Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Penconazole

EC Number: 266-275-6

CAS Number: 66246-88-6

ECHA/RAC/CLH-O-0000002679-61-01/A2

Adopted

11 July 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Penconazole
CAS number: 66246-88-6
EC number: 266-275-6

General comments

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
01/03/2011	France / MSCA	We disagree with the proposed toxicological classification and suggest instead (please see detailed comments below): Directive 67/548/EEC: Repr. Cat.3; R63 Xn; R22 R48/22 GHS criteria : Acute Tox.4 H302 STOT RE. 2 H373 Repr. 2 H361d	Please see detailed response below	We acknowledge the support of the Acute tox 4 classifications and the comment about the addition of two classifications, one for Reprotox and the other for repeated dose toxicity. Others also made comments on both suggestions, so please also read

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
				other sections of this table.
03/03/2011	Spain / Manuel Carbo / MSCA	In general we are in agreement with the environmental classification proposal, but we have some remarks: 1) The application of the H phrases: According to CLP Regulation the application of the H400 and the H410 together are redundant, therefore the H410 alone should be applied. 2) The M factor proposal: Although the surrogate system is applied to assign the long term hazards categories and only one M factor is derived for acute and long term hazards, it would be useful if in the M factor proposal was added that the M factor derived is for both hazards in order to be more clear.	Thank you for the support. As far as labelling is concerned, we agree and only H410 is proposed. However, if a substance is classified for both acute and chronic aquatic toxicity, both Hazard statements are assigned (compare Article 27 of EC 1272/2008 and Tab. 4.1.6 CLP-Guidance). Hence, we maintain H400 and H410 for the classification section. We agree and a clarification is added (p. 5).	We acknowledge the support to environmental hazard proposals made by DS. We fully agree with DS argument which refers to the legal rules. Noted.

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
03/03/2011	Portugal / Maria do Carmo Palma / Portuguese Environment Agency	Considering the present proposal, we agree to establish a harmonised classification & labelling for PENCONAZOLE. The proposed environmental classification and labelling fulfils the criteria established both in CLP Regulation and 67/548/EEC Directive. Therefore, we support this proposal.	Thank you for the support.	We acknowledge the support to all DS' classification proposals.

Carcinogenicity

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
02/03/2011	UK / MSCA	Page 27. We note that the top dose tested in each study was low and that the maximal tolerated dose was not achieved in rats. Notwithstanding, we agree that the available information does not support classification for carcinogenicity.	Thank you for the support	We will add this remark in our opinion. And We acknowledge the support.

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
02/03/2011	UK / MSCA	Page 26. We agree that classification for mutagenicity is not required.	Thank you for the support	We acknowledge the support.

Toxicity to reproduction

Date	Country/ Person/ Organisation /MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
25/02/2011	Denmark / The Danish EPA / National Authority	*ECHA's comment: ECHA has copied the comment below from the attachment: comments regarding penconazole.doc* Dear Sir /Madam Denmark does not agree with the arguments made by Germany about the classification concerning R62 and R63. Reproductive toxicity studies: R62. Even though an increased incidence of dystocia is only seen in the first 2.generation study and not in the second 2.generation study this effect is important and has been seen with other triazoles. We assess the effect as an effect of the active substance and therefore penconazole should be classified as R62. R63: Because of the effects seen in the developmental studies at high dose levels (cervical ribs in rat and microphtalmia in rabbits) penconazole should be classified as R63. Microphtalmia has also been observed with other triazoles.	We disagree with a classification as R62 because the effects on pregnancy and parturition are not reproducible and appear to depend on the impurity content of the test substance. We disagree with a classification as R63 because the effects in rats occur in the maternally lethal dose range and the incidence of microphthalmia in rabbits lies within the historical control range.	RAC agrees with the dossier submitter that classification for H361f/R62 is not warranted. However, RAC agrees with the Danish CA that H361d/R63 is warranted on grounds specified in the opinion document.
01/03/2011	Switzerland / Nikolaus Zenz / Syngenta Crop Protection A / Company-Manufacturer	pp. 28-31: No classification for impaired fertility is required. Observations noted at the high dose level in a former 2-generation study could not be repeated in a more recent study using higher dose levels. No classification for dev tox is required. In the rat, embryotoxicity (extra cervical ribs) was restricted to dose levels where maternal toxicity occurred. No such effects were noted in a more recent study. In the rabbit, microphthalmia observed in a former study at the top dose is within historical control data and thus, not treatment-related. Furthermore,		Noted.

