Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

ipconazole (ISO); (1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol [CAS No. 125225-28-7 (all stereoisomers); CAS No. 115850-69-6 (cis-cis racemate); CAS No. 115937-89-8 (cis-trans racemate)]

EC Number: -
CAS Number: -

CLH-O-0000001412-86-198/F

Adopted

9 March 2018

9 March 2018

CLH-O-0000001412-86-198/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: **ipconazole (ISO); (1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol**

[CAS No. 125225-28-7 (all stereoisomers);

CAS No. 115850-69-6 (cis-cis racemate);

CAS No. 115937-89-8 (cis-trans racemate)]

EC Number: **-**

CAS Number: **-**

The proposal was submitted by the **United Kingdom** and received by RAC on **15 December 2016.**

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 **14 March2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **28 April 2017**.

ADOPTION OF THE OPINION OF RAC

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

Co-Rapporteur, appointed by RAC: **Katalin Gruiz**

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 **9 March 2018** 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 and ATE	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	603-RST-VW-Y	ipconazole (ISO); (1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol [CAS No. 125225-28-7 (all stereoisomers); CAS No. 115850-69-6 (cis-cis racemate); CAS No. 115937-89-8 (cis-trans racemate)]	-	-	Repr. 2 Acute Tox. 4 STOT RE 2 Aquatic Chronic 1	H361d H302 H373 (eyes, skin, liver, gastrointestinal tract) H410	GHS08 GHS07 GHS09 Wng	H361d H302 H373 (eyes, skin, liver, gastrointestinal tract) H410		M=100	
RAC opinion					Repr. 1B Acute Tox. 4 STOT RE 2 Aquatic Chronic 1	H360D H302 H373 (eyes, skin, liver) H410	GHS08 GHS07 GHS09 Dgr	H360D H302 H373 (eyes, skin, liver) H410		oral: ATE = 500 mg/kg bw M=100	
Resulting Annex VI entry if agreed by COM					Repr. 1B Acute Tox. 4 STOT RE 2 Aquatic Chronic 1	H360D H302 H373 (eyes, skin, liver) H410	GHS08 GHS07 GHS09 Dgr	H360D H302 H373 (eyes, skin, liver) H410		oral: ATE = 500 mg/kg bw M=100	

GROUNDS FOR ADOPTION OF THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

In a standard flammability study (EEC A.10., Comb, A. 2005(a) DAR B.2.1.20), ipconazole melted and burned, but did not sustain combustion on removal of the ignition source.

In addition, experience in handling and use indicates that the substance is not pyrophoric and does not emit flammable gases in contact with water.

In a standard study (EEC A.17., Comb, A. 2005(a) DAR B.2.1.23), ipconazole was not found to be oxidising.

In a standard study (EEC A.14., Comb, A. 2005(a) DAR B.2.1.22), ipconazole was not found to be sensitive to the effects of heat, shock or friction.

Comments received during public consultation

One comment was received from a Company-Manufacturer, agreeing with the 'no classification' proposal for physical hazards.

Assessment and comparison with the classification criteria

During the RAC consultation, one RAC member commented that the A.14. method used in the assessment does not entirely cover the requirements of CLP, and that the same situation was encountered in the dossier for another substance (mefentrifluconazole). Both substances are triazole compounds with similar usage.

Ipconazole does not meet the criteria for classification as a flammable solid, as it did not sustain combustion on removal of the ignition source and as noted above, experience in handling and use indicates that **the substance is not pyrophoric and does not emit flammable gases in contact with water**.

Ipconazole **does not meet the criteria for classification as an oxidising solid** as the relevant test was negative.

To define ipconazole as "not explosive", the results of a series of three tests should be negative (CLP Guidance: Annex I: Figure 2.1.2). These are: (1) Detonation test (UN gap test, zero gap); (2) Koenen test; (3) Ignition under confinement (time/pressure test). In addition, the larger frame of the physical hazard profile including such properties as flammability, oxidising and pyrophoric ability, indicates that **ipconazole is not a reactive substance**.

Ipconazole is not sensitive for heat, shock or friction measured by A.14., but *the time/pressure test* from the three necessary tests has not been performed, as required by *UN 1* (c) (i) and *UN 2* (c) (i).

As all of the measured explosive properties are negative and, based on the weight of the evidence reviewed, RAC agreed **not to classify ipconazole as explosive**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute toxicity: oral route

Rats

Ipconazole was tested for acute oral toxicity in Sprague-Dawley rats (5 male and 5 female per dose), according to a Japaneses guideline (no deviation from OECD TG 401; GLP) (Kureha Corporation,1989(16)[1]). Ipconazole was administered orally at 300 to 3400 mg/kg bw in males and from 600 to 2400 mg/kg bw in females.

The calculated oral LD_{50} values were 1338 and 888 mg/kg bw for male and female rats, respectively, and were within the range for classification in acute toxicity Category 4 ($300 < LD_{50} \leq 2000$).

Mice

Ipconazole was tested for acute oral toxicity in CD-1 mice (5 males and 5 females per dose), according to a Japaneses guideline (no deviation from OECD TG 401; GLP) (Kureha Corporation, 1989 (17)). Ipconazole was administered orally in males and females at 300 to 1200 mg/kg bw.

The calculated oral LD_{50} values were 537 and 468 mg/kg bw for male and female mice, respectively, and were within the range for classification in acute toxicity Category 4 ($300 < LD_{50} \leq 2000$).

Therefore, classification for Acute Tox. 4; H302, for the oral route was proposed by the DS.

Acute toxicity: dermal route

Ipconazole was tested for acute dermal toxicity in Sprague-Dawley rats (5 males and 5 females per dose), according to a Japaneses guideline (no deviation from OECD TG 402; GLP) (Kureha Corporation, 1989 (20)).

The LD_{50} values for both male and female rats were > 2000 mg/kg bw, which is above the limit for classification in acute dermal toxicity Category 4 ($1000 < LD_{50} \leq 2000$). The DS did not propose classification for acute dermal toxicity

Acute toxicity: Inhalation

In an acute inhalation study conducted according to OECD TG 403 (Kureha Corporation, 2003 (18)), the LC_{50} value for ipconazole was > 1.88 mg/L for rats. The mean mass aerodynamic diameter (MMAD) was 3.9 µm. In another acute inhalation study conducted according to OECD TG 403 (Kureha Corporation, 1991 (19)), the LC_{50} value for ipconazole was > 3.53 mg/L for rats. The mean mass aerodynamic diameter (MMAD) was 5.3 µm. The DS did not propose classification for acute inhalation toxicity for ipconazole.

[1] The reference numbering given here refers to that of the Background Document throughout.

Comments received during public consultation

4 MSCAs and one industrial organisation supported classification of ipconazole as Acute Tox. 4, H302: Harmful if swallowed.

One MSCA asked for harmonisation of an acute toxicity estimate (ATE) value for acute oral toxicity as it would facilitate classification of mixtures containing ipconazole.

Assessment and comparison with the classification criteria

Taking into account the data presented on acute toxicity by the oral, inhalation and dermal routes, RAC is of the opinion that ipconazole meets the classification criteria for **Acute Tox. 4; H302**, via the oral route but no classification is required for the other routes, in line with what was proposed by the DS.

