS's proposal to not classify flutianil for skin corrosion/irritation.

Assessment and comparison with the classification criteria

In the available study, no skin irritation reactions were observed in any of the three tested rabbits at any time after removal of the test material (all scores were 0). RAC supports the proposal for **no classification for skin corrosion/irritation**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The eye irritation potential of flutianil was tested in a standard eye irritation GLP compliant study (OECD TG 405) in six female Japanese White rabbits. In the three animals where the eyes were not washed after treatment, conjunctival redness and discharge (grade 1) in 3/3 and conjunctival chemosis in 1/3 animals at 1 hour only were observed. These effects had fully resolved in all animals by 24 hours. In the other three animals where the eyes were washed after treatment no eye irritation reactions were observed in the cornea, iris or conjunctivae. As the individual eye irritation scores for corneal, iridial and conjunctival redness and chemosis were 0 over 24-72 hours, the DS proposed no classification for eye irritation.

Comments received during public consultation

Two MSCAs supported the DS's proposal not to classify flutianil for serious eye damage/eye irritation.

Assessment and comparison with the classification criteria

Application of flutianil to the eyes (not washed with water after treatment) of three rabbits resulted in conjunctival redness, discharge and chemosis after 1 hour, whereas the cornea and the iris were not affected. Responses seen were completely reversed within 24 hours of application. In all six rabbits (three with eye washed and three without eye washing) the mean scores over 24-72 hours for corneal opacity, iritis, conjunctival redness and chemosis were below

the threshold values for classification (1, 1, 2 and 2, respectively). RAC therefore agrees with the DS that **classification for eye damage/irritation is not required**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The potential of flutianil to cause skin sensitisation was investigated in a GLP compliant Magnusson and Kligman Guinea Pig Maximisation test according to OECD TG 406. The induction phase consisted of intradermal injections of 2% (w/v) of the tested substance in olive oil; topical induction and challenge were with 50% and 25% flutianil, respectively, in olive oil. No skin reactions were observed following the challenge.

Based on the absence of skin reactions, the DS proposed no classification for skin sensitisation.

Comments received during public consultation

Two MSCAs supported the DS's proposal to not classify flutianil for skin sensitisation potential.

Assessment and comparison with the classification criteria

In the Magnusson and Kligman Guinea Pig Maximisation the criterion for classification as a skin sensitiser (≥30% of animals exhibiting a positive reaction) was not met, therefore RAC agreed with the proposal for **no classification for skin sensitisation**.

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

Summary of the Dossier Submitter's proposal

The CLH dossier contains several standard repeated dose toxicity studies on flutianil using the oral route in mice (28-day and 90-day), in rats (28-day and 90-day) and in dogs (28-day, 90-day and 1-year) and the dermal route in rats (28-day). In addition, there are chronic toxicity studies in rats and mice, reported in the section on carcinogenicity. Based on results of these studies, the DS did not propose classification for STOT RE.

Oral

Studies on repeated dose toxicity after oral administration are summarised in the table below:

MOUSE		
Method	Results (effects of major toxicological significance)	Remarks
28-day, mouse (CD1) (6 animals/sex/group) (dosing: 28 Dec 2004 – 25 Jan 2005) oral: feed 0, 100, 1000, 3000, 10000 ppm equiv. to 0, 14, 138, 424, 1393 (♂) and 0, 16, 155, 497, 1601 mg/kg bw/d (♀)	**100**, **1000**, **3000**, **10000 ppm**: No adverse effects noted NOAEL: *ca* 10000 ppm (1393/1601 mg/kg bw/d ♂/♀)	Well conducted, GLP compliant study Purity: 99.38%

MOUSE		
Method	Results (effects of major toxicological significance)	Remarks
OECD TG 407 (1995), GLP **GV for STOT RE 2 for a 28-day study = 300 mg/kg bw/d[a]**		
90-day, mouse (CD1) (10 animals/sex/group) (dosing: 13 June 2005 – 13 Sept 2005) oral: feed 0, 1000, 3000, 10000 ppm equiv. to 0, 138, 409, 1387 (♂) and 0, 159, 481, 1555 mg/kg bw/d (♀) OECD TG 408 (1998), GLP **GV for STOT RE 2 for a 90-day study = 100 mg/kg bw/d[a]**	**10000 ppm:** 1/10 ♂: atrophy of the seminiferous tubules of the testes 2/10 ♀: hepatic microgranuloma **3000 ppm**: 1/10 ♂: died after 5 days. Had 33% bw loss and atrophy of the seminiferous tubules of the testes **1000 ppm:** No adverse effects NOAEL: *ca* 1000 ppm (138 mg/kg bw/d)	Well conducted, GLP compliant study Purity: 99.26%
RAT		
Method	Results (effects of major toxicological significance)	Remarks
28-day, rat (Wistar) (6 animals/sex/group) (dosing: 26 March 2004 – 26 April 2004) oral: feed 0, 20, 200, 2000, 20000 ppm equiv. to 0, 2, 16, 159, 1555 (♂) and 0, 2, 17, 171, 1714 mg/kg bw/d (♀) (analytical conc.) OECD TG 407 (1995), GLP **GV for STOT RE 2 for a 28-day study = 300 mg/kg bw/d[a]**	**20000 ppm:** Kidney: ↑ absolute (12%) and relative (14%) wt in ♂; 5/6 ♂ with hyaline droplet deposition in the proximal tubular cells **2000 ppm:** Kidney: 2/6 ♂ with hyaline droplet deposition in the proximal tubular cells **200 ppm:** Kidney: 2/6 ♂ with hyaline droplet deposition in the proximal tubular cells **20 ppm:** No observed adverse effects NOAEL: *ca* 20000 ppm (1555 mg/kg bw/d)	Well conducted, GLP compliant study Purity: 99.38%
90-day, rat (Wistar) (10 animals/sex/group) (dosing: 22 June 2004 – 24 Sept 2004) oral: feed 0, 20, 200, 2000, 20000 ppm equiv. to 0, 1, 13, 122, 1271 (♂) and 0, 1, 14, 149, 1500 mg/kg bw/d (♀) OECD TG 408 (1998), GLP **GV for STOT RE 2 for a 90-day study = 100 mg/kg bw/d[a]**	**20000 ppm:** Kidney: 10/10 ♂ with hyaline droplet deposition in the proximal tubular cells Liver: ↑ relative wt (9% in ♂; 13% in ♂), with accompanying centrilobular hepatocellular hypertrophy (7/10 ♂) ↓ total bilirubin (14% in ♂ and 29% in ♀) **2000 ppm:** Kidney: 10/10 ♂ with hyaline droplet deposition in the proximal tubular cells **200 ppm:** No observed adverse effects NOAEL: 2000 ppm (122 mg/kg bw/d)	Well conducted, GLP compliant study Purity: 99.38%