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		these findings were not seen in a more recent rabbit developmental toxicity study. See further details in the attached document 'Penconazole Classification - Syngenta response to Annex VI Report for CL Feb 2011'. --- *ECHA's comment: ECHA has copied comment below from the attachment Penconazole Classification - Syngenta response to Annex VI Report for CL Feb 2011.doc* Penconazole Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by Germany November 2010 **Syngenta agrees with the proposed non-classification of Penconazole for Reproductive and Developmental Toxicity as contained in the Annex VI Report submitted by Germany. The following comments provide additional support for this position.** **<u>Effects on Fertility</u>** A classification for possible risk of impaired fertility is not required for the reasons outlined below. Penconazole has been fully investigated for potential to cause effects on fertility in two multi-generation studies in the rat. In one of the studies, a slight increase in dam mortality during the post-partum period was observed at the high dose level (2000 ppm) only. In Syngenta's opinion, neither studies provides evidence that these effects are due to dystocia. The alignment of dam mortality to dystocia following penconazole treatment is considered inappropriate following reasons: • Dystocia (or any other similar description) was not used as a descriptor by the conducting test laboratory to describe the clinical signs in the dams • All dams managed to deliver their entire litter; there was no failure to complete parturition which would have been indicative of dystocia. • Most of the deaths occurred during lactation rather than immediately post-partum. • No diagnosis of the maternal deaths was included; therefore, the maternal mortality is considered to be a sign of general toxicity • In the second study, neither dam mortality nor dystocia was observed at any dose level up to and including 2500 ppm. In addition, the test material contained a	The number of stillborn litters was clearly increased in the first study at 2000 ppm. The test material used in this study contained 5.8 % of a penconazole isomer not present in current batches. High dose females would have consumed about 10 mg/kg bw/d of this isomer. We agree that extrapolation of a mode of action is speculative, whereas the similarities between the toxicological profiles of penconazole (isomer) and piroxicam are apparent from the study findings.	RAC agrees not to classify penconazole for H361f/R62 However, RAC disagrees not to classify for developmental toxicity as justified in the opinion and BD. RAC notes that the provided historical controls covers five years on each side of the date of the study, rather than the recommended two. However. One study within the two year period also exceeds the levels in the Giese study.

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		higher concentration of penconazole (98.7% versus 91.7% in the first study). These data are described in more detail in Appendix 1. The alignment of the toxicological profile of penconazole with the non-steriodal antiphlogistic drug piroxicam and extrapolation of a mode of action for delayed parturition by penconazole is purely speculative, and there is no evidence to support this. No data has been generated for penconazole on inhibition of the enzymes involved in the arachidonic acid pathway or changes in the expression levels of genes associated with this pathway. Developmental Toxicity A classification for developmental toxicity is not required. Penconazole has been fully investigated for its potential to cause developmental toxicity in two studies in rats and two studies in rabbits. In rats, a slight increase in the incidence of cervical ribs was observed in one of the two studies, at a dose level causing marked maternal toxicity demonstrated by maternal deaths, clinical signs and reduced bodyweight gain and food consumption. This isolated effect is typical of the spectrum of effects that can occur secondary to maternal toxicity and is not considered to warrant classification for developmental toxicity. In rabbits, bilateral microphthalmia was observed in the high dose group (150 mg/kg/day) at an incidence higher than the concurrent control group. However, the incidence was within the historical control range for the test laboratory and is therefore considered not to be an effect of treatment. There were no incidences of microphthalmia in a second study in the rabbit which was notably conducted at a higher dose level (200 mg/kg/day). These data are described in more detail in Appendix 2. **<u>Appendices</u>**	The litters found dead shortly after parturition in mid and high dose groups (almost all from dams with a pregnancy duration of more than 21 days) indicate the presence of parturition problems/dystocia even though this term is not used in the study report. Moreover, in the study report the 3 high dose F1 females are noted as having died during delivery. Female 152 is the only animal for which the cause of death can be considered clearly unrelated to parturition problems.	