To facilitate consistent classification of mixtures containing ipconazole, a harmonised ATE value is also proposed. According to the CLP regulation, the ATE value for a substance should be derived using the LD_{50} where available. The lowest LD_{50} value in female mice was 468 mg/kg bw and 888 mg/kg bw in female rats. Taking these data into account, and in line with table 3.1.2, Annex I of CLP, RAC is of the opinion that the converted ATE for ipconazole should be used, and proposes to assign **an ATE of 500 mg/kg bw for acute oral toxicity**.

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

Summary of the Dossier Submitter's proposal

The information from the acute oral and dermal toxicity studies did not indicate toxicity to specific organs after a single exposure.

There were some clinical signs indicative of respiratory tract irritation after acute inhalation exposure, which included red followed by clear nasal discharge and moist rales. Data from medical surveillance of manufacturing plant personnel and clinical cases / poisoning incidents did indicate respiratory irritation in humans.

Taking into account the existing human and animal data the DS did not propose classification of ipconazole for STOT SE.

Comments received during public consultation

One industrial organisation supported no classification of ipconazole for STOT SE.

Assessment and comparison with the classification criteria

Taking into account the data in the CLH report, RAC is of the opinion that ipconazole **does not warrant classification for STOT SE**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for skin corrosion/irritation.

The skin irritation potential of ipconazole was assessed in a study carried out according to a Japaneses guideline (similar to OECD TG 404, but six animals were used; GLP compliant) (Kureha Corporation, 1997 (21)) in six male Japanese White rabbits.

Very slight erythema (score 1) was observed in two rabbits one hour after patch removal, which was fully reversed 24 hours after removal.

Comments received during public consultation

One industrial organisation supported no classification of ipconazole for skin corrosion/irritation.

Assessment and comparison with the classification criteria

Since in an acceptable study, the CLP criteria for skin irritation (a mean score of ≥ 2.3 for erythema/eschar or for oedema) were not met in any of the tested animals, RAC considers that ipconazole **does not warrant classification for skin corrosion/irritation**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for eye damage/irritation.

The eye damage/irritation potential of ipconazole was assessed in a GLP-compliant study carried out according to a Japaneses guideline (similar to OECD TG 405, but 9 rabbits were used and in 3 rabbits the eyes were washed 2 minutes after application) (Kureha Corporation, 1997 (22)).

The mean scores 24, 48 and 72 hours after application for corneal opacity, iris lesion, conjunctival redness and chemosis were below the scores leading to classification according to the CLP criteria. All responses were fully reversed 7 days after application.

Comments received during public consultation

One industrial organisation supported no classification of ipconazole for eye damage/irritation.

Assessment and comparison with the classification criteria

Since in the acceptable study, effects meeting the CLP criteria for classification were not observed in any of the tested animals, RAC considers that ipconazole **does not warrant classification for eye damage/irritation**.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for respiratory sensitisation due to lack of information on the potential of ipconazole to induce respiratory sensitisation.

Comments received during public consultation

One MSCA and one industrial organisation supported no classification of ipconazole for respiratory sensitisation

Assessment and comparison with the classification criteria

As there are not data suggesting that ipconazole may cause respiratory sensitisation, RAC **proposes no classification for respiratory sensitisation**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for skin sensitisation.

The skin sensitisation potential of ipconazole was assessed in a Guinea Pig Maximisation Test (GPMT) (Kureha Corporation, 1997(23)) carried out according to OECD TG 406. No dermal responses were noted in any of the ipconazole treated animals, whereas all positive control animal had strong skin responses.

Comments received during public consultation

One industrial organisation supported no classification of ipconazole for skin sensitisation.

Assessment and comparison with the classification criteria

Taking into account the lack of skin sensitisation responses in Guinea pigs in an acceptable GPMT, RAC considers that ipconazole **does not warrant 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 contained data from several repeated dose toxicity studies of ipconazole:

Oral toxicity

- in rats (in diet, 28-day and 90-day), in mice (in diet, 28-day and 90-day) and in dogs (in capsules, up to 22 days, for 28 days, for 90 days and for one year). In addition, non-neoplastic findinds in 1- and 2-year carcinogenicity studies in rats and in a 78-week study in mice were considered in the evaluation of STOT RE.

Inhalation toxicity

- in rats (28-day)

Dermal toxicity

- in rats (28-day)

A summary of the findings at doses relevant for STOT RE classification of ipconazole is presented in the table below:

Study design	Guidance cut-off value (mg/kg bw/d)	Findings at doses relevant for STOT RE Category 1	Findings at doses relevant for STOT RE Category 2
Rat 28-day dietary	Cat. 1: 30 Cat. 2: 300	Lowest dose 30.5 mg/kg bw/d: no adverse effects in males	31.3 mg/kg bw/d: reduced body weight and food consumption in females 91 mg/kg bw/d: adrenal glands (prominent sinusoidal lining cells), females; lesions of the oesophagus*. 164-236 mg/kg bw/d: severe toxicity led to early termination
Rat 90-day, dietary	Cat. 1: 10 Cat. 2: 100	5.8-7 mg/kg bw/d: no adverse effects	33.2 mg/kg bw/d: kidney effects (corticomedullary mineralisation, minimal or slight, females) 52.2 mg/kg/d: liver (focal inflammation)
Rat 2-year dietary	Cat. 1: 1.25 Cat. 2: 12.5	1.6 / 1.2 mg/kg bw/d: no adverse effects	> 13.3 mg/kg bw/d: liver (centrilobular hepatocyte hypertrophy, males only)
Rat 28-day inhalation	Cat. 1: 0.06 mg/L/6h/d Cat. 2: 0.6 mg/L/6h/d	0.03 mg/L/6h/d: no adverse systemic effects; local effects on hard palate and larynx*	≥ 0.1 mg/L/6h/d: local effects on oesophagus, hard palate, larynx
Rat 28-day, dermal	Cat. 1: 60 Cat. 2: 600	10 mg/kg bw/d: no adverse effects	150 mg/kg bw/d: no adverse effects Next dose: 1000 mg/kg bw/d
Mouse 28-day dietary	Cat. 1: 30 Cat. 2: 300	Lowest dose 44.8 / 53.4 mg/kg bw/d	≥ 44.8 / 53.4 mg/kg bw/d: liver effects ≥ 152 mg/kg bw/d: lesions in the oesophagus*; focal hepatocyte necrosis
Mouse 90-day dietary	Cat. 1: 10 Cat. 2: 100	4.4 / 5.1 mg/kg bw/d: no adverse effects	≥ 20 mg/kg bw/d: liver (hepatocyte vacuolation) ≥ 70 mg/kg bw/d: adrenal gland (cortical vacuolation)
Mouse 18-month dietary	Cat. 1: 1.9 Cat. 2: 19	1.9 / 2.3 mg/kg bw/d: centrilobular hepatocyte vacuolation (females only)	≥ 24 mg/kg bw/d: liver (generalised hepatocyte vacuolation, parenchymal inflammatory cells)
Dog 28-day oral (capsule)	Guidance values based on rat study	Lowest dose: 24 mg/kg bw/d ≥ 24 mg/kg bw/d: liver effects ≥ 60 mg/kg bw/d: ocular effects (opacities, cataracts, lenticular degeneration)	
Dog 90-day oral (capsule)	Guidance values based on rat study	2 mg/kg bw/d: no adverse effects ≥ 10 mg/kg bw/d: skin reddening and hair loss 40 mg/kg bw/d: ocular effects (opacities, cataracts, lenticular degeneration); adrenal glands (fatty vacuolation); liver effects	

Study design	Guidance cut-off value (mg/kg bw/d)	Findings at doses relevant for STOT RE Category 1	Findings at doses relevant for STOT RE Category 2
Dog 1-year oral (capsule)	Guidance values based on rat study	1.5 mg/kg bw/d: no adverse effects ≥ 5 mg/kg bw/d: skin reddening 20 mg/kg bw/d: ocular effects (opacities, cataracts, lenticular degeneration); adrenal glands (fatty vacuolation)	

* Statistically significant at $p \leq 0.05$.