MOUSE		
Method	Results (effects of major toxicological significance)	Remarks
DOG		
Method	Results (effects of major toxicological significance)	Remarks
28-day, dog (Beagle) (2 animals/sex/group) 6 months of age at start of dosing (dosing: 31 Aug 2004 – 27 Sept 2004) oral: capsule 0, 10, 300, 1000 mg/kg/ bw/d OECD TG 409 (1998), GLP **GV for STOT RE 2 for a 28-day study = 300 mg/kg bw/d[a]**	**1000 mg/kg bw/d**: Testes: ↑ absolute (22%) and relative (16%) wt; 1/2 (*vs* 0/2 in controls) with immature organ Prostate: ↑ absolute (62%) and relative (50%) wt; 1/2 (*vs* 2/2 in controls) with immature organ Uterus: ↑ (59%) relative and (61%) absolute wt **300 mg/kg bw/d**: Prostate: ↑ absolute (54%) and relative (33%) wt; 1/2 (*vs* 2/2 in controls) with immature organ Testes: 2/2 (*vs* 0/2 in controls) with immature organ Uterus: ↑ absolute (10%) and relative (27%) wt **10 mg/kg bw/d**: Testes: 1/2 (*vs* 0/2 in controls) with immature organ NOAEL: *ca* 1000 mg/kg bw/d	Well conducted, GLP compliant study Purity: 99.38%
90-day, dog (Beagle) (4 animals/sex/group) 6 months of age at start of dosing (dosing: 15 June 2005 – 12 Sept 2005) oral: capsule 0, 30, 300, 1000 mg/kg bw/d OECD TG 409 (1998), GLP **GV for STOT RE 2 for a 90-day study = 100 mg/kg bw/d[a]**	**1000 mg/kg bw/d**: Prostate: 2/4 with cell infiltrate (1 mild, 1 minimal) *vs* 1/4 in controls (minimal); 3/4 (*vs* 4/4 in controls) with immature organ Testes: 3/4 atrophy of seminiferous tubules (2 mild, 1 minimal) *vs* 1/4 in controls (minimal) Uterus: ↑ wt (300%) **300 mg/kg bw/d**: Prostate: 2/4 with cell infiltrate (both minimal) *vs* 1/4 in controls (minimal); 2/4 (*vs* 4/4 in controls) with immature organ Uterus: ↑ wt (300%) **30 mg/kg bw/d**: Testes: 3/4 atrophy of seminiferous tubules (all minimal) *vs* 1/4 in controls (minimal) Prostate: 3/4 (*vs* 4/4 in controls) with immature organ Uterus: ↑ wt (200%) NOAEL: *ca* 300 mg/kg bw/d	Well conducted, GLP compliant study Purity: 99.38%
52-week, dog (Beagle) (4 animals/sex/group) 6 months of age at start of dosing (dosing: 19 Oct 2006 – 18 Oct 2007)	**1000 mg/kg bw/d:** No adverse effects NOAEL: *ca* 1000 mg/kg bw/d	Well conducted, GLP compliant study

MOUSE		
Method	Results (effects of major toxicological significance)	Remarks
oral: capsule 0, 30, 300, 1000 mg/kg bw/d (analytical conc.) OECD TG 452 (1981), GLP		Purity: 99.22%

NB: The values for NOAEL are provided for information only: they are the values derived from the DAR for flutianil
↓ = decrease compared to control ↑= increase compared to control
[a]The STOT RE guidance values (GV) for triggering a STOT RE 2 classification are provided for information

In the mouse, no treatment-related effects on any organ were seen in the 28-day or 90-day studies up to dietary concentrations well in excess of the guidance values. Testis atrophy was noted in a single male in the 90-day study from a dose of 409 mg/kg bw/d, but the incidence was within the laboratory historical control data (HCD) range. Testis atrophy was also noted in the 90-day study at the top dose of 1086 mg/kg bw/d, but, again, it was considered unrelated to treatment as it fell within the laboratory HCD range.

In the rat studies the kidney and liver were the main target organs of toxicity. Hyaline droplet nephropathy of the kidney was noted in males exposed at a dose of 16 mg/kg bw/d for 28 days, at a dose of 122 mg/kg bw/d for 90 days and at a dose of 82 mg/kg bw/d for 2 years (see Carcinogenicity section). These findings were associated with accumulation of $\alpha_{2\mu}$-globulin and are therefore considered not relevant to humans. Increased liver weight (usually associated with hepatocellular hypertrophy) and decreases in bilirubin in blood were noted at the high dose of 1271/1500 mg/kg bw/d (males/females) for 90 days and at 1130 mg/kg bw/d for 2 years.

In dogs, there were no clear treatment-related effects relevant for STOT RE classification, up to the limit dose in the 28-day, 90-day and 1-year studies.

Dermal

Study on repeated dose toxicity after dermal administration is summarised in the table below:

Method	Results (effects of major toxicological significance)	Remarks
28-day, rat (Wistar) (10 animals/sex/group) (dosing: 5 Nov 2007 – 18 Dec 2007) dermal: occluded, 6 h/d, 7 d/week 0, 1, 100, , 500, 1000 mg/kg bw/d OECD TG 407 (1995), GLP **(GV STOT RE 2 for a dermal 28-day study = 600 mg/kg bw/d[a])**	**1000 mg/kg bw/d:** No observed adverse effects NOAEL: *ca* 1000 mg/kg bw/d	Well conducted, GLP compliant study Purity: 99.22%

NB: The values for NOAEL and LOAEL are provided for information only: they are the values derived from the DAR for flutianil. ↓ = decrease compared to control. ↑= increase compared to control.
[a]The STOT RE guidance values (GV) for triggering a STOT RE 2 classification are provided for information

The DS concluded that there are no treatment-related findings in rats after dermal administration (28 days) of flutianil up to the maximum dose of 1000 mg/kg bw/d.