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Appendix 1 Syngenta position on effects on parturition

A 2 generation study in rats using diet inclusion levels of 0, 80, 400 and 2000 ppm was conducted by Fritz (1983) and dam mortality during the period post-parturition and lactation was observed at 0, 400 and 2000 ppm at an incidence of 1, 2 and 6 dams respectively. A summary of dam mortality during parturition and lactation is included in Table 1.

Table 1: 2-generation rat (1st study) – Detailed dam mortality during parturition and lactation phases

Dose (ppm)	Dam (generation)	Duration of gestation (days)	Died	Foetuses
0	206 (F1)	22	Day 19 p.p.	4 live
400	96 (F0)	21	Immediately p.p.	11 (uncertain)
400	412 (F1)	21	At delivery	12 (uncertain)
2000	126 (F0)	22	Day 4 p.p.	14 (uncertain)
2000	152 (F0)	22	Day 11 p.p.	10 (live)
2000	156 (F0)	23	Shortly after delivery	15 (uncertain)
2000	516 (F1)	25	Day 4 p.p.	14 (uncertain)
2000	524 (F1)	23	Day 2 p.p.	16 (uncertain)
2000	536 (F1)	23	Day 2 p.p.	14 (uncertain)

p.p. = post partum
p.m. = post mortem
wt = weight

The descriptor dystocia was not used by the conducting laboratory to describe effects in the dams and was not included in the study report. Dystocia is defined as a difficulty with labour and delivery, caused by a failure of the cervix to expand or a trapping of the foetus in the birth canal. Although body condition was reported to be checked throughout the study, clinical condition and observations are not included within the study report and therefore dystocia as clinical observations indicating prolonged or difficult delivery have not been described. In the absence of reported clinical signs or additional information regarding the duration of labour, the assignment of the term dystocia to maternal mortality can not be definitely confirmed or refuted. However, there is no evidence in the study report that dams died before parturition was complete (i.e. stillborn foetuses still present in the uterus). For the dams that died several days post-partum, it is unlikely that

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the cause of death was associated with difficulties during parturition due to the length of time post-partum that the mortality occurred.
In a second 2-generation study in rats conducted by Schardein (1987) at diet inclusion levels of 0, 25, 250 and 2500 ppm, there were no deaths reported among the dams at or after parturition. The purity of the test substance was also higher in this second study (98.7% versus 91.7% in the first study).
With regard to duration of pregnancy, there was a shift towards longer pregnancy duration at 2000 ppm in the first study only (Table 2). There were no effects on this parameter in the second study conducted at a higher dose level (2500 ppm).

Table 2: Comparison on the duration of pregnancy in the two 2-generation studies.