No data on human repeated dose toxicity were provided.

Taking the results of these studies into account, the DS proposed classification of ipconazole as STOT RE 2; H373 - May cause damage to organs (eyes, skin, liver, gastrointestinal tract) through prolonged or repeated exposure.

Comments received during public consultation

Four MSCAs and one industrial organisation supported the DS's proposal to classify ipconazole for STOT RE 2; H373 - May cause damage to organs (eyes, skin, liver, gastrointestinal tract) through prolonged or repeated exposure.

One MSCA asked for more information on the mode of action (MoA) for ipconazole with regard to steroid hormone synthesis and if a MoA is known, for consideration of the endocrine disrupting potential. This MSCA also asked why the adrenal glands are not included as a target organ. In their response, the DS informed that ipconazole inhibits 14-C demethylation in the ergosterol biosynthesis pathway of fungi which cause plant disease. The endocrine disruption potential of ipconazole was not considered in the report, since this does not relate directly to classification; the MoA of the adverse effects is assumed to be relevant to humans and ipconazole has been proposed to be classified accordingly. Effects in the adrenal gland were somewhat inconsistent, since they occurred in rats exposed for 28 days, but not for 90 days or two years; and in mice exposed for 90 days but not for 18 months. Therefore, the adrenal gland was not identified as a primary target organ in the proposed classification.

Assessment and comparison with the classification criteria

As noted by the DS repeated-dose administration of ipconazole resulted in a number of adverse effects in rats, mice and dogs. When compared with the classification criteria for STOT RE 2, the significant findings can be summarised as:

- *significant organ damage noted at necropsy and/or subsequently confirmed at microscopic examination:*
  - ocular effects (opacities, cataracts, lenticular degeneration) in dogs exposed for 28 days at doses ≥ 60 mg/kg bw/d, exposed for 90 days at dose of 40 mg/kg bw/d and exposed for one year at dose 20 mg/kg bw/d; these effects were potentially related to a decrease in plasma cholesterol;
- *multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity:*
  - focal hepatocyte necrosis (graded as minimal to slight) in mice exposed for 28 days at doses > 152 mg/kg bw/d, in dogs exposed for 22 days (males) and 24 days (females) or 28 days (males and females) at 150 mg/kg bw/d and in female dogs exposed for 90 days at 40 mg/kg bw/d;
- *morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction*:

- fatty deposits in the liver; fatty vacuolation in the adrenal glands in rats and mice exposed for 28 days and 90 days at doses within the guidance values for STOT RE 2.

A further systemic finding of concern and in support of classification was skin reddening in dogs following oral administration in a capsule. The skin reddening largely occurred at doses that were consistent with a classification in STOT RE 2; there were no findings that indicated that Category 1 would be a more appropriate classification.

Since adverse effects were recorded after oral, dermal and inhalation exposure, it is not proposed to specify a route of exposure. The primary target organs of specific toxicity were the eyes, liver and skin. RAC did not agree with the DS's proposal to include the gastro-intestinal tract as a target organ because the effects were not considered sufficiently severe and were only seen at high doses in short term studies, but not in longer term studies.

Taking the above into account, RAC is of the opinion that ipconazole warrants classification as **STOT RE 2; H373 (May cause damage to organs (eyes, liver, skin) through prolonged or repeated exposure)**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Ipconazole was negative in four *in vitro* genotoxicity assays assessing bacterial mutation, mammalian cell mutation, mammalian chromosome aberration and DNA repair. Ipconazole was also negative in a guideline-compliant micronucleus assay in which evidence of bone marrow toxicity was demonstrated, indicating that sufficiently high doses were administered.
Based on these data the DS concluded that ipconazole does not warrant classification for germ cell mutagenicity.

Comments received during public consultation

One MSCA and one industrial organisation supported no classification of ipconazole as a germ cell mutagen.

Assessment and comparison with the classification criteria

Taking into account the negative results in several *in vitro* studies and in one *in vivo* assay, RAC considers that ipconazole should **not be classified for germ cell mutagenicity**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

No information on carcinogenicity of ipconazole in humans is available. The carcinogenicity of ipconazole has been investigated in one study in rats and one study in mice by the oral route. There were no carcinogenicity studies in animals by inhalation or dermal route.

Rats

In the study in rats (Kureha Corporation, 2006 (41); OECD TG 453, GLP), males received ipconazole in the diet at doses of 0, 1.6, 4.2, 10.9, 15.9 mg/kg bw/d for 52 weeks in the chronic

toxicity phase and at doses of 0, 1.3, 3.6, 9.0, 13.3 mg/kg bw/d for 104 weeks in carcinogenicity phase. Female rats were given ipconazole in the diet at doses of 0, 2.2, 5.9, 9.1, 15.0 mg/kg bw/d for 52 weeks in the chronic toxicity phase and at doses of 0, 1.9, 4.9, 7.3, 12.6 mg/kg bw/d for 104 weeks in carcinogenicity phase.

Histopathology at 52 weeks did not reveal any adverse effects of treatment. Substance-related non-neoplastic histopathology findings at 104 weeks were found in the fore-stomach (epithelial hyperplasia in males: 0%, 4%, 2%, 10%, 8% at 0, 1.3, 3.6, 9.0, 13.3 mg/kg bw/d, respectively), liver (centrilobular hepatocyte hypertrophy in males: 14%, 18%, 14%, 14%, 26% at 0, 1.3, 3.6, 9.0, 13.3 mg/kg bw/d, respectively) and urinary bladder (oedema: 16%, 15%, 9%, 9%, 29% in males at 0, 1.3, 3.6, 9.0, 13.3 mg/kg bw/d, respectively), 8%, 17%, 9%, 22%, 14% in females at 0, 1.9, 4.9, 7.3, 12.6 mg/kg bw/d, respectively). Additional findings in females at 7.3 and 12.6 mg/kg/d were epithelial keratinisation of the vagina (33% compared with 16% in controls, both above the historical control range of 0-6%) and interstitial cell hyperplasia of the ovary (12% compared with 4% in controls, historical control range 0-10%).

There was no consistent effect of treatment on sensory reactivity, grip strength and motor activity (measured during week 50).

Tumour findings

Thyroid: the incidence of follicular adenoma was slightly increased in the high-dose groups (males: 4%, 4%, 5%, 10%, 10% at 0, 1.3, 3.6, 9.0, 13.3 mg/kg bw/d, respectively; females: 0%, 6%, 3%, 0%, 8%* at 0, 1.9, 4.9, 7.3, 12.6 mg/kg bw/d, respectively). The historical control range (same strain and laboratory) for males was 4-17% (mean 8.4%) and for females 0-10.2% (8 studies). There was no increase in the incidence of cystic follicular cell hyperplasia, follicular cell carcinoma nor substance-related increase in the incidence of c-cell hyperplasia. There were no other neoplastic findings of note.