Inhalation

No relevant information is available.

Comments received during public consultation

Two MSCAs supported the DS's proposal to not classify flutianil for STOT RE.

Assessment and comparison with the classification criteria

Classification with STOT RE is triggered by the occurrence of *significant* (and/or *severe* for Category 1) *toxic effects* at doses below specified guidance values. For STOT RE Category 2, the relevant guidance values for oral exposure are ≤ 100 mg/kg bw/d (rat 90-day study) and ≤ 300 mg/kg bw/d (rat 28-day study) according to table 3.9.2-a of *Guidance on the application of the CLP criteria* v.4.1. 2015.

Target organ toxicity (repeated exposure) means specific, target organ toxicity arising from repeated exposure to a substance or mixture. However, specific toxic effects that are covered by classifications in sections 3.1 to 3.8 and 3.10 of CLP Regulation are not relevant for STOT RE classification. Therefore, the effects in reproductive organs reported in mice and dogs are evaluated under reproductive toxicity.

In the mouse, no treatment-related effects relevant for STOT RE classification were seen in the 28-day, 90-day and chronic studies up to dietary concentrations well in excess of the limit dose.

In the rat, the kidney and the liver were the main target organs of toxicity. The kidney effects (hyaline droplet nephropathy associated with $\alpha_{2\mu}$-globulin accumulation in males) were considered not relevant to humans. The liver effects (increased liver weight, hepatocellular hypertrophy and decreases in bilirubin in blood) were not considered sufficiently significant and/or adverse to fulfil the criteria for classification (CLP Regulation point 3.9.2.7 and 3.9.2.8). These effects were also noted at the high dose of 1271/1500 mg/kg bw/d (males/females) for 90 days and at 1130 mg/kg bw/d for 2 years above the guidance value for STOT RE 2.

In the dog, there were no clear treatment-related effects relevant for STOT RE classification up to the limit dose in the 28-day, 90-day and 1-year studies.

As described above, in the mouse and dog studies, no significant toxic effects relevant for STOT RE classification occurred at any dose. In the rat, the only toxic effects of relevance to humans were seen in the liver; however, these occurred at dose levels well in excess of the specified guidance values for classification with STOT RE Category 2.

On this basis, RAC is of the opinion that **classification of flutianil for STOT RE is not warranted**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The DS concluded that flutianil does not warrant classification as mutagenic, because the substance did not induced a mutagenic effect on bacterial and somatic cells in several *in vitro* and one *in vivo* assay.

Comments received during public consultation

One MSCA and one organization supported the proposal to not classify for mutagenicity, and one MSCA did not object the proposed lack of classification for mutagenicity.

Assessment and comparison with the classification criteria

Flutianil was non-mutagenic in a bacterial (Ames) assay for gene mutation when tested up to the maximum recommended dose (5000 µg/plate). In human peripheral cultured blood lymphocytes flutianil did not induce chromosomal aberrations when tested in excess of its solubility and in a mammalian cell gene mutation test assessing mutation at the *tk* locus in mouse lymphoma cells, flutianil was deemed not mutagenic up to precipitating doses.
The *in vivo* mouse bone marrow study was negative confirming the lack of potential to induce genotoxic damage *in vivo*.

Taking that data into account, RAC is of the opinion that **flutianil does not warrant classification for germ cell mutagenicity**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

The carcinogenicity of flutianil has been examined in guideline-compliant 2-year rat and 18-month mouse studies performed according to GLP, summarised in the table below:

<table>
<tr><th>Method</th><th>Results (effects of major toxicological significance)</th><th>Remarks</th></tr>
<tr><td>Combined chronic and carcinogenicity study

2-year, rat (Wistar)

Dietary
♂: 0, 60, 600, 2000, 6000 ppm equiv. to equiv. to 0, 2.5, 25, 82, 249 mg/kg bw/d

♀: 0, 60, 2000, 6000, 20000 ppm approx. equiv. to 0, 3, 111, 334, 1130 mg/kg bw/d

Carcinogenicity study:
51 animals/sex/dose

Chronic study:
12 ♂ and ♀/gp, except 21 ♂ and 21 ♀/gp at the top dose</td><td>Note: Every animal in each dose group was given a gross pathological examination. However, microscopic evaluations were only carried out on all animals in the control and top dose groups and on those animals that died early or had gross abnormalities at the end of the study.

Neoplastic findings:
Liver:
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>60</th><th>600</th><th>2000</th><th>6000</th><th>20000</th></tr>
<tr><td>♂: cholangioma (Be)</td><td>0/51</td><td>0/18</td><td>0/6</td><td>0/11</td><td>0/51</td><td>-</td></tr>
<tr><td>♀: cholangioma (Be)</td><td>0/51</td><td>0/21</td><td>-</td><td>0/12</td><td>1/17</td><td>1/51</td></tr>
<tr><td>♂: cholangiocarcinoma (Ma)</td><td>0/51</td><td>1/18</td><td>0/6</td><td>0/11</td><td>0/51</td><td>-</td></tr>
<tr><td>♀: cholangiocarcinoma (Ma)</td><td>0/51</td><td>0/21</td><td>-</td><td>0/12</td><td>0/17</td><td>0/51</td></tr>
</table>
Pancreas:
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>60</th><th>600</th><th>2000</th><th>6000</th><th>20000</th></tr>
<tr><td>♂: Pancreas: islet cell adenoma (Be)</td><td>1/51</td><td>0/10</td><td>0/4</td><td>0/6</td><td>4/51</td><td>-</td></tr>
<tr><td>♀: Pancreas: islet cell adenoma (Be)</td><td>1/51</td><td>0/17</td><td>-</td><td>0/7</td><td>0/13</td><td>0/51</td></tr>
<tr><td>♂: Pancreas: islet cell carcinoma (Ma)</td><td>1/51</td><td>0/10</td><td>0/4</td><td>1/6</td><td>0/51</td><td>-</td></tr>
<tr><td>♀: Pancreas: islet cell carcinoma (Ma)</td><td>1/51</td><td>0/17#</td><td>-</td><td>0/7#</td><td>0/13#</td><td>2/51</td></tr>
</table></td><td>Well conducted, GLP compliant study

