Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 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)]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance 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: -
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Germany		MemberState	1
Comment received				
The German CA strongly urges the dossier submitter to propose harmonised ATE values for the acute toxicity class. Harmonised ATE values will greatly facilitate harmonised classification of mixtures and will improve legal certainty for suppliers and increase the safety of workers and consumers.				
Dossier Submitter's Response				
Two acute oral toxicity studies are available, one in rats with a lowest LD50 of 888 mg/kg bw, and one in mice with a lowest LD50 of 468 mg/kg bw. Both studies followed OECD guideline 401 and were conducted in accordance with GLP. The lowest overall LD50 of 468 mg/kg bw could therefore be taken as the ATE. However, the dossier submitter notes that the rat is the standard species for the investigation of acute oral toxicity, which would support an ATE of approximately 800 mg/kg bw. Since a range of values is available, all of which fall within the classification criteria for Acute Tox 4, an alternative approach would be to apply the converted ATE of 500 mg/kg bw from Table 3.1.2 of CLP Annex I.				
RAC's response				
A harmonised ATE value has been proposed by RAC.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 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)]

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany		MemberState	2

Comment received

On the cover sheet and in Part A of the CLH Report no CAS number is stated directly. However, in table 1.1 of Part A the Dossier submitter (DS) refers to table 4 in Part B. Ipconazole is the ISO common name for "(1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol". The ISO entry stated also the CAS number 125225-28-7 which is a generic number and covers the mixture of all stereoisomers.
In the PPP implementing regulation for Ipconazole the stated identifier of Ipconazole (IUPAC name and CAS number) are given together with the CAS numbers 115850-69-6 (for ipconazole cc, cis-cis isomer) and 115937-89-8 (for ipconazole ct, cis-trans isomer). As stated in section 1.2 of part B the active substance and test substance is a 12:1 ratio of the cc and ct racemates. Therefore, the use of the generic CAS number and the ISO name Ipconazole associated with the IUPAC name (1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol is not appropriate.
The correct identification for the test substance would be (1α,2α,5α)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol, CAS No. 115850-69-6 (cis-cis racemate).

Therefore, please check which substance or substances should be classified with this entry. Based on the given ID data we would propose to generate a group entry for the following three substances:

International Chemical Identification CAS No
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)
(1α,2α,5α)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol CAS No. 115850-69-6 (cis-cis racemate)
(1α,2α,5β)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol CAS No. 115937-89-8 (cis-trans racemate)]

Dossier Submitter's Response

Thank you for your comments. This is addressed in the CLH report. The ISO name Ipconazole is associated with the CAS number 125225-28-7 and the IUPAC name (1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol. The substance is therefore identified as such in the CLH report for consistency. It is, however, acknowledged that the active substance contains > 80% of ipconazole-cc isomers (CAS 115850-69-6). As such, it is proposed to include the CAS numbers 125225-28-7, 115850-69-6 and 115937-89-8 in the description of the substance in Annex VI of CLP as related chemical identifiers. This is in line with the approach taken in the Commission Implementing Regulation (EU) 571/2014.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	3
Comment received				
Arysta Life Science agree with all the proposal for consideration by RAC on page 5				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	4
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Germany		MemberState	5
Comment received				
At least one specific comment must be added				
Dossier Submitter's Response				
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RAC's response				
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Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	6
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 59				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	7
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	8
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 55				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Spain		MemberState	9
Comment received				

Fertility

The Spanish CA agree with the fact that Ipconazole does not fulfil the criteria for classification for effects on fertility.

Marginal and inconsistent reductions in some reproductive parameters (reductions in total litter size (F2 only) and live birth index (F1 only)) were seen in a two-generation study in rats. However, these were only marginally below the historical control ranges, were inconsistent across the generations and did not show statistical significant differences from the controls. Therefore they are not considered to provide evidence of a specific treatment related effect.