Study	Generation	F_0				F_1			
Fritz, 1983	**Dose (ppm)**	**0**	**80**	**400**	**2000**	**0**	**80**	**400**	**2000**
	Females mated	20	20	20	20	19	19	18	20
	Mean duration of pregnancy (d)	21.1	21.3	21.4	21.8*	21.4	21.4	21.1	22.2
	Females with pregnancy >21 d	2	4	6	10	4	6	2	14
Schardein, 1987	**Dose (ppm)**	**0**	**25**	**250**	**2500**	**0**	**25**	**250**	**2500**
	Females mated	29	26	26	19	18	21	21	22
	Mean duration of pregnancy (d)	22.1	21.9	22.0	22.1	22.0	22.0	22.1	22.0
	Females with pregnancy >21 d	4	2	2	4	2	5	3	4

Statistical significance: * $p \leq 0.05$ (one-tailed Student's t-test)

CONCLUSION

Following analysis of the available data it is concluded that penconazole does not warrant a classification for possible risk of impaired fertility.
This is based on:

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		• **Although duration of pregnancy was slightly extended at high dose in one study, there is no clear evidence of dystocia** • **The timing of the maternal deaths post-partum suggests they are more likely to be due to general toxicity, than to dystocia** • **In a second study, conducted at a higher diet inclusion level, dam mortality was not observed and there was no difference in duration of pregnancy when compared to controls.** **References** EFSA (2008). Conclusion regarding the peer review of the pesticide risk assessment of the active substance penconazole. *EFSA Scientific Report* (2008) 175, 1-104. Fritz H (1983). Report on CGA 71818 Tech.: 2-Generation Toxicity Study In Rats; unpublished report No. 811416, and Fritz H. (1983b). Two-Generation Reproduction Toxicity Study In Rats With CGA 71818 Technical – Additional Data Submission; Complementary Tables To Unpublished Report No. 811416, CIBA-GEIGY Ltd., Stein, Switzerland. Study dates: 2 November 1981 (start of experiment), completion of experimental work not specified. (Syngenta File No.: CGA71818/0755 main report, CGA71818/0910 data supplement) Schardein J (1987). Two-Generation Reproduction Study In Albino Rats With CGA-71818. International Research and Development Corporation, Mattawan, MI 49071, USA, unpublished report No. 382-119. Dates of experimental work: 12 March 1986 (animals received) to 7 January 1987. (Syngenta File No.; CGA71818/0756) **Appendix 2 Syngenta position on the incidence of bilateral microphthalmia in the rabbit** Microphthalmia was observed in only 1 of the 2 rabbit studies at an incidence of 3/125 foetuses from 3/16 litters in the high dose group (150mg/kg bw/day). There were no incidences of bilateral microphthalmia or other malformations relating to the eye at lower dose levels (25 and 75 mg/kg/day). The incidence of microphthalmia (2.4%) was higher than the cumulative historical control incidence (0.26%) in the original study report. However an evaluation of the studies in the applicants regulatory study database, for developmental toxicity studies performed at the same laboratory in the same strain for 5 years either side of the study date (n=19), indicate that the incidence of bilateral microphthalmia in control groups ranged from 0 - 4.1% (Table 1). Therefore the incidence of 2.4% in this study was well within the historical control range, leading to a conclusion that this is unlikely to be an effect of treatment.		

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		Table 1 – Historical Control Data for bilateral microphthalmia in chinchilla rabbits from control data at Ciba-Geigy Ltd., Stein, Switzerland testing facility 1978-1987.		

Title	Issue/Signed date	Control Incidence microphthalmia Foetuses (litters)	Foetal % incidence (litters)
Teratology study (Seg. II) in rabbits.	22.11.1980	0	
Teratology study in rabbits.	24.12.1981	**2/147 (1/18)**	**1.36 (5.6)**
Teratology study in rabbits.	01.06.1983	0	
Segment II reproductive study in rabbits.	25.06.1982	0	
Teratology study in rabbits.	03.03.1987	0	
Teratology study in rabbits	08.01.1982	0	
Teratology study (SEG II) in rabbits.	27.09.1979	0	
Teratology study (SEG. II) in rabbits.	11.09.1980	0	
Reproduction study rabbit Seg. II (test for teratogenic or embryotoxic effects).	25.08.1978	0	
Teratology study in rabbits	01.08.1982	0	
Teratology study (Seg. II) in rabbits.	10.09.1980	0	
Teratology study in rabbits.	13.11.1981	0	
Teratology study in rabbits.	01.11.1982	**5/141 (2/16)**	**2.80 (12.5)**
Reproduction study - rabbit, SEG II (Test for teratogenic or embryotoxic effects).	28.11.1978	0	
Teratology study in rabbits.	01.05.1982	0	
Teratology study in rabbits.	20.06.1986	**5/121 (2/16)**	**4.13 (12.5)**
Seg. II reproductive study in rabbits.	07.03.1979	0	
Teratology study in rabbits.	01.03.1982		
Reproduction study - rabbit - CGA 48988 tech. Seg. II (Test for teratogenic or embryotoxic effects).	06.12.1978	0	