Purity: 99.26%</td></tr>
</table>

<table>
<tr><th>Method</th><th>Results (effects of major toxicological significance)</th><th>Remarks</th></tr>
<tr><td>(dosing: 17 Mar 2005 – 28 Mar 2007)

OECD TG 453 (1981), GLP</td><td>Non-neoplastic effects:
20000 ppm (in ♀):
Liver: ↑ relative wt (17% not statistically significant) at 52 wks;

Bile duct: ↑ hyperplasia (33% vs. 8% in controls) at 52 wks;
↑ severity of hyperplasia at 104 wks, but same incidence as controls;
↓ bilirubin (43%);

Uterus: isolated histopathological findings at 52 wks and 104 wks;

6000 ppm:
Kidney: hyaline droplet deposition in proximal tubular cells in ♂;
Pancreas: islet cell hyperplasia in 2/51 ♂ (vs. 0/51 in controls);
Reproductive organs in ♂: atrophy of testis seminiferous tubule (10/51 vs.7/51 in controls); oligospermia of epididymis (6/51 vs. 4/51 in controls), atrophy of seminal vesicle (2/51 vs. 0/51 in controls) and atrophy of the glandular epithelial cell of the coagulating gland (2/51 vs. 0/51 in controls);

2000 ppm:
Kidney: hyaline droplet deposition in proximal tubular cells in ♂ (not relevant for humans);

♂: A NOAEL of 2000 ppm equivalent to 82 mg/kg bw/d;
♀: A NOAEL of 6000 ppm equivalent to 334 mg/kg bw/d</td><td></td></tr>
<tr><td>78wk, mouse (CD1)
(52 animals/sex/gp)
(dosing: 15 Dec 2005 – 25 June 2007)

oral: feed

0, 1000, 3000, 10,000 ppm equiv. to 0, 106, 321, 1084 mg/kg bw/d (♂) and 0, 105, 316, 1063 mg/kg bw/d (♀)

OECD TG 451, GLP</td><td>Neoplastic findings:

Liver:
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>1000</th><th>3000</th><th>10000</th></tr>
<tr><td>♂: Liver: hepatocellular adenoma (Be)</td><td>15/52</td><td>11/35</td><td>18/35</td><td>16/52</td></tr>
<tr><td>♀: Liver: hepatocellular adenoma (Be)</td><td>3/52</td><td>1/16</td><td>1/21</td><td>0/52</td></tr>
<tr><td>♂: Liver: hepatocellular carcinoma (Ma)</td><td>5/52</td><td>10/35</td><td>9/35</td><td>10/52</td></tr>
<tr><td>♀: Liver: hepatocellular carcinoma (Ma)</td><td>1/52</td><td>1/16</td><td>0/21</td><td>0/52</td></tr>
</table>
Non-neoplastic effects:
10000 ppm:
Testes: ↑ testes softening at gross pathology (21% vs. 5.8% in controls), ↑ testis atrophy at gross pathology (15% vs. 1.9% in controls), ↑ testis atrophy at microscopic pathology (34.6% vs. 25% in controls), ↑ interstitial cell hyperplasia (3.8% vs. 1.9% in controls);

Epididymis: ↑ oligospermia (21% vs. 11.5% in controls);</td><td>Well conducted, GLP compliant study

Purity: 99.26%</td></tr>
</table>

Method	Results (effects of major toxicological significance)	Remarks
	3000 ppm: Testes: ↑ atrophy at microscopic pathology (30.8% *vs.* 25% in controls); **1000 ppm**: No treatment-related effects identified. ♂: A NOAEL of 1000 ppm, equivalent to 105 mg/kg bw/d; ♀: A NOAEL of 10000 ppm, equivalent to 1063 mg/kg bw/d	

NB: The values for NOAEL are provided for information only: they are the values derived from the DAR for flutianil.
↓ = *decrease compared to control.* ↑= *increase compared to control.*
Ma = malignant, Be = benign; # Only tissues of animals showing macroscopic lesions were examined

The DS concluded that there is insufficient evidence for a carcinogenic effect in rats and mice, therefore no classification for carcinogenicity was proposed.

Comments received during public consultation

Two MSCAs disagreed with the DS proposal of no classification for carcinogenicity. They indicated that the occurrence of tumours in rats (pancreatic islet cell adenomas and cholangiomas) has been considered during the PRAPeR meeting by the EFSA Peer Review experts as sufficient for classification of flutianil as Carcinogenic, Category 2.

One organisation agreed with the DS proposal that there is insufficient evidence to suggest that flutianil is carcinogenic.

Assessment and comparison with the classification criteria

In the combined chronic toxicity/carcinogenicity study in the rat there was no increase in the incidence of tumours in any organ, except a very slight increase in adenomas of islet cells of the pancreas, which was observed in males in the top dose group (4/51 - 8% compared to 1/51 – 2% in controls). The combined incidence of adenoma and carcinoma was slightly higher in the males given the highest dose of 249 mg/kg/d (4/51- 8%) versus control males (2/51 – 4%). It is noted that the frequency of pancreas islet cell carcinoma in the concurrent control male rats (1/51) was higher than in males given the highest dose of 249 mg/kg bw/d (0/51). None of the differences in the incidence of tumours in male and female rats at the top dose and concurrent control groups was statistically significant in the Fisher exact probability test ($p > 0.05$). In addition, the incidence of tumours was low and no dose-response relationship was observed. There was no increase in islet cell carcinoma in either female or male rats at any dose level. Therefore it was concluded that the observed tumours originating from the islet cells of the pancreas were not treatment related.

The incidence of adenomas of islet cells of the pancreas, observed in males, in the top dose group (4/51 - 8%) only marginally exceeded (by one animal) the laboratory HCD upper range of 3/51 (6%). It is noted that the incidences of adenomas of islet cells of the pancreas in the control and treated animals in this study [28] were relatively low when compared with the HCD upper range value of 44% from the RCC database (RCC Ltd.) and of 15.8% from the publication of Carlus *et al.* (2013).
In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil in the islet cells of the pancreas.