Developmental toxicity

Findings indicative of developmental toxicity were observed in four developmental studies (two in rats and two in rabbits). These included, microphthalmia and short/kinky tails in both rats and rabbits along with visceral defects (e.g., abnormalities of major blood vessels associated with the aortic arch and increased incidence of left umbilical artery in rats). There were also increases in fetal resorptions/deaths resulting in reduced live fetuses per litter in rats and rabbits.

Considering that signs of maternal toxicity were observed and the majority of findings were only reported in preliminary studies the Spanish CA agree with the dossier submitter that ipconazole meets the criteria for classification for reproductive toxicity category 2 – H361d – Suspected of damaging the unborn child.

Dossier Submitter's Response

The dossier submitter notes the support for the proposal.

RAC's response

After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	10

Comment received

Table 18 page 63 Developmental toxicity study in rat:
During the PRAPeR Expert Meeting 95, a NOAEL for developmental toxicity in rats of 3 mg/kg bw/d was agreed based on increased incidence of malformations of major blood vessels. Indeed, the single incidence of right aortic arch found at the mid-dose level (10 mg/kg bw/day) was considered related to other malformations of the aortic arch observed in 2 fetuses/2litters at 30 mg/kg bw per day.
Furthermore, increased incidence of supernumerary ribs is observed from 10 mg/kg bw/d onwards (not statistically significant at mid-dose level, this effect is dose related and above the HCD). Developmental toxicity is therefore observed in the absence of maternal toxicity.

Page 76. Comparison with criteria
It is agreed that classification for developmental toxicity is warranted.
Considering the different types of malformations, common pattern of effects among studies and species identified (microphthalmia, short/kinky tails) and since neither the severity of maternal toxicity nor any specific mode of action support that those structural abnormalities could be considered as secondary non-specific consequence of other toxic effects, the category should be more discussed.

Dossier Submitter's Response

Thank you for the comments.

The single incidence of right aortic arch in a foetus at 10 mg/kg bw/d is not a clear treatment-related effect, since this malformation did not occur at 30 mg/kg bw/d and has been reported in the time-relevant historical control data from the same laboratory. The affected foetus did not show the malformations of the aortic arch that were observed in two foetuses of the high-dose group. The increased incidence of supernumerary ribs at 10 mg/kg bw/d was not statistically significant. Some uncertainty surrounds the developmental/teratogenic significance of supernumerary ribs, in particular their post-natal reversibility or otherwise; those that are small in size are generally considered to be unlikely to persist post-natally and thus are of no developmental significance. Therefore, the dossier submitter concludes that clear evidence of developmental toxicity occurred only in the presence of maternal toxicity. We also note that, after consideration of the same data, EFSA concluded that a classification of Repr. 2 – H361d was appropriate.

RAC's response
After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Netherlands	RIVM/BR	National Authority	11
Comment received				
The Netherlands agree with the opinion that the marginal and inconsistent reductions in some reproductive parameters (reduced sperm concentration in the caudal epididymides (F0 only), reductions in total litter size (F2 only) and live birth index (F1 only)) in a rat two-generation study should not be considered as a specific treatment related effect and therefore, no classification for effects on fertility is proposed. The Netherlands agrees with the Repro. Cat. 2 (H361d) classification due to the teratogenic effects in rats and in rabbits. These included, microphthalmia and short/kinky tails in both rats and rabbits along with visceral defects (e.g., abnormalities of major blood vessels associated with the aortic arch and increased incidence of left umbilical artery in rats). There were also increases in fetal resorptions/deaths resulting in reduced live fetuses per litter in rats and rabbits. The observed effects are considered relevant for humans and therefore classification is warranted. The developmental effects were primarily observed in the dose-range finding studies and not in the main studies and further, the role of litter effects (for some of the observed developmental effects) can also not be excluded, which might give some uncertainty to these findings. However, it is noted that the highest dose tested in the rat main study is below the effective dose level in the rat dose range finding study and therefore, the negative effect in the rat main study is not inconsistent with the positive effect in the dose-range finding study. Based on all the information we consider that Category 2 would be the more appropriate classification. Therefore, we agree with the proposed classification.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Japan	KUREHA Corporation	Company-Manufacturer	12
Comment received				
We agree with RMS/HSE that a classification for reproductive toxicity category 2. The four developmental toxicity studies were performed with ipconazole (preliminary and main studies in rats and rabbits), and microphthalmia and short/kinky tails were observed in these studies. Increased incidences above the historical control data (HCD) of these findings occurred only at marked maternal toxic doses in the rat and rabbit preliminary studies (50, 100				