Mice

In the study in mice (Kureha Corporation, 2007 (42); OECD TG 453, GLP), males received ipconazole in diet at doses of 0, 1.9, 24.1, 45.3 mg/kg bw/d for 78 weeks and female mice were given ipoconazloe in the diet at doses 0, 2.3, 26, 57 mg/kg bw/d for 78 weeks (0, 15, 175 and 350 ppm, respectively).

Tumour findings

Haemopoietic system: histiocytic sarcomas were recorded in 0, 1, 0, 2 males and 0, 1, 1, 3 females at 0, 15, 175 and 350 ppm, respectively. The incidences in the high-dose groups (4% males, 6% females) were within the historical control range of 6 studies conducted at the same test laboratory and same time period (0-4% males, mean 1.3%; 0-10% females, mean 4.8%). They were also within the range (0-8% males, 0-18% females) reported for US-bred CD-1 mice from 51 studies initiated between 1987 and 1996.

Based on the results of these studies the DS concluded that the available data were conclusive, but not sufficient for classification of ipconazole for carcinogenicity.

Comments received during public consultation

One MSCA and one industrial organisation supported no classification of ipconazole for carcinogenicity.

Assessment and comparison with the classification criteria

Taking into account the lack of carcinogenic effects in two acceptable studies (one in rats and one in mice) RAC is of the opinion that ipconazole should **not be classified for carcinogenicity**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The effect of ipconazole on fertility and sexual function was assessed based on results of the 2-generation study in rats (Kureha Corporation, 2006 (43); OECD TG 416, GLP). The developmental toxicity was assessed based on one preliminary prenatal toxicity study in rats (Kureha Corporation, 1990 (40); no guideline, GLP), one prenatal toxicity study in rats (main study; Kureha Corporation, 1990 (45); OECD TG 414, GLP), one preliminary prenatal toxicity study in rabbits (Kureha Corporation, 1990 (46), no guideline, GLP), and one prenatal toxicity study in rabbits (main study; Kureha Corporation, 1990 (48); OECD TG 414, GLP).

Sexual function and ferility

The DS concluded that there was no evidence of any adverse effects on sexual function and fertility in the 2-generation study in rats (Kureha Corporation, 2006 (43); OECD TG 416, GLP; see background document for detailed data).

Developmental toxicity

There were two (preliminary and main) developmental toxicity studies available in rats (Kureha Corporation, 1990 (44 and 45)).

Rats

In the preliminary developmental toxicity study (no guideline, GLP), 6 or 7 mated female Sprague-Dawley rats per group were given ipconazole by gavage at doses of 0, 1, 10, 50, 100, 250, 500 mg/kg bw/d in 1% aqueous sodium carboxy-methylcellulose on gestation days (GD) 6-15. Dams were sacrificed on GD 20.

- Scope of investigations in the dams: gross pathology, ovaries and uterine contents examined, gravid uterine weights, corpora lutea and implantations determined.
- Investigations in the foetuses: number, sex & weights of live foetuses and placentae, incidences of resorptions and foetal deaths; live foetuses examined for external abnormalities.
- There was no examination for visceral or skeletal malformations and variations.

Maternal toxicity

Deaths occurred in 6/7 and 7/7 females at 250 and 500 mg/kg bw/d, respectively, on GD 8-10. At 100 mg/kg bw/d the clinical signs included red discharge from the vagina (3/7), soiled fur (1/7), eye discharge (1/7) and loose faeces (1/7). Clinical signs were not reported in 3/7 dams. At 100 mg/kg bw/d the dams also lost weight up to GD 10 (up to 13% decrease in body weight). Maternal body weight in the preliminary study (from detailed data submitted by industry) is given in the table below.

Table: Ipconazole - Preliminary rat study, maternal body weight performance

Dose level (mg/kg bw/d)	Cumulative body weight gain ( ) or loss (-) in grams during GDs									
	6-7	6-8[a]	6-9[a]	6-10[a]	6-11	6-12	6-13	6-14	6-15	6-20
0	1	2	5	7	11	15	18	22	30	102
1	0	0	3	8	11	14	20	25	30	107
10	-1	-1	4	8	11	17	21	26	30	101
50	-14	-21	-14	-7	-6	-4	-3	6	10	80
100	-18	-31	-37	-39	-34	-32	-28	-20	-19	34

[a] GD 6–10=critical period for eye and axial skeleton development

These data indicate weight loss on GD 6-13 in dams exposed at doses of 50 mg/kg bw/d and on GD 6-15 after exposure to 100 mg/kg/d. At 100 mg/kg bw/d, there was a statistically significant weight loss in dams up to day 10; and overall there was a marked reduction in body weight gain (↓ 85% on GD 0-15 and ↓ 52% on GD 0-20), which was statistically significant. Body weight gain was also reduced at 50 mg/kg bw/d (↓ 24% on GD 0-15 and ↓ 14% on GD 0-20) but this was not statistically significant. Additionally, food consumption was markedly decreased on GD 6–9 (38% and 67% reduction in dams exposed at 50 and 100 mg/kg bw/d, respectively, compared with control values) and on GD 9–12 (19% and 59%, respectively, compared with control values), which could indicate that the females were nutritionally compromised at these times. It was noted that gastrointestinal irritation after ipconazole has been shown, which could explain the decreased food consumption.

It is noted that the maternal weight loss occurred at a period which covers a large part of organogenesis. However, the maternal body weights adjusted for uterine contents were only slightly reduced at 50 mg/kg bw/d (by 2%) and at 100 mg/kg bw/d, which could be explained by the increase in resorptions and the lower pup weight. In addition, the data indicate that effects on body weight were marked at doses of 50 and 100 mg/kg only during treatment days with relatively quick recovery after treatment cessation.

Developmental toxicity

Ipconazole did not affect the number of corpora lutea or implantation sites when administered in doses ≤ 100 mg/kg bw/d. In the one surviving dam at 250 mg/kg bw/d, there was 100% foetal resorption/death. At 100 mg/kg bw/d, there was a reduction in the number of live foetuses per litter, an increase in the % of foetal resorptions and deaths, and decreased foetal weight (all statistically significant). The same parameters were affected at 50 mg/kg bw/d, but without statistical significance.

Table: Maternal and fetal body weight and number of fetuses/resorptions per litter

Dose (mg/kg bw/d)	0	1	10	50	100
Maternal body weight (g) day 20	405	416	408	386 (-5%)	336 (-17%)
Gravid uterine weight (g)	74	84	73	64 -14%	26** -65%
Adjusted maternal body weight (g)	330	332	335	322 (-2%)	310 (-6%)
Live fetuses/litter	13.4	14.7	13.2	12.3	4.9**
% foetal resorption/deaths	7.7%	5.8%	13.6%	19.7%	69.3%**
Mean foetal weight males (mg)	3453	3589	3532	2926 (-15%)	2026** (-41.3%)
Mean foetal weight females (mg)	3299	3365	3185	2895 (-12%)	2181** (-34%)

** Statistically significant at p ≤ 0.01

Table: External abnormalities in foetuses:

Dose (mg/kg bw/d)	**0**	**1**	**10**	**50**	**100**
No. foetuses (litters)	94/7	88/6	79/6	86/7	34/6
Meningoencephalocoele	0	0	0	0	1
Exencephaly	0	1	0	0	0
Microphthalmia	0	1	0	2 (1)	7*** (4)
Open eyelid	0	1	0	0	0
Micrognathia	0	0	0	0	1
Omphalocoele	0	0	0	0	1
Kinky and/or short tail	0	0	0	1 (kinky)	7*** (2) short=2 kinky=6
Total no. foetuses with abnormalities (litters with affected foetuses)	0	2 (2)	0	3 (1)	11*** (4*)

*Statistically significant at $p \leq 0.05$; ***Statistically significant at $p \leq 0.001$

In the preliminary rat study, no foetuses were obtained at the highest doses of 250 and 500 mg/kg bw/d because of extensive maternal deaths. At the next doses of 50 and 100 mg/kg bw/d, there were increased incidences of microphthalmia and kinky/short tail (statistically significant at 100 mg/kg bw/d). There were also single foetal incidences of meningoencephalocoele (protrusion of brain tissue through the skull), micrognathia (one jaw unusually small) and omphalocoele (umbilical hernia) at 100 mg/kg bw/d.