Bile duct cholangioma, a benign lesion, occurred in 1/17 and 1/51 females in the 334 mg/kg bw/d and 1130 mg/kg bw/d dose groups, respectively, but not in the concurrent controls (0%). These differences in the incidence of cholangioma in female rats exposed at 334 mg/kg bw/d and 1130 mg/kg bw/d and in the concurrent control groups were not statistically significant in the Fisher exact probability test ($p > 0.25$ and $p > 0.5$ respectively).

It is noted that the incidence of cholangioma in this experiment was within the HCD upper range value of 2% from the RCC database (RCC Ltd.) and of 6% from public domain sources. There were no malignant bile duct tumours in any female rat and, despite the slightly increased incidence/severity of bile duct hyperplasia in the top dose females, no toxic effects were reported in this organ in either sex. In males, there were no benign tumours of the bile duct. Malignant chloangiocarcinoma was seen in 1/18 low dose males. However, there were no such tumours in any other group treated with higher doses. In addition, there were ascites and severe hepatocellular necrosis in this animal. In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil on the bile duct.

In summary, flutianil was not carcinogenic in the rat in this study [28] up to the limit dose in females (1130 mg/kg bw/d) and up to a dose causing kidney toxicity in males (249 mg/kg bw/d).

In a GLP and guideline compliant carcinogenicity study in the mouse [29] flutianil was administered to 52 male and 52 female CD1 mice/group for a minimum of 78 weeks. The dose levels were 1000, 3000 and 10000 ppm (equivalent to 106/105, 321/316 and 1084/1063 mg/kg bw/d in males/females). There were no treatment-related effects on survival. At the end of the study body weights and body weight gains for males and females were comparable to the control group. No notable changes in weight of any organ, in either sex at any dose were observed.

A marginal increase in hepatocellular carcinoma was seen in males in all dose groups. The increase did not reach statistical significance when compared with the concurrent control group.

The incidence of hepatocellular carcinoma in the 1084 mg/kg bw/d group (10/52) exceeded the maximum laboratory HCD rate (9/52) for years 2003-2012 by a single case. Hepatocellular adenoma was increased in the mid dose group, but showed no dose response relationship. These findings in males are considered to be incidental, as there was no association with an increase in pre-neoplastic findings or benign tumours, and similar findings were not seen in females.

No inhalation or dermal carcinogenicity studies were performed.

Taking into account that there is not sufficient evidence of a carcinogenic effect in rats and mice, and considering the lack of genotoxicity of flutianil, RAC, in line with the DS, is of the opinion that **flutianil does not warrant classification for carcinogenicity**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

No effects of flutianil on reproductive performance and fertility were observed in a guideline compliant multi-generation study in rats and the minor changes seen in reproductive organs were within HCD range. According to the DS, the available evidence shows that flutianil has no effects on reproductive performance and fertility, therefore the existing harmonised classification of flutianil for effects on fertility and sexual function is not justified.

However, based on data from the developmental toxicity study in rabbits showing a slight increase in the foetal incidence of visceral hydrocephalus at the top dose of 1000 mg/kg bw/d (3 foetuses in 1 litter *vs.* 0 in controls) which was marginally higher than the HCD range over 2005-2006 (maximum of 2 foetuses in a single litter) the DS concluded that classification of flutianil as Repr. 2; H361d (Suspected of damaging the unborn child) was justified.

Comments received during public consultation

Three MSCAs supported the proposed classification for developmental effects as Repr. 2; H361d for flutianil. One MSCA agreed with the DS that the substance should not be classified for effects on fertility, since no consistent or clear findings related to this hazard were reported. One MSCA indicated the need for further data in order to conclude on a possible endocrine-mediated mode of action (MoA).

One individual noted that the incidence of litters with visceral hydrocephalus in rabbits treated at the highest dose of flutianil was not increased in comparison with HCD, and the number of malformed foetuses in one affected litter was only increased by one foetus in comparison with HCD, therefore the substances was not proposed for classification as a developmental toxicant. One organisation provided a discussion document with arguments that the incidence of hydrocephalus in litters (the more relevant effect for evaluation) was within the laboratory's HCD range and public domain data, therefore its relationship to treatment with flutianil was considered questionable.

Assessment and comparison with the classification criteria

Effects on fertility and sexual function

In the mouse, testis atrophy was noted in single males in a 90-day study given a dose of $\geq$ 409 mg/kg bw/d, but the incidence was within the laboratory HCD range. Testis atrophy was also noted in the chronic toxicity/carcinogenicity study at the top dose of 1086 mg/kg bw/d, but this was considered unrelated to treatment as the incidence also fell within the laboratory HCD range.

In the rat chronic/carcinogenicity study, isolated histopathological findings of the uterus (cysts, luminal dilatation, hyperplasia and polyps) were seen in females at 1130 mg/kg bw/d and a slight increase in the incidence of histopathological findings in the male reproductive organs (atrophy of testes, seminal vesicle and coagulating gland and oligospermia of epididymis) was observed at the top dose of 249 mg/kg bw/d. Given the low incidences of these isolated findings in the uterus and in the male reproductive organs, it is unclear whether these observations were treatment-related or incidental.

In the dog, organ weight changes of the testis, prostate and uterus, and histopathological findings in testes (atrophy of seminiferous tubules) and prostate (cell infiltration) were seen from relatively low doses (10-30 mg/kg bw/d) in the 28-day and 90-day studies, but they were not confirmed in the 1-year study at similar dose levels.

The results of repeated dose toxicity/carcinogenicity studies on mice, rats and dogs do not provide evidence to suggest adverse effects on sexual function and fertility, which meet the classification criteria.

In the two-generation study in rats, there were no significant effects on fertility and reproductive performance up to the top dose of 20000 ppm (1286/2002 mg/kg bw/d in males/females) at which liver and kidney toxicity occurred. The mean number of F2 pups (10.0) delivered in the high dose group (1286/2002 mg/kg bw/d in males/females) was significantly lower than that in the concurrent control group (11.8) and also marginally below the laboratory HCD range for this finding (10.4 – 12.8). However, in the absence of effects on any other reproductive parameters and given that this finding was only just outside the laboratory HCD range, did not occur in F1 pups and was noted at a dietary concentration well in excess of the limit dose, it can be concluded that there is insufficient evidence of an effect of flutianil on reproduction in this study.