mg/kg/d in rats, 100 mg/kg/d in rabbits).
The one case of microphthalmia at 1 mg/kg/d in rat main study is considered to be an incidental finding because of the absence of this effect at 3 and 10 mg/kg/d. This malformation occurred at 30 mg/kg/d in this study, however, the litter and fetal incidences were within HCD for the same strain of the test laboratory. Therefore, the finding at this dose might have been incidental finding. Moreover, the single occurrence of vestigial tail at 10 mg/kg/d of the rat main study should be interpreted as a spontaneous malformation.
With regard to maternal toxicity, we disagree with RMS/HSE consideration that maternal toxicity at 50 mg/kg/d in rats was minimal, with a very slight (2%) reduction in body weights adjusted for uterine contents, and there were no clinical signs of toxicity.
Reduced maternal weight gain is the best characterized effects in early treatment (before gestation day (GD) 12) as thereafter the increasing weight of uterus and contents contributes the major part of overall weight gain. Maternal animals at 50 mg/kg/d showed a net loss of 21 g (controls gained 2 g) in the period GD 6-8, and a net loss of 4 g (controls gained 15 g) in the period of GD 6-12. Marked decrease in body weight gain continued throughout dosing period (GD 0-15 and 6-15, -27% and -67%, respectively). Therefore, we considered that maternal toxicity of 50 mg/kg/d in the rat preliminary study is "marked".
Majority of fetuses with microphthalmia and/or short/kinky tail had severely suppressed body weights when compared with fetuses without these malformations (CLH Report Section 8.1, page 125). We predicted that these malformations were induced in some fetuses as the manifestation of secondary effect of the treatment through maternal toxicities and subsequent delay in fetal development.
Other malformations which observed in the developmental toxicity studies in rats and rabbits were considered not to be treatment-related.
Single incidences of cleft palates in the high-dose groups in the rat (30 mg/kg/d) and rabbit (50 mg/kg/d) studies were reported. The affected rat fetus also had a cleft lip and microphthalmia in addition to the cleft palate, which was within the available historical control range (maximum of 1.54% in cleft palate and 0.3% in cleft lip, HCD of this stock of rats in Japanese laboratories including the test site). Moreover the weight of this fetus was 42% lower than its litter-mates (1947 g versus 3333 g). Neither cleft lip nor cleft palate was found in the 50 and 100 mg/kg/d of the preliminary study. In rabbits, no cases of cleft palate were seen in the preliminary study at 100 mg/kg/d and 1/155 fetuses affected at 50 mg/kg/d in the main study. The maternal animal (no. 70) of this litter had eaten no food during GD 12-27 and shown marked body weight loss (805 g between GD 6-27) which was atypical of the group. Mean fetal weight of the affected litter was only 40% of group mean (14.4 g versus 33.2 g), so that it is possible that the failure of palatine closure related to sever systemic maternal effects and delay in fetal development rather than a specific adverse effect upon palate development itself. The isolated occurrence of this case of cleft palate is considered to be toxicological irrelevant.
Cardiovascular malformations such as right aortic arch, double aortic arch and coarctation of the aorta were found in the 10 mg/kg/d or 30 mg/kg/d of the rat main study. The findings occurred sporadically as a single case in each group (right aortic arch accompanied by coarctation of the aorta, 1 fetus/168 examined (0.59%) in the 30 mg/kg/d). HCD at the test site demonstrated the right aortic arch had been observed in this stock of rats (1 fetus/163 examined, 0.61%). The other large vessels malformation is an aberrant right subclavian artery which occurred together with an agenesis (absence) of the spleen and is probably a chance event. Therefore, we considered that cardiovascular malformations which observed in the rat main study were spontaneous malformations.