Only external investigations were undertaken in this study, not visceral examinations. It is unclear how thoroughly the eye was examined, and hence if the reported finding of microphthalmia truly fitted the description of this malformation as given in the harmonised nomenclature for developmental toxicity (microphthalmia=defined as small eye, eyeball or globe of eye upon visceral examination; can be compared with the external finding of small eye bulge, which 'may be associated with microphthalmia'). However, in the absence of more detail, RAC considered the reported microphthalmia as a malformation.

Overall, 11 fetuses in four litters of the 100 mg/kg bw/d group in the preliminary study were recorded to have malformations. Six of these foetuses were in one litter (from dam number 1015, 6/8 foetuses affected: 2 with microphthalmia alone, two with kinky tail alone, one with short tail alone, one with microphthalmia, kinky tail, micrognathia and meningoencephalocele). Three foetuses were in another litter (dam number 1016, 3/5 foetuses affected: one with microphthalmia and kinky tail; one with microphthalmia and kinky plus short tail; one with kinky tail and omphalocele). The remaining two litters had one foetus each with microphthalmia (1/1 and 1/4 foetuses affected, respectively). The mean foetal weight was lower in the litter from dams 1015 than in the other four litters obtained at this dose and much lower than mean foetal body weight in the control group. At 50 mg/kg bw/d, the three foetuses with malformations (2 with microphtalmia and 1 with kinky tail) were all in the same litter.

In the main developmental toxicity study (OECD TG 414, GLP), 24 mated female Sprague-Dawley rats per dose group were given ipconazole by gavage at doses of 0, 3, 10, 30 mg/kg bw/d in 1% aqueous sodium carboxy-methylcellulose on GD 6-15. Dams were sacrificed on GD 20.

The study differs from the current test guideline (OECD TG 414, 2001) in that the litter was not used as the unit for the analysis of foetal effects; instead, analysis was based solely on the foetal

incidences. However, litter incidence data were reported in the study report. The period of dosing is less than what is currently preferred (normally from GD 5 in rodents).

Maternal toxicity

There were no maternal deaths or clinical signs of toxicity at any dose.

At 30 mg/kg bw/d: maternal body weights were lower than in controls on GD 7-20, although no significant differences were noted for body weight adjusted for gravid uterine weight. Reductions in weight gain by 17-24% were recorded during the dosing period but there was no change over GD 0-20. Reduction in food consumption was recorded at certain points during gestation in this group, but was comparable with controls during the post-dosing period. There were no treatment-related gross necropsy findings.

Developmental toxicity

Gravid uterine weights, numbers of corpora lutea, implants, live foetuses and sex ratio were unaffected. The incidence of foetal resorptions and deaths was 3.9%, 3.8%, 7.2% and 7.6% at 0, 3, 10 and 30 mg/kg bw/d, respectively. The incidences in the mid- and high-dose groups were within the laboratory's historical control range (4.5-8.5% for 6 studies conducted 1988-1992; 4.5-9.3% for 10 studies 1987-1993). The incidences in the control and low-dose groups were lower than the historical control range.

Foetal body weight was reduced at 30 mg/kg bw/d in both sexes (↓ 6-7%*) but not at 3 and 10 mg/kg bw/d.

The findings of note from fetal examinations are summarised in the table below:

Dose (mg/kg bw/d)	**0**	**3**	**10**	**30**
External malformations				
Number of foetuses	324	352	339	354
Number of litters	23	23	24	23
Microphthalmia	0	0	0	2 (0.6%) 2 litters
Cleft lip	0	0	0	1 (0.3%)
Cleft palate	0	0	0	1 (0.3%)
Vestigial tail	0	0	1 (0.3%)	0
Total number of affected foetuses (litters)	0	0	0	2 (2)
Visceral malformations				
Number of foetuses	155	169	163	168
Number of litters	23	23	24	23
Double aortic arch	0	0	0	1 (0.6%)
Coarctation of the aorta	0	0	0	1 (0.6%)
Right aortic arch	0	0	1 (0.6%)	0
Aberrant right subclavian artery	0	0	0	1 (0.6%)
Agenesis of the spleen	0	0	0	1 (0.6%)
Total number of affected foetuses (litters)	0	0	1	2 (2)

Dose (mg/kg bw/d)	0	3	10	30
Visceral variations				
Number of foetuses	155	169	163	168
Number of litters	23	23	24	23
Left umbilical artery, number of affected foetuses (litters)	1 (0.6%)	2 (1.2%) (2)	2 (1.2%) (2)	7* (4.2%) (6)
Skeletal variations				
Number of foetuses	169	183	176	186
Number of litters	23	23	24	23
Supernumerary ribs	3 (1.8%) (3 litters)	1	8 (4.5%) (6 litters)	13* (7%) (7 litters)

* Statistically significant at $p \leq 0.05$

Historical control data

- Microphthalmia

Studies conducted in the same laboratory and rat strain (conducted 1985-1995) indicated that microphthalmia was observed in 3 out of 20 control groups in other studies. The foetal/litter incidences in a first historical control group was 0.64%/4.17% (1/1), in a second historical control group 0.83%/4.55% (1/1) and in a third group 0.65%/9.52% (2/2). In 17 other historical control groups, there was no microphtalmia observed. The overall mean incidence in all 20 historical control groups was 0.06% (4/6439 fetuses).

- Cardiovascular malformations

In 20 studies conducted in the same laboratory and rat strain (1985-1995) there were no incidences of double aortic arch or coarctation of the aorta. There was one case of right aortic arch in one study (1/163 foetuses, 0.61%). One pup (out of 121) with aberrant right subclavian artery was observed in a treatment group of one historical control study from 1987-1988.

- Cleft lip and cleft palate

Data gathered from Japanese laboratories from the same rat strain between 1994 and 2000 indicated a background incidence of cleft lip of 0.04% (range 0 – 0.3%) in one laboratory, with no cases in another 11 laboratories. Cleft palate was recorded in three laboratories, with incidences ranging from 0 – 0.4%.

- Supernumerary ribs

Data from the same laboratory and rat strain, 3 studies conducted 1987-1988, showed a range of 1.2-2.8%

Summary of developmental effects observed in the two rat studies

In the main rat study, sections taken of the head did not include the eyes and those were hence not subjected to histological examination. However, the eyes were examined for external alterations after removing the palpebral skin, enabling a close examination of the size of the eyeball. The microphthalmia observed at 30 mg/kg bw/d was unilateral, with one bulb being less than 2/3 the size of the other. The two cases occurred in two separate litters. One of the foetuses with microphthalmia also had a cleft lip and cleft palate. One rat foetus in the 10 mg/kg bw/d group of the main study had a vestigial tail, but this abnormality was not recorded at 30 mg/kg/d.