Taking into account that the available data do not show evidence of an adverse effect of flutianil on sexual function and fertility, RAC is of the opinion that flutianil does not warrant classification for this hazard class.

Developmental toxicity

Rats

The data generated in the developmental toxicity range finding study in rats [41] and in the developmental toxicity main study in which flutianil was administered by oral gavage to pregnant rats (25 females/group) from GD 6 to 19 at a dose of 100, 333 and 1000 mg/kg bw/d (York, 2006) do not indicate developmental toxicity of flutianil. There was a low incidence of skeletal variations (asymmetry) of the sternal centra in foetuses at a dose of 333 mg/kg bw/d (in 1/22 litters *vs*. 0/21 in control; or in 1/129 foetus *vs*. 0/114 in control) and at a dose of 1000 mg/kg bw/d (in 2/22 litters *vs*. 0/21 in control; or 2/135 foetus *vs*. 0/114 in control); however, these findings are

considered to be of minimal toxicological significance. No mortality was observed in the dams, with all rats surviving to the scheduled necropsy. No discernible effects on maternal bodyweight/body weight gain or food consumption were observed.

Rabbits

In the developmental toxicity range finding study [43] flutianil was administered by oral gavage to time-mated pregnant New Zealand White rabbits (NZW) (6 females/group) from GD 6 to 28. Dose levels were 0, 100, 300, 1000 mg/kg bw/d. There were no treatment related effects at any dose. In the main developmental toxicity study [44], flutianil was administered by oral gavage to time-mated pregnant NZW rabbits (25 females/group) from GD 6 to 28 at dose levels of 0, 100, 300, 1000 mg/kg bw/d. No discernible effects on maternal body weight, body weight gain or food consumption were observed. No treatment-related gross pathological findings were evident in any dose group at necropsy on GD 29 in the dams.

The total number of foetuses with any malformation was the same in the top dose and in control groups (4 foetuses in 2 litters at 1000 mg/kg bw/d *vs.* 4 foetuses in 4 litters in controls).

Summary of malformations observed in the rabbit developmental toxicity main study

Parameter	Dose level (mg/kg bw/d)			
	0	100	300	1000
No. of litters examined	25	20	22	22[a]
No. of foetuses examined	219	173	187	185
External malformations (%/litter ± sd) [no. of foetuses affected/no. of litters affected]				
Foetal oedema (localised)	(0 ±0) [0/0]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(0 ±0) [0/0]
Micropthalmia and/or anopthalmia	(0 ±0) [0/0]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(0 ±0) [0/0]
Visceral malformations (%/litter ± sd) [no. of foetuses affected/no. of litters affected]				
Hydrocephaly	(0 ±0) [0/0]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(1.5 ±7.1) [3/1]
Interventricular septal defect	(0 ±0) [0/0]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(0 ±0) [0/0]
Skeletal malformations (%/litter ± sd) [no. of foetuses affected/no. of litters affected]				
Sternebrae fused	(0.7 ±3.3) [1/1]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(0.5 ±2.1) [1/1]
Vertebral anomaly with or without associated rib anomaly	(0.4 ±2.0) [1/1]	(0.6 ±2.8) [1/1]	(0 ±0) [0/0]	(0 ±0) [0/0]
Total no. of foetuses with any malformation	(1.8 ±4.5) [4/4]	(0.6 ±2.8) [1/1]	(1.8 ±4.8) [3/3]	(2.0 ±7.2) [4/2]

Values in () = mean % per litter ± standard deviation
Values in [] = number of foetuses/litters affected
[a]23 ♀ survived to necropsy but one ♀ (animal no. 48771) had no viable foetuses

In the 1000 mg/kg bw/d group, three foetuses in the same litter had visceral hydrocephalus (presenting as increased cavitation of the lateral, bilateral and third ventricles). Visceral hydrocephalus was also seen in one foetus (in one litter) at 100 mg/kg bw/d, but the foetus presented multiple malformations (localised oedema of thorax, bilateral micropthalmia, interventricular septal defect) and the observation was within the relevant HCD range. Therefore, this finding at the low dose was considered not to be treatment-related.

The developmental toxicity study for flutanil was conducted between 19 February and 16 March 2007. The laboratory HCD (as provided by the DS) in rabbits from the same laboratory for the period February 2005 – June 2006, thus roughly 6 months before the study was done, showed

that two foetuses with visceral hydrocephalus in a single litter was the maximum incidence in untreated rabbits. The litter incidence of hydrocephalus observed in animals treated with flutanil at the top dose of 1000 mg/kg bw/d was not higher than in these historical controls, however, the foetal incidence (3/185, *i.e.* 1.6%) at the top dose exceeded the control range by one foetus (maximum 2/189, *i.e.* 1.1%, observed in the period February 2005 – June 2006). However, HCD data on NZW rabbits from the same source, provided during public consultation (based on 51 developmental toxicity studies performed January 2005 - January 2007; thus closer to the period when the developmental study of flutanil was done), showed that hydrocephalus was found in 8 out of 922 examined litters (0.87% of all examined control litters), and in 12 out of 7621 examined foetuses (0.16% of all examined control foetuses) with a maximum number of 4 foetuses with hydrocephalus in one litter.

Other HCD data on NZW rabbits from the same source, also provided during public consultation (based on 49 developmental toxicity studies performed January 2007 - January 2009) showed that moderate or marked hydrocephalus was found only in 2 litters out of 936 examined litters (0.21%), and in 6 foetuses out of examined 7708 foetuses (0.078%) with maximum 5 foetuses with hydrocephalus in one litter.

Although these HCD data show that the frequency of visceral hydrocephalus in control time-mated pregnant NZW rabbits is very low, RAC considered that the occurrence of hydrocephalus in 3 foetuses in one litter (out of 22, 4.5%) in dams exposed to 1000 mg/kg bw/day of flutanil is likely not to be treatment-related. Although hydrocephalus is a rare malformation, and it also occurred in one pup in one litter at a lower dose (100 mg/kg bw/d), the finding is within the HCD range for NZW rabbits, and only 1 pup above the HCD for the laboratory where the study was performed. RAC noted that there are some uncertainties related to the relevance of the finding, but considered that the study in NZW rabbit did not yield robust evidence of a developmental effect of flutianil.