With regard to fetal resorption/deaths, a reduction in the number of live fetuses per litter, an increase in fetal resorptions and deaths, and decreased fetal weight were reported at 100 mg/kg/d in the rat preliminary study. Although changes in these parameters also occurred at 50 mg/kg/d, they were not statistically significant. These parameters were also affected in the rabbit preliminary study of 100 mg/kg/d dose group, at this dose maternal toxicity was severe (maximum weight loss of 269 g whilst 34 g gain in controls in GD 6-11, and 44-63 % reduction in food consumption compared with the controls in GD 6-12). Therefore, these changes in the 100 mg/kg/d dose group of the preliminary study in rats and rabbits are considered to be secondary effects of the treatment through marked maternal toxicity. Overall, we believe that no treatment-related malformations on rat and rabbit fetuses were seen in the absence of marked maternal toxicity. In conclusion, in light of the classification criteria for reproductive toxicant (Table 3.7.1 (a) of the CLP Regulation), Repr. 2 classification proposed by RMS/HSE is considered appropriate for ipconazole.
Dossier Submitter's Response
The dossier submitter notes the support for the proposal and additional interpretation of the observed maternal toxicity and malformations.
RAC's response
After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Sweden		MemberState	13
Comment received				
SE CA does not agree with the DS proposal to classify ipconazole as Repr. 2 H360f. We propose that Repr. 1B H360D should be considered. We agree that the following effects are relevant to classification of ipconazole for developmental toxicity, as stated in the CLH-report. - Increased incidence of microphtalmia in rats and rabbits - Increased incidence of tail malformations in rats and rabbits - Increased incidence of left umbilical artery (variation) in rats - Increased incidences of fetal resorptions and deaths in rats and rabbits However, we consider the increased incidence of microphtalmia in rats and rabbits as clear, and not some evidence and that there not sufficient grounds to conclude that category 2 is more appropriate than category 1B. Importantly, there was a dose-dependent increase in incidence of microphthalmia in rats in the preliminary study (GLP but no guideline), both on fetal (2/86 (2.3%) at 50 mg/kg/d, and 7/34 (21%) at 100 mg/kg/d) and on litter (1/7 (14%) at 50 mg/kg/d and 4/6 (67%) at 100 mg/kg/d) basis, and there was no findings of microphtalmia in control group. The DS submitter states that there is a litter effect of the external malformations in the preliminary study, however, we consider that 4/6 litters with increased incidences of microphtalmia as a high incidence, and unlikely to have been related to genetic problems in the dams. (Incidences in individual litters were 4/8, 2/5, 1/1 at 100 mg/kg/d and 1/4 at 50 mg/kg/d). In the main study (OECD TG 414) from the same laboratory, there was an increased incidence of microphtalmia at the highest dose tested, 30 mg/kg/d with a fetal incidence of 2/354 (0.6%) and litter incidence of 2/23 (8.7%). The historical control data (from 1985-1995) from the same laboratory and same rat strain				