CONCLUSION

Following analysis of the available data it is concluded that penconazole does not warrant classification for developmental effects.

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		This is based on: • The incidence of bilateral microphthalmia was within the historical control range. • This observation was only present at a dose level which was also toxic to the dams. • Was not present in the second rabbit study at a higher dose (200mg/kg bw/day) using a higher grade purity of test substance (98.7% versus 91.7% in the first study).		
01/03/2011	France / MSCA	P30, point 5.9.4 Other relevant information: Dystocia observed could also result from an anti-aromatase effect as it is reported for other triazoles. In absence of clear data to establish the mechanism of action (mechanistic studies and/or hormonal analysis are lacking) endocrine disruptive effect cannot be ruled out. However we support the RMS to not classify R62. P 31, point 5.9.5 summary of reproductive toxicity: According to historical control population, microphtalmia observed is within the control ranges of the laboratory, while internal hydrocephaly (2/125foetus) has not been observed in this strain before (DAR). Hydrocephaly is known to be a class effect of triazoles in Rabbit. In one of the rat developmental studies cervical ribs occurrence is increased at high dose and ribs variations incidences also observed in other triazoles compounds. Furthermore one of the main metabolite 1,2,4-triazole (15% of the dose) is currently classified in the EU: Xn, Repr. Cat.3 R63. For those reasons a Repr. 2 H361d (Repr. Cat. 3 R63) classification of penconazole seems to be warranted. P 28 and 29, point 5.9 Toxicity for reproduction: Since the claimed purity of the technical material is 95%, the argument relating to non reproductible effects with higher purity material is not acceptable.	We disagree with a classification as R63 because the effects in rats occur in the maternally lethal dose range and the incidence of microphthalmia in rabbits lies within the historical control range. Internal hydrocephaly was not reproducible in a rabbit strain which tends to produce this malformation at low incidence in controls and should thus be considered susceptible to teratogenic augmentation of this trend (Nemec, 1985). No malformations	Without data on hormone levels, it is difficult to draw conclusions on this argument. However RAC agrees with the dossier submitter and the French CA that classification for H361f/R62 is not warranted. However, RAC agrees with the French CA that H361d/R63 is warranted on grounds found in the opinion document.

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			similar to those elicited by 1,2,4-triazole were observed in any of the studies. Purity of the test substance in the 1st 2-gen study and in the 1st rabbit study was 91.7 %. For equivalence of batches see response to manufacturer.	
02/03/2011	UK / MSCA	Page 27. Fertility. It is reported that dystocia did not occur in the second fertility study in which the top dose level, expressed in ppm, was slightly higher than in the first study. Was the top dose of the second study also higher than in the first study when the actual substance intakes were calculated (i.e. expressed as mg/kg/d)? Page 28. Table 5.9-1. Please include information on the mg/kg/d equivalents in the dose level column and more details on the effects observed, for example: the number of animals affected by dystocia and the doses involved; if parturition was started but not completed or if it failed to start; the incidences of perinatal mortality at the different doses; the magnitudes of effects on body weight gain and liver weight at the different doses. Page 29. Table 5.9-2. We would appreciate the addition of more information to the table, for example the magnitudes of maternal effects and the incidences of embryolethality, extra ribs, microphthalmia (and historical control data for this malformation). Also, are historical control data for hydrocephalus in Chinchilla rabbits available? If so, they should be included. Page 30. Other relevant information, summary and discussion of fertility. As stated in the report, the events leading to the initiation of parturition are different in humans from	Top doses in the 2nd study were 18 % higher for F0 females and 8 % higher for F1 females on a mg/kg bw basis. Penconazole has been reviewed in the programme covered by Commission Regulation (EC) No 1490/2002. Detailed information on these studies can be found in the Draft Assessment	We acknowledge the confirmation that the top dose – expressed in mg/kg/d - was higher in the second study. RAC note the argument "Since prostaglandin