Malformations of major blood vessels associated with the aortic arch were recorded in two rat foetuses at 30 mg/kg bw/d, one with a double aortic arch and coarctation (narrowing) of the aorta, the other (from a different litter) with an aberrant right subclavian artery and also agenesis (absence) of the spleen. In the high-dose group there was also an increase in the incidence of left umbilical artery (in rats the umbilical artery is normally on the right side), which was seen in six litters and was outside the historical control range. The study authors were uncertain of the toxicological significance of this finding, and there is no description of a malpositioned or transposed umbilical artery in ECETOC (2002, (49)) nor Makris *et al*. (2009 (50)). According to the DevTox project (www.devtox.org/index.htm) this finding is not classified as either a malformation or a variation.

Dilatation of the renal pelvis and/or ureter, classified as a visceral variation, was recorded in rat pups, but in the absence of a clear dose-response relationship (1, 7, 3, 8 at 0, 3, 10, 30 mg/kg bw/d, respectively) it was not considered further. A predominant malformation in the rabbit preliminary study was the occurrence of short tails at a dose of 100 mg/kg bw/d, which occurred in 12.5% of the fetuses and three of the four litters. In this dose group, a kinky tail was also recorded in one foetus.

- Skeletal findings

Several skeletal findings were recorded in the studies. These included low but increased incidences of skeletal malformations in rabbits from 10 mg/kg bw/d, but in the absence of concurrent historical control data these findings are difficult to interpret. Supernumerary ribs were recorded in both rat and rabbit foetuses, but uncertainty surrounds the developmental/teratogenic significance of such ribs, in particular their post-natal reversibility or otherwise. The presence of supernumerary ribs that are small in size may be considered to be less significant with respect to teratogenic potential than ribs that are more than half the size of a full rib, which are considered to be more likely to persist post-natally. Cervical ribs were also reported in the main rabbit study; these are not classified as either malformations or variations by the DevTox project, and are considered to be of low to moderate concern by ECETOC (2002 (50)).

- Foetal resorptions and deaths

Although there appeared to be a slight (not statistically significant) increase in foetal resorptions and deaths at 10 and 30 mg/kg bw/d in the main rat study, the increase was within the historical control data and was compounded by the atypically low incidences in the controls and low-dose group (below the historical control range). A reduction in the number of live foetuses per litter, an increase in foetal resorptions and deaths, and decreased foetal weight were also reported in the preliminary study, at 50 mg/kg bw/d and 100 mg/kg bw/d (statistically significant in the latter and associated with maternal toxicity). These parameters were also affected in the rabbit preliminary study (100 mg/kg bw/d), as was the sex ratio, in association with maternal toxicity. There were no effects in the main study, in which the maximum dose was 50 mg/kg bw/d.

Rabbits

There were two (preliminary and main) developmental toxicity studies in rabbits (Kureha Corporation (1990 (46 and 48))

In the preliminary developmental toxicity study (ref 46; non guideline, GLP) 5 mated female rabbits (Japanese White) per group were given ipconazole by gavage at doses of 0, 10, 100, 300 and 1000 mg/kg bw/d in 1% aqueous sodium carboxy-methylcellulose from GD 6-18. Dams were sacrificed on GD 27.

Scope of the investigations in the dams: gross pathology, ovaries and uterine contents examined, gravid uterine weights, corpora lutea and implantations determined; investigation for very early

resorptions when no uterine implants were grossly visible. Investigations in the foetuses: number, sex and weights of live foetuses and placenta, incidences of resorptions and foetal deaths; live foetuses examined for external abnormalities. There was no examination for visceral or skeletal malformations and variations.

Maternal toxicity

All dams given 300 and 1000 mg/kg bw/d died during the dosing period. Clinical signs of toxicity (discharge from the eyes and soiling of fur) were seen only in these dose groups.

At 100 mg/kg bw/d, dams lost 264 g (up to 6%) from GD 6 to 18, compared with a gain of 53 g for the controls and 66 g for the 10 mg/kg bw/d group. Food consumption was reduced up to about gestation day 12 in the 100 mg/kg bw/d group but was thereafter comparable to or higher than in the controls.

At gross necropsy of the animals that died before scheduled sacrifice, changes were recorded in the stomach (ulcer/erosion and/or petechia) and liver (accentuated lobular pattern and pale colour). One animal at 100 mg/kg bw/d had hair loss, hydropericardium and erosion of the stomach.

Developmental toxicity

Ipconazole did not affect the number of corpora lutea or implantation sites when administered in doses ≤ 100 mg/kg bw/d. At 100 mg/kg bw/d there was a decrease in gravid uterine weight, the number of live foetuses, an increase in foetal resorptions/deaths, slightly reduced foetal weight and placental weight and a change to the foetal sex ratio (see table below).

A predominant malformation in the rabbit preliminary study was the occurrence of short tails at a dose of 100 mg/kg/d, which occurred in 12.5% of the fetuses and three of the four litters. In this dose group, a kinky tail was also recorded in one foetus.

Table: Maternal and foetal body weight and number of foetuses/resorptions per litter

Dose (mg/kg bw/d)	**0**	**10**	**100**
Maternal body weight (g) day 27	4296	4333	4364
Gravid uterine weight (g)	452	427 -6%	265 -41%
Adjusted maternal body weight (g)	3844	3906	4099
Live foetuses/litter	8.8	7.3	4.8
% foetal resorption/deaths	13.8%	4.8%[a]	58.5%*
Mean foetal weight males (g)	36.8	41.3	29.4
Mean foetal weight females (g)	37.2	37.8	31.4
Sex ratio (male/total)	0.477	0.591	0.750*

[a]One dam had implantation sites but no foetuses, and so was excluded from the analysis by the study authors. The study report did not provide the number of implantation sites in this animal, so it was not possible to determine the number of foetal resorptions.
* Statistically significant at $p \leq 0.05$

The adverse findings from foetal external examination are shown in the table below:

Dose (mg/kg bw/d)	**0**	**10**	**100**
No. foetuses (litters)	44 (5)	22 (3)	24 (4)
Acephaly	0	0	1
Microphthalmia	0	0	1
General oedema	0	0	1
Vestigial tail	0	0	1
Short tail	0	0	3* (3)
Kinky tail	0	0	1
Total no. foetuses with abnormalities (litters with affected foetuses)	0	0	6** (3*)

* Statistically significant at $p \leq 0.05$
** Statistically significant at $p \leq 0.01$

Historical control data

- Microphthalmia

From studies conducted in the same laboratory and strain (2001-2010), the mean incidence was 0.24% (range 0 - 2.32%) from 13 studies (2262 foetuses) (ref 47).

- Short or absent tail

From studies conducted in the same laboratory and strain (2001-2010), the mean incidence of short tail was 0.07% (range 0 – 0.53%) from 13 studies (2262 fetuses). There were no cases of absent tail (ref 47). The total number of foetuses with malformations in this historical control data was 6 / 2262 (0.27%).

In the main developmental toxicity study (ref 48; non guideline, GLP) 18 mated female rabbits (Japanese White) per group were given ipconazole by gavage at doses of 0, 2, 10 and 50 mg/kg bw/d in 1% aqueous sodium carboxy-methylcellulose from GD 6-18. Dams were sacrificed on GD 27.