presented in the CLH-report showed that microphtalmia was detected in 3/20 studies in 4/6439 fetuses with a mean incidence of 0.06% (no range was given in the report), indicating that microphtalmia is a rare malformation in this rat strain and in the performing laboratory. Moreover, the fetal incidences in preliminary study is much above the HCD mean (despite low statistical power of the study) and the incidence of the main study is also above the HCD mean value, indicating that the observed malformations are not incidental but real findings.
Micropthalmia was also detected in the rabbit preliminary study (GLP, but no guideline) at 100 mg/kg/d with a fetal incidence of 1/24 (4%) (1/4 litters) in rabbits at 100 mg/kg/d. There was no appropriate HCD available; the HCD included in the report was conducted 9 years later than the current study. However, it is noted that the HCD from 2001-2010 had a mean incidence of 0.24%, range 0-2.32% from 13 studies (2262 fetuses). No microphtalmia was detected in the main rabbit study (OECD TG4141) at 50 mg/kg/d which was the highest dose tested.
In the preliminary rat study, maternal toxicity was manifested at 100 mg/kg as clinical signs (in 4/7 dams, including the dam with no viable fetuses), and as effects on body weight and body weight gain. In the CLH-report (as well as in the Annex B.6 of the DAR) it is stated that dams lost weight up to day 10 (up to 13% decrease), and then gained very little weight. Body weight gain was reduced compared to control (85% reduction over days 0-15, 52% reduction over days 0-20).
According to OECD Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment (number 43), a feed restriction study clearly showed that severe weight loss or decrease in body weight gain per see induced minor changes in skeleton development but no effects on viability or malformations in the rat (Fleeman, 2005). Thus, there are no conclusive evidence to link the observed malformations to the maternal toxicity.
In relation to the increased incidences of fetal resorptions and deaths at 100 mg/kg/d in the preliminary rat study, it would have been helpful for the interpretation of maternal toxicity if the body weight at various time points during gestation could be provided. It is not clear whether the weight loss occurred already starting from GD 0 (indicating that the dams were not properly acclimatised) or if the weight loss started at the time of dosing at GD 6.

Dossier Submitter's Response

The dossier submitter acknowledges that the data could be interpreted to meet the criteria for category 1B for developmental toxicity. Overall, however, for reasons explained in the report, we concluded that there were sufficient uncertainties to support Category 2.

With regards to the maternal body weight at time points during gestation in the rat preliminary study, body weight of the high-dose dams was statistically significantly lower than the controls from GD 8 onwards.

RAC's response

After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2017	Denmark		MemberState	14
Comment received				
Because of the following reasons, DK agree with the proposed classification Repr. 2; H361d: - Microthalmia is considered a malformation and was seen in both rats and rabbits, and was outside of historical control - Short and kinky tail seen outside of the historical control in rats and rabbits at 100 mg/kg/d preliminary studies and at 50 mg/kg/d in rat preliminary study. - Treatment-related, statistical significant left umbilical artery in rats at 100 mg/kg/d preliminary study. - Statistically significant increases in fetal resorptions/deaths, resulting in reduced live fetuses per litter, in rats and rabbits at 100 mg/kg/d, preliminary studies and non-statistically significant in rats at 50 mg/kg/d (and at 10 mg/kg/d) preliminary study The effects are irreversible and should not be disregarded because of maternal toxicity. The maternal effects in rats and rabbits are transient reduced body weight gain and food intake and in rats significant reduced gravid uterine weight.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	15
Comment received				
Arysta Life Science accept the Current proposal for the classification by RAC on page 11 and page 78 of Repr 2; H361d - Suspected of damaging the unborn child. Arysta Life science also support the additional information provided by Kureha Corporation re historical control data on some of the effects noted.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
After the RAC plenary discussion, RAC is of the opinion that ipconazole warrants classification as Repr. 1B, H360D (May damage the unborn child).				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	16
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	17
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 30				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Spain		MemberState	18
Comment received				
The Spanish CA supports the proposed classification of Ipconazole as harmful for acute toxicity via the oral route as the ATE values ranged from 468 – 1338 mg/kg. Acute Tox 4; H302 – Harmful if swallowed (limits 300 < ATE ≤ 2000 mg/kg bw, according to CLP classification criteria).				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	19
Comment received				
Proposal for classification H302 is supported.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Germany		MemberState	20
Comment received				
The German CA strongly urges the dossier submitter to propose harmonised ATE values for the acute toxicity class. Harmonised ATE values will greatly facilitate harmonised				