In conclusion, since the properly conducted developmental studies in rats and rabbits did not yield robust evidence of development toxicity of flutanil, RAC is of the opinion that it does not warrant classification

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Flutianil is a thiazolidine fungicide exhibiting both fungitoxic and fungistatic contact action. The DS proposed to classify the substance as Aquatic Chronic 1; H410 with an M-factor of 100, based on the substance being not rapidly degradable and very toxic to aquatic organisms. The lowest chronic toxicity value was a NOEC of 0.000781 mg/L for fish *Pimephales promelas* in a fish early life stage test. There was no acute toxicity recorded at the limit of water solubility and flutianil is, thus, not proposed to be classified for acute hazard.

Degradation

All the studies on the fate and behaviour of flutianil in the environment were performed under GLP and according to the appropriate test guidelines. They are considered to be sufficient and reliable for hazard classification purposes. Radiolabelled studies were conducted with flutianil labelled in two different positions ([CF_3Ph-U-^{14}C] and [MeOPh-u-^{14}C]).

In a standard OECD TG 111 hydrolysis study, flutianil was shown to be hydrolytically stable at pH 5, 7 and 9 at 50°C. The aqueous photolysis study was conducted in accordance with OECD TG 316 and gave a DT_{50} of 1.1 - 1.2 days in natural water with radiation source adjusted to UK/US indicating that under suitable conditions sunlight may contribute to the dissipation of flutianil in

the aqueous environment. The soil photolysis study was conducted in accordance with SETAC 1995 guideline. Flutianil was degraded by photolysis from 91.8% to 69.1% over 45 days with the MeOPh labelled test material from 97.4% to 68.3% with the CH_3Ph labelled test material. There was minimal degradation in the dark controls. A significant photolysis product was detected from the CH_3Ph labelled treated soil at a maximum of 10.7% of the applied radioactivity (AR).
The ready biodegradation of flutianil was studied according to the OECD TG 301B where 0% of the theoretical CO_2 from flutianil was produced at day 28. Consequently flutianil cannot be considered as readily biodegradable.

Aerobic sediment/water studies were conducted in accordance with OECD TG 308 with two different water-sediment systems. The half-lives are presented in the table below. The physical properties of flutianil indicate that the disappearance time 50[1] (DT_{50}) of < 1 days in water phase is due to rapid partition of flutianil into sediment.

Water/sediment system, 20°C	DT_{50}/DT_{90}, days, whole system	DT_{50}/DT_{90}, days, water	DT_{50}/DT_{90}, days, sediment
Site A (1 MeOPh	504/1673	<1/15	1000
Site A (1 CH_3Ph	550/1826	<1/14	1000
Swiss Lake (2 MeOPh	651/2162	<1/19	1000
Swiss Lake (2 CH_3Ph	752/2498	<1/26	1000
Geometric mean	607/2015	1/18	

(1 Site A (silt loam sediment with 4.2% organic carbon), water pH of 8.14)
(2 Swiss Lake (sandy sediment, 0.6% organic carbon, water pH 5.99)

Similar metabolites were identified in the sediment as were found in the soil metabolism studies: OC 53276, OC 53279 and OC 56574. The formation and occurrence of the metabolites suggested that they were formed in the sediment and then partitioned into the water.
The degradation of flutianil was studied in a single soil with the rate of degradation also investigated in a further 3 soils under aerobic conditions. The study was undertaken according to OECD TG 307. In general, degradation of parent flutianil was slow, between 66% and 77% remaining after 120 days. Flutianil is degraded under aerobic conditions in soil forming a single major metabolite at the end of the study - OC 56574. The normalised DT_{50}s range from 262.6 to 338.4 days. Field dissipation studies were carried out in accordance with Directive 91/414/EEC 1991. The rate of flutianil degradation in the field varied considerably and did not follow first order kinetic at most sites. The best fit DT_{50} values ranged from 0.083 to 1616.1 days from six trial sites. The variation was considered to be due to photodegradation.

Bioaccumulation

Flutianil has a measured log Kow of 3.1 (OECD TG 117) however, this figure should be considered unreliable due to flutianil's low water solubility. A fish bioconcentration study with radiolabelled flutianil has been conducted according to OECD TG 305. *Oncorhynchus mykiss* were continuously exposed to [^{14}C]-Flutianil, at nominal concentrations of 0.5 µg/L and 5.0 µg/L for a period of 28 days under flow-through conditions. The kinetic bioconcentration factors, normalised to the common basis lipid content but not including growth corrections, for the whole fish were 380 and 345 for the 0.5 µg/L and 5.0 µg/L concentrations, respectively.

Aquatic toxicity

A summary of the aquatic toxicity studies conducted with flutianil is presented in the tables below. The key studies highlighted in bold were considered valid and reliable. Many of the studies were conducted at concentrations in excess of the limit of water solubility which is around 0.0079 mg/L at 20°C.

Method	Test species	Test duration	Effect parameter	Effect (mg/L)	Description of the test
OECD TG	*Oncorhynchus*	96 h	LC_{50}	>0.01 m*	Limit test, nominal 100 mg/L,

1 DT50 = Disappearance time 50 is the time within which the initial concentration of the test substance is reduced by 50%.