The study differs from the current test guideline (OECD TG 414, 2001) in that the litter was not used as the unit for the analysis of foetal effects; instead, analysis was based solely on the foetal incidences. However, litter incidence data were reported in the study report, although there is no listing of the abnormalities and other findings for each individual foetus. All foetal rabbit heads were examined internally by a single transverse section, which is considered to be adequate for the detection of hydrocephalus.

Maternal toxicity

There were no deaths or clinical signs of toxicity.

Maternal body weights were reduced compared with controls at 50 mg/kg bw/d throughout the dosing period (by up to 106 g / 3%, not statistically significant). Mean body weight change of dams at this dose was reduced on several days during dosing (e.g. -73 g between days 6 and 15). At this dose, food consumption was slightly lower than controls (not statistically significant).

Reproductive parameters (gravid uterine weights, numbers of corpora lutea, implants, live foetuses, resorptions/foetal deaths and sex ratios) were unaffected by treatment. There were no statistically significant effects on mean foetal body weight and placental weight.

Developmental toxicity

One foetus with cleft palate was observed in the 50 mg/kg bw/d group. There were no substance-related adverse findings upon visceral examination.

The findings of note upon skeletal examination are shown in the table below (there were several findings with single incidences in different treatment and control groups, not shown).

Dose (mg/kg bw/d)	**0**	**2**	**10**	**50**
Number of foetuses (litters)	111 (16)	163 (17)	137 (16)	155 (17)
External findings:				
Cleft palate	0	0	0	1 (0.7%)
Skeletal malformations:				
Splitting of nasal bones	0	0	1 (0.7%)	1 (0.7%)
Hemi-vertebrae	0	0	1 (0.7%)	2 (1.3%) (2 litters)
Bifurcation of the ribs	0	0	0	2 (1.3%) (2 litters)
Fusion of the sternebrae	1 (0.9%)	3 (1.8%)	0	5 (3.2%) (3 litters)
Number of affected foetuses (litters)	1 (1)	3 (2)	2 (2)	8 (4)
Skeletal variations:				
Splitting of parietal bones	2 (1.8%)	1 (0.6%)	2 (1.5%)	20*** (12.9%)
Cervical ribs	0	0	0	3
Supernumerary ribs	9 (8.1%)	18 (11%)	16 (11.7%)	24 (15.5%)
Lumbarisation of the sacral vertebrae	0	1 (0.6%)	1 (0.7%)	3 (1.9%)
Asymmetry of sternebrae	0	1 (0.6%)	1 (0.6%)	4 (2.6%)

***Statistically significant at $p \leq 0.001$

Historical control data

Based on examination of 1116 foetuses from 150 litters, the historical control data from the same laboratory and test strain (1986-1989) were

- splitting of the parietal bones: foetal incidence 1.7%, range 0-14.3%
- supernumerary ribs: foetal incidence 21.8%, range 13.9-30.1%
- lumbarisation of the sacral vertebrae: foetal incidence 1.3%, range 0-4.9%
- asymmetry of the sternebrae: foetal incidence 0.3%, no value for range

Data from the same laboratory and test strain, 2001-2010 (ref 46), 13 studies (2262 foetuses)

- cleft palate: no cases
- hemivertebrae: thoracic – mean 0.04, range 0-0.48; lumbar – mean 0.13, range 0-0.70
- bifurcation of the ribs: 0.12 (0-0.95)
- fusion of the sternebrae: 0.67 (0-2.57)

The DS concluded, based on increased incidences of microphthalmia and tail malformations, and foetal resorptions/deaths, occurring at what was considered as maternally-toxic doses in preliminary studies, that ipconazole meets the criteria for classification as Repr. 2; H361d (Suspected of damaging the unborn child).

Comments received during public consultation

Three MSCAs supported classification of ipconazole as Repr. 2; H361d, as well as no classification for adverse effects on sexual function and fertility.

One MSCA asked for more discussion on developmental toxicity before deciding on classification.

One MSCA disagreed with the proposed classification and instead proposed classification as Repr. 1B; H360D.

Two industrial organisations supported classification of ipconazole as Repr. 2; H361d, as well as no classification for adverse effects on sexual function and fertility.

Assessment and comparison with the classification criteria

Effects on sexual function and fertility

In the two-generation study in rat, sperm concentrations in the caudal epididymides in F0 males were reduced, but in the absence of consistent changes in the F1 generation, these minor differences were considered not to be of toxicological significance. Minimal reductions in the number of implantation sites (not statistically significant) and litter sizes on post-natal days 1, 4 and 21 were generally within relevant historical control data. Overall, fertility parameters were unaffected in this study. Offspring toxicity was evident in the reduced body weight gains in the mid- and high-dose groups, but there was no indication of specific developmental toxicity. Some changes in the weights of female reproductive organs in the preliminary study were not confirmed in the two-generation study.

Taking into account the results of main two-generation study, RAC is of the opinion that ipconazole does not warrant classification for effects on sexual function and fertility.

Developmental toxicity

As no human evidence exists for ipconazole, classification in Category 1A is not appropriate.

For classification in Category 1B, there should be clear evidence (usually from animal studies) of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects the developmental effect should not be considered to be a secondary non-specific consequence of other toxic effects.

Category 2 is considered to be appropriate when there is some evidence of an adverse effect on development, but it is not sufficiently convincing to place the substance in Category 1. Deficiencies in the study that make the quality of evidence less convincing might lead to a classification in Category 2, as could mechanistic information that raises doubt about the relevance of the effect for humans.

For ipconazole, increases in foetal resorptions/deaths were reported in the preliminary studies in both rats and rabbits. Furthermore, increases in specific malformations were reported in the preliminary studies in rats and rabbits (microphthalmia and tail effects) as well as in the main study in rats (microphthalmia). Microphthalmia was seen at two doses in the preliminary rat study (2 foetuses in the same litter at 50 mg/kg bw/d and 7 foetuses in 4 litters at 100 mg/kg bw/d). In the main rat study microphthalmia was seen in 2 foetuses in 2 different litters at 30 mg/kg bw/d (highest dose tested), and in the preliminary rabbit study it was seen in 1 foetus at 100 mg/kg bw/d (highest dose tested). The highest dose in the main rat study was below the dose at which malformations and foetal resorptions/deaths were reported in the preliminary study.

There was some uncertainty associated with the investigation of microphthalmia in these studies; however, in the absence of further information RAC has regarded this finding as a malformation. Effects on the left umbilical artery in rats were categorised as variations by the study authors, which are normally regarded to be of lower concern than malformations.

There is no mechanistic information indicating that the findings are not relevant to humans.

In conclusion, specific malformations (mainly microphthalmia and kinky/short tail) were seen after ipconazole exposure. The concern is increased as microphthalmia was seen in two different species, in three out of four available studies, occurring in several litters in two of the studies. The effects are not considered as secondary, non-specific consequences of other toxic effects. Therefore, overall, the evidence is considered as clear, and there are sufficient grounds to conclude that Category 1B is more appropriate than Category 2.

Taking into account the above analysis RAC is of the opinion that ipconazole warrants classification as **Repr. 1B; H360D (May damage the unborn child)**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Regarding the substance identity, the following was provided by the DS:

CAS 125225-28-7 – all stereoisomers
CAS 115850-69-6 – *cis-cis* (cc) racemate: 87.5–93%
CAS 115937-89-8 – *cist-trans* (ct) racemate: 6.5–9.5%

Water solubility (– EEC A.6., Comb, 2001, 2007; DAR B.2.1.11) ranged between 4-11 mg/L in different pHs and the octanol-water partition coefficient (Log K_{OW}) between 4.3-4.65. Regarding sorption, a K_{oc} of 1,724–3,214 mL/g was derived, with a mean value of 2,431 mL/g, determined in six different soil types (Hatzenbeler & Long, 2001b; Wanner, 2006).