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		those in rodents, in that the death of the corpus luteum of rodents leads to a fall in progesterone levels, whereas a 'functional progesterone withdrawal' in humans is effected by a repression of prostaglandin responsive genes. However, the mechanism of action of the dystocia induction explained in the report pertains to a down-regulation of the prostaglandin E3 receptor by penconazole, which results in reduced uterine contractility. Since prostaglandin E3 is involved in myometrial contractions in humans, this mechanism of action would appear to be relevant to humans as well as rodents. Under CLP, adverse effects on sexual function and fertility include effects on parturition; therefore, the statement that 'the finding of dystocia which only occurs in pregnant animals would not warrant a classification for fertility impairment' should be changed, since it is possible to classify for fertility on the basis of dystocia. We suggest that further discussion of the significance of the dystocia findings and their relevance to humans, and a possible classification for fertility, be included, particularly as other triazoles have been reported to induce this effect. Page 30. Summary and discussion of developmental toxicity. In rats, the possible developmental effects observed were post-implantation loss, retarded bone ossification and an increased incidence of extra ribs. The first two of these effects were probably related to maternal toxicity, although more information in Table 5.9-2 would clarify this association. The third effect, that of extra ribs, has been reported in studies of other triazole substances; from the information provided on penconazole, it is not clear if these were associated with maternal toxicity, so clarification of this point would be helpful. Uncertainty surrounds the developmental/teratogenic significance of supernumerary ribs, in particular their post-natal reversibility or otherwise. Generally, findings of this nature are not used as evidence for classification. In rabbits, an increased incidence of microphthalmia in one study was stated to be within the historical control range (please provide the incidences in the study and the historical control data). An increased incidence of hydrocephalus occurred in one rabbit study (please provide historical control data if it is available) but not in a second rabbit study or two rat studies that employed higher top doses. Overall, therefore, we agree that a classification for developmental effects is not required.	Report. The finding of dystocia was not reproducible in the 2nd fertility study which is considered the more relevant.	E3 is involved in myometrial contractions in humans, this mechanism of action would appear to be relevant to humans". RAC have evaluated the effects in detail in the opinion and BD
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	It should be considered to classify penconazole as a Reproductive toxicant Category 2 (H361) according to Reg. (EC) No 1272/2008 and Repro Cat 3 (R62) according to Directive 67/548/EEC based on information from the DAR Annex B-6. It should be considered if dystocia reported in both rat and rabbit, implantation loss in rats and aspermatogenesis in rat justifies a Category 2 classification (for more details see also	We disagree with a classification as R62 because the effects on pregnancy and	RAC agrees with the dossier submitter that classification