203 (1992), GLP	*mykiss* (rainbow trout)	(semi-static)			no mortality or sub-lethal effects, not reliable
	Oncorhynchus mykiss (rainbow trout)	96 h (semi-static)	LC_{50}	>0.9 m	Limit test, nominal 1 mg/L (mean measured 0.90 mg/L), measured levels 70-110% of nominal, no mortality or toxic symptoms observed.
	Pimephales promelas (fathead minnow)	96 h (semi-static)	LC_{50}	>0.00472 m*	5 concentrations tested, no mortality or sub-lethal effects, not reliable
	Cyprinus carpio (carp)	96 h (semi-static)	LC_{50}	**>0.87 m** [a]	Limit test, nominal 1 mg/L (mean measured 0.87 mg/L), 78-96% of nominal during exposure, no mortality nor clinical observations.
OECD TG 210 (1992), GLP	*Pimephales promelas* (fathead minnow)	Early life stage (flow-through)	NOEC	0.008 n (survival)	Nominal concentrations 0.024, 0.076, 0.244, 0.781, 2.5 and 8.0 µg/L; solvent stock 103-113% of nominal; clear treatment-related effect on total length at the top two dose concentrations.
			NOEC	**0.000781 m (length)**[a]	

Method	Test species	Test duration	Effect parameter	Effect (mg/L)	Description of the test
OECD TG 202 (2004), GLP	*Daphnia magna*	48 h (semi-static)	EC_{50}	>0.009 m (filtered)* 32.3 m (unfiltered)*	Unfiltered: measured concentrations 32.3-105% of nominal; filtered: not detected/0.0017-0.609% of nominal; no immobility observed.
	Daphnia magna	48 h (static)	EC_{50}	**>1.0 n** [a]	Measured concentrations 100 (initiation) and 91% (termination) of the nominal, no immobility was observed
OECD TG 211 (1989), GLP	*Daphnia magna*	21 days (semi-static)	NOEC	**0.00697 m**[a]	Nominal concentrations 0.191, 0.61, 1.95, 6.25 and 20 µg/L; mean measured 35-41 of nominal; no dead juveniles, no effect on dry weight or lengths.

Method	Test species	Test duration	Effect parameter	Effect (mg/L)	Description of the test
OECD TG 201 (2006), GLP	*Pseudokirchneriella subcapitata*	96 h	EC_{50} NOEC	**>0.0127** **0.0127 m**[a]	Nominal concentrations 3.13, 6.25, 12.5, 25, 50 and 100 mg/L. Mean measured concentrations 0, 0, 0.023, 0.011, 0.0062 and 0.013 % of nominal; no growth inhibition
	Pseudokirchneriella subcapitata	96 h	EC_{50} NOEC (cell density) EC_{50} NOEC (growth rate inhibition)	>0.067 0.067 m >0.085 0.085 m	Limit test nominal 320 µg/L, mean measured 0-72h: 85 µg/L and 0-96h: 67 µg/L; no effect on cell densities, growth rate or biomass.

Method	Test species	Test duration	Effect parameter	Effect (mg/L)	Description of the test
OECD TG 218 (2004), GLP	*Chironomus riparius (aquatic insect- midge)*	28 days	EC50 NOEC spiked sediment	>718 mg/kg 718 mg/kg m	No adverse effect on the emergence success, sex ratio or development rate.

* not reliable e.g. due to excessively low recovery of the substance and/or measured concentrations below the limit of determination and/or insufficient information on the appearance and behaviour of the test medium
[a] endpoints used in the classification for the respective groups.
[m] measured concentration of the test substance
[n] nominal concentration of the test substance

Both acute and chronic aquatic toxicity tests have been conducted for fish, aquatic invertebrates and algae. Whilst the studies were all affected by flutianil's low water solubility, adequate reliable acute and chronic endpoints are available for each trophic group. The results indicate that acute toxicity is not envisaged at the limit of solubility for flutianil and no acute hazard classification is proposed. The long-term aquatic data shows toxicity at concentrations below 0.1 mg/L. The results indicate that fish are the most chronically sensitive taxa with a NOEC of 0.000781 mg/L for *Pimephales promelas*. Based on this result, flutianil, as a non-rapidly degradable substance, is proposed to be classified in Aquatic Chronic category 1; H410, M-factor of 100.

Comments received during public consultation

Two MSCAs and one organisation agreed with the DS's proposal for Aquatic chronic 1; H410, M=100.

Assessment and comparison with the classification criteria

Flutianil is hydrolytically stable and not rapidly degradable based on 0% degradation in a ready biodegradability test and halflives of 504 -752 days in a water/sediment test. Metabolites were also identified both in a water/sediment test and a soil degradation test. No information to allow classification of the metabolites is available in the CLH report. RAC considers the substance not rapidly degradable because it does not pass the ready biodegradability test, is not demonstrated to be primarily degraded biotically or abiotically in the aquatic environment (half-life < 16 days) to environmentally non-classifiable metabolites.

Regarding bioaccumulation, comparison with the classification criteria BCF ≥ 500 and log Kow ≥ 4 shows that the substance is not bioaccumulative based on a fish BCF of 380 and 345 for the 0.5 µg/L and 5.0 µg/L concentrations, respectively. The measured log Kow is 3.1 but the value is considered unreliable due to the low solubility of flutianil.

There is adequate acute toxicity data available for all three trophic levels. The results indicate that toxicity is not encountered at the limit of solubility and thus no acute hazard classification is needed. This kind of situation is described in Annex I of the ECHA Guidance on the Application of the CLP Criteria v.4.1:

> *"I.4.2.b where no acute toxicity is recorded at levels in excess of the water solubility, the L(E)C50 for classification purposes may be considered to be greater than the measured water solubility. In such circumstances, consideration should be given to whether the category Chronic 4 should apply. In making a decision that the substance shows no acute toxicity, due account should be taken of the techniques used to achieve the maximum dissolved concentrations. Where these are not considered as adequate, the test should be considered as invalid for classification purposes;"*

Aquatic Chronic Category 4 is not applicable in the case of flutianil because although the substance is not readily degradable it is not bioaccumulative. Thus RAC agrees with the DS proposal **not to classify flutianil for the aquatic acute hazard**.

There is adequate chronic data available for all three trophic levels. The lowest chronic toxicity value is a NOEC of 0.000781 mg/L for the fish *Pimephales promelas* which is in the range 0.0001 < NOEC ≤ 0.001. Because flutianil is not rapidly degradable, RAC agrees to the DS proposal to classify flutianil as **Aquatic Chronic 1; H410 with an M-factor of 100**.

ADDITIONAL REFERENCES:

Historical Control data, Covance New Zealand White Rabbits, Denver P.E, as compiled by Charles River Labolatories, PCS-PA 2005 to 2013

Summary of Reproductive Indices' New Zealand White Rabbits [Hra:(Nzw)Spf], Day 29 Caesarean-Section, Period: January 2005 - January 2007

Summary of Reproductive Indices' New Zealand White Rabbits [Hra:(Nzw)Spf], Day 29 Caesarean-Section, Period: January 2007 - January 2009

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).