Degradability

Aquatic photolysis is not likely due to the lack of absorption at >290 nm. No measured data.

Photolysis on soil surface: DT_{50} ≈ 241 days of summer sunlight at 40°N – SETAC, 1995 (Shaw, 2005b).

Hydrolytically stable: DT_{50} >1 year at 25°C, at pH 5, 7 & 9 – OECD TG 111 (Hatzenbeler & Long, 2001a).

Not readily biodegradable: less than 60% of theoretical CO_2 production was reached within 29 days – OECD TG 301B (Barnes, 2005b)

Simulation studies: biodegradation DT_{50} >>100 days in whole water–sediment systems – OECD TG 308 (Shaw, 2005d) and in soils under aerobic or anaerobic conditions – OECD TG 307 (Shaw, 2005a,c; Mellor, 2006).

Ipconazole showed only slow degradation in the environment; the DS proposed to consider the substance as non-rapidly degradable for the purpose of environmental hazard classification.

Degradation products

A number of ipconazole degradation products have been identified (UK, 2011; EFSA, 2013), predominantly in soil. By use of radio-labelled ipconazole, more than 10 minor degradants could be differentiated in soil, corresponding to 11–13% in total. None of the major degradants, such as the hydroxylated forms of ipconazole, the cleaved triazole moieties and clorobenzoic acid, -aldehyde or -alcohol derivatives – were identified in the EFSA conclusion (2013) as equally or more hazardous than ipconazole.

Bioaccumulation

Bioconcentration in fish: steady state BCF 225–283 L/kg in *Lepomis macrochirus* – OECD TG 305 (Kureha Corporation, 2006).

Despite a Log K_{OW} = 4.28–4.65, the substance has a low potential for bioaccumulation.

Aquatic toxicity – summary table

Method	***Results***	***Remarks***	***Reference***
Acute fish toxicity – OECD TG 203	96h-LC_{50} = 1.5 mg/L mm *Oncorhynchus mykiss*	GLP	Kureha Corporation, 2001a
Acute fish toxicity – OECD TG 203	96h-LC_{50} = **1.3** mg/L mm *Lepomis macrochirus*	GLP	Kureha Corporation, 2001b
Chronic fish toxicity – OECD TG 210	28d-NOEC = **0.00044** mg/L mm *Pimephales promelas*	GLP	Kureha Corporation, 2007
Acute invertebrate toxicity – OECD TG 202	48h-EC_{50} = 1.7 mg/L mm *Daphnia magna*	GLP	Palmer et al., 2001c
Chronic invertebrate toxicity – OECD TG 211	21d-NOEC = 0.0109 mg/L mm *Daphnia magna*	GLP	Flatman, 2007
Toxicity to algae – OECD TG 201	96h-E_rC_{50} >2.2 mg/L nominal 96h-$NOEC_r$ = 0.22 mg/L nominal *Pseudokirchneriella subcapitata*	GLP	Flatman, 2006a
Long-term toxicity *Chironomus riparius* OECD TG 219	28d-NOEC = 3.52 mg/L	GLP	Flatman, 2006b

mm = mean measured

Proposal of DS for classification

The DS proposed no classification for acute aquatic hazards, based on acute toxicity above the CLP cut-off value of 1 mg/L.

For chronic classification, toxicity data are available for fish, *Daphnia magna* and algae. Based on a lowest NOEC value of 0.00044 mg/L and the fact that ipconazole is considered non-rapidly degradable, the DDA proposed classification as Aquatic Chronic 1 (H410, very toxic to aquatic life with long lasting effects), with an M-factor of 100.

Comments received during public consultation

Five commenting Member States agreed with the proposed classification and no one opposed.

Some minor clarifications were requested by two commenting parties concerning the concrete values of NOEC and BCF values, on which the classification as Aquatic Chronic 1 with an M of 100 are based. However, even if the lowest NOEC value would change based on the conclusion on the statistical significance of mortality effects at a given concentration (see following paragraph), it would not change the proposed classification.

One MSCA commented that they would use a NOEC value of 0.00018 mg/L, instead of a NOEC of 0.00044 mg/L as proposed by the DS – taking into account the 20% mortality at a 1.1 µg/L ipconazole concentration, which was considered as not significant by DS and therefore not used. The DS replied that the NOEC value proposed is outside the acceptability criterion of 30% (being only 22%), and that the NOEC of 0.00044 mg/L is supported by other endpoints such as fish weight and length besides fish mortality. An additional argument is the EFSA peer review conclusion for ipconazole, with the same lowest NOEC value of 0.00044 mg/L (EFSA, 2013).

The same MSCA also commented that the final concentration of THF (tetrahydrofuran) solvent used in the chronic fish and daphnia studies was lacking. The DS complemented this information with the value of 0.1 mL THF/L diluent water and clarified that the *"comparison of the solvent and blank controls does not reveal any adverse effects from use of this solvent in either test".*

Another MSCA commented that the lipid normalised BCF value for fish was lacking, and that they were not satisfied with the DS's conclusion that the final lipid content of the studied fish is close to 5%. The MSCA calculated and proposed a lipid normalised BCF using a 0–48 days time-averaged lipid content.

Assessment and comparison with the classification criteria

Ipconazole is hydrolytically stable, not readily biodegradable and has a half-life in whole water-sediment systems DT_{50} >>16 days. Therefore, the substance is considered to be non-rapidly degradable for the purposes of hazard classification.

The substance has a low potential to bioaccumulate, as the steady-state BCF has been experimentally determined in fish to be 225–283 L/kg. RAC prefers to calculate the lipid normalised BCF according to OECD TG 305, Annex 5, which states that "*If the same fish were used for measuring chemical concentrations and lipid contents at all sampling points, this requires each individual measured concentration in the fish to be corrected for that fish's lipid content." and "For the steady-state BCF, the mean value recorded at the end of the uptake phase in the treatment group should be used*". Taking the worst case scenario into consideration, the maximum lipid normalised BCF would be 338 L/kg, which is calculated from the highest measured BCF = 283 L/kg x 5%/4.19% (the lowest lipid content at the end of the uptake phase), which is still below the CLP cut-off value of 500.

The results from all aquatic acute toxicity studies gave LC/EC_{50} values above the CLP cut-off criterion of 1 mg/L (fish: 1.3 mg/L; daphnia: 1.7 mg/L; algae: 2.2 mg/L. Therefore, it is proposed that the substance is not classified for Aquatic Acute hazards.

Concerning chronic aquatic toxicity, RAC agrees with the DS that the most appropriate fish (*Pimephales promelas*) NOEC value is 0.00044 mg/L. This is also the value to be used for chronic classification, as aquatic invertebrate and algae NOECs were higher than this value (*Daphnia Magna* NOEC = 0.0109 mg/L; algae NOErC = 0.22 mg/L). Thus, the substance should be classified as **Aquatic Chronic 1 - H410**. As 0.0001 < NOEC ≤ 0.001 and the substance is considered non-rapidly degradable, the appropriate chronic **M-factor is 100**.

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 RAC (excluding confidential information).