classification of mixtures and will improve legal certainty for suppliers and increase the safety of workers and consumers.
Dossier Submitter's Response
Please see response to comment number 1.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2017	Denmark		MemberState	21
Comment received				
DK agree with the proposed classification Acute tox 4; H302.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	22
Comment received				
Arysta Life Science agree with the proposed classification on page 10 and page 25 of Acute Tox 4; H302 – Harmful if swallowed				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	23
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 27				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	24
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 28				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	25
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 29				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	26
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 26				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Spain		MemberState	27
Comment received				
Repeated-dose administration of ipconazole resulted in a number of adverse effects in rats, mice and dogs at doses below the relevant guidance values for classification in category 2. This included ocular effects (potentially related to a decrease in plasma cholesterol), hepatocyte necrosis, lesions in the oesophagus, pharynx, larynx and hard palate, fatty deposits in the liver and fatty vacuolation in the adrenal glands. A further systemic finding of concern to support classification was skin reddening in dogs following oral (capsule) administration. Effects at doses relevant for classification were noted after oral, dermal and inhalation exposure and consequently it is not proposed to specify a route of exposure. Therefore, the Spanish CA supports the proposal to classify ipconazole with STOT-RE 2; H373 – May cause damage to organs (eyes, skin, liver and gastrointestinal tract) through prolonged or repeated exposure.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	28
Comment received				
Proposal for classification H373 is supported.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Germany		MemberState	29
Comment received				
Page 51 Can the dossier submitter please provide information on ipconazole´s mode of action with regards to steroid hormone synthesis (as mentioned at the end of section 4.7.4 Summary and discussion of repeated-dose toxicity relevant for classification as STOT RE according to CLP Regulation)? If a mode of action is known, then consideration needs also to be given to the endocrine disrupting potential of ipconazole. Page 53 Please clarify why the adrenal glands have not been included as target organs in the classification STOT-RE 2 (in section 4.7.6), when adverse effects on the adrenal glands were seen in mice at 70 mg/kg/d and in dogs at 40 mg/kg/d (90-d) and at 20 mg/kg/d				

(1-yr) and in rats at 91 mg/kg/d (28-d). As outlined in Table 14.6, the two former values are below the category 2 cut-off of 100 mg/kg/d and the latter two below the cut-offs of 25 and 300 mg/kg/d respectively.
Dossier Submitter's Response
Ipconazole inhibits 14-C demethylation in the ergosterol biosynthesis pathway of plant disease fungi. The endocrine disruption potential of ipconazole has not been considered in the report, since this does not relate directly to classification; the mode of action of the adverse effects is assumed to be relevant to humans and so ipconazole has been 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, we did not list them as a primary target organ in the proposed classification, but acknlowedge that they could be included.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2017	Denmark		MemberState	30
Comment received				
DK agree with the proposed classification STOT RE 2; H373.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	31
Comment received				
Arysta Life Science agree with the proposed classification on page 10 and page 53 of STOT-RE 2; H373 – May cause damage to organs (eyes, skin, liver and gastrointestinal tract) through prolonged or repeated exposure.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	32
Comment received				

Arysta Life Science agree there is no aspiration hazard for ipconazole as outlined on page 9
Dossier Submitter's Response
The dossier submitter notes the support for the proposal.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Netherlands	RIVM/BR	National Authority	33
Comment received				
The Netherlands agrees with the classification for Chronic Category 1; H410 – Very toxic to aquatic life with long lasting effects, with an M factor of 100. We have, however, a different opinion on the proposed NOEC value for classification. The NOEC value proposed by the DS was 0.00044 mg/l for growth in a valid fish early-life stage test for Pimephales promelas. Looking into the details of this study, however, we found that mortality was statistically significant at concentrations of 0.44 and 2.9 µg/l (33 and 78%, respectively). Although it can be argued that this is not dose-dependent effects considering the mortality of the interim level of 1.1 µg/l was not significant, we suggest that the effects observed at 0.44 µg/l should not be ignored. Therefore, the NOEC value should be 0.00018 mg/L. This value, however, does not influence the proposal of Chronic Category 1; H410 and M factor of 100. In addition, the final concentration of the solvent tetrahydrofuran (THF) in the fish test and in the Daphnia test was not specified. This essential information should be added in the study descriptions.				
Dossier Submitter's Response				
We agree that there was some variability in overall mortality in the chronic fish study. However, although statistically significant, that seen at 0.44 µg/L (33 %) was not part of a clear trend and was close to the control acceptability criterion of 30%. The NOEC for mortality was therefore set at 1.1 µg/L (where there was 22% overall mortality) and that for weight and length was more clearly 0.44 µg/L. This was also the lowest NOEC agreed in the EFSA peer review conclusion for ipconazole (EFSA Journal 2013;11(4):3181). The final concentration of THF solvent used in the chronic fish and daphnia studies was 0.1 mL/L diluent water. Comparison of the solvent and blank controls does not reveal any adverse effects from use of this solvent in either test. The lowest chronic endpoint can be decided by RAC, however, we agree it would not affect the chronic classification proposal.				
RAC's response				
RAC's opinion – in agreement with the DS – is that 0.44 µg/L is the most appropriate fish NOEC value, as the lowest mean measured chronic NOEC value from this study. In any case, the choice of a NOEC value from this study would not affect the chronic classification. RAC proposes Aquatic Chronic 1 and M=100 based on a NOEC value of 0.44 µg/L.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 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)]

Date	Country	Organisation	Type of Organisation	Comment number
25.04.2017	France		MemberState	34
Comment received				
We agree with the classification and the chronic M factor proposed for Environmental hazards.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
RAC notes the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2017	Germany		MemberState	35
Comment received				
page 103 point 5.3.2 Summary and discussion of aquatic bioaccumulation: The calculated BCF values for steady state, whole fish and total radioactive residues of 283 L/kg of the 13 µg/L treatment group and 225 L/kg of the 1.3 µg/L treatment group have to be normalized to lipid content (5%), because there is a relevant difference in lipid content of test fishes during exposure phase. Lipid content on day 0 is 2.79% and lipid content on day 28 is 4.86% with an average of 3.8% during exposure phase. These lipid normalized steady state BCF values are 372 L/kg for the 13 µg/L treatment group and 296 L/kg for the 1.3 µg/L treatment group. Page 118 point 5.5 comparison with criteria for environmental hazards: The relevant lipid normalized steady state BCF values are 372 L/kg for the 13 µg/L treatment group and 296 L/kg for the 1.3 µg/L treatment group				
Dossier Submitter's Response				
Thank you for calculating and correcting the fish BCF values from 225-283 L/kg to 296-372 L/kg (lipid normalised). These revised values remain below the CLP cut-off value of 500 L/kg, indicating a low potential for ipconazole to bioaccumulate.				
RAC's response				
RAC would prefer to use the actual (same sampling time as for BCF) lipid content for lipid normalisation, instead of a 0–28 days time-average, taking also into account OECD TG 305, Annex 5: "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". The lipid content was 4.19–5.53% at the end of the exposure phase: very close to 5%. Assuming worst case, the maximum value of lipid normalised BCF can be 338 L/kg (283x5/4.19), much smaller than the cut-off value of 500, resulting: No bioaccumulative potential of ipconzole.				

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2017	Denmark		MemberState	36
Comment received				
No comments. DK agree with the proposed classification.				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				

RAC's response
RAC noted the agreement with the DS's proposal.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	37
Comment received				
Arysta Life Science agree with the proposed classification on page 11 and page 118 Chronic Category 1; H410 – Very toxic to aquatic life with long lasting effects, with an M factor or 100				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
RAC noted the support of Arysta.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	38
Comment received				
Arysta Life Science agree ipconazole is not hazadourous to the ozone layer as stated on page 9				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Arysta Life Science	Company-Manufacturer	39
Comment received				
Arysta Life Science agree with the Current proposal for no classification by RAC on page 10 and page 20				
Dossier Submitter's Response				
The dossier submitter notes the support for the proposal.				
RAC's response				
Noted.				