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		enclosed appendix "Reproductive toxicity penconazole). The results are further supported by the findings of histopathological changes in the testes and epididymidis from the 1 yr study in dogs.	parturition are not reproducible and appear to depend on the impurity content of the test substance.	for H361f/R62 is not warranted. However, RAC agrees with the Swedish CA that H361d/R63 is warranted on ground found in the opinion document. RAC disagree on the relevance of the 1 yr dog study.
03/03/2011	Spain / Elina Valcarce / MSCA	p. 31 Summary and discussion of reproductive toxicity In the CLH report German CA considered that a classification for fertility effects or developmental toxicity was not required. The draft EFSA Scientific Report (2008) proposed a classification of Xn R63 and that a classification as Xn R62 (?) should be considered. Summary and discussion on effects on fertility The Spanish CA considers that a classification is warranted for Penconazol as Xn; Repr. Cat. 3 R62 (Possible risk of impaired fertility) according to Directive 67/548/EC and as Repr. 2 (H361f: Suspected of damaging fertility) according to Regulation EC 1272/2008. This proposal is based on prolonged gestation, dystocia and increased parturition mortality of dams and pups observed in a two generation study in rats dosed with 200 mg/kg bd/day (Fritz, 1983) and taking into account the new criteria on Regulation EC 1272/2008 that considers dystocia an adverse effect on fertility. Although no similar effects were observed in a second study (Schardein, J., 1987), the rat strain used and purity were different. According to Germany, penconazole toxicity on arachidonic acid pathway is based on the	We disagree with a classification as R62 because the effects on pregnancy and parturition in the 1st fertility study are not reproducible and appear to depend on the impurity content of the test substance.	RAC agrees with the dossier submitter that classification for H361f/R62 is not warranted. However, RAC agrees with the Spanish CA that H361d/R63 is warranted on grounds found in the opinion document.

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		fact that of other triazole-type fungicides (miclobutanil, propiconazol, triadimefon) can induce changes in the prostaglandin EP3 receptor, which is found in the uterus and in the corpus luteum. The luteolytic function of prostaglandin receptors in the ovary, which is required for the initiation of parturition in rodents, is not necessary in human, where progesterone production shifts from the corpus luteum to the placenta early in pregnancy, so an alteration over this function would not affect human initiation of parturition. However, EP3 receptor is one among several contractile associated proteins in the uterus and its down-regulation could be involved in the prolongation of pregnancy/dystocia seen in one rat study at doses of about 200 mg/kg bw/day, which could be relevant to humans. Besides, delayed parturition, dystocia and increased maternal deaths seen in the first multigeneration study in rats (Fritz, 1983), are similar to the effects seen with some other triazoles. A hormonal mechanism (as has been shown for other substances of this group) appears to be a likely basis for these findings and add weight to the argument for classification. In addition, marked reduction in spermatogenic activity, characterised by atrophy of the seminiferous epithelium associated with formation of giant cells, and absence of spermatozoa in the epididymis (which contained cellular debris) were observed in subchronic dog studies (Gfeller, W., 1984). Marked toxicity, especially when including inflammatory processes, is known to affect spermatogenesis and impair sperm production, so it might be a secondary effect of the toxicity observed. However, a direct effect via steroid hormone availability cannot be excluded, as reproductive toxicity studies indicate a potencial interference with steroid hormone syntesis/levels. Increased prostate and adrenal weights at ≥ 9,8 mg/kg bw/day were also observed in a 107 weeks carcinogenicity study in mouse (Basler, W.,1985), together with increased ovarian weights in a 1 year study in dog (Gfeller, W., 1984). These effects may also indicate a mode of action as endocrine disruptor. Summary and discussion of Developmental toxicity The Spanish CA considers that a classification is warranted for Penconazol as Xn; Repr. Cat. 3 R63 (Possible risk of harm to the unborn child) according to Directive 67/548/EC and as Repr. 2 (H361d: Suspected of damaging the unborn child) according to Regulation EC 1272/2008.	The 1-yr study in dogs was conducted with the same batch of penconazole that was used in the 1st fertility study in rats. We disagree with a classification as R63. See response to France.	RAC does not consider the effect seen for this compound as a group effect and should be viewed separately from other triazoles. RAC does not consider the Gfeller study relevant for the classification for reprotoxicity

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		This proposal is based on an increased incidence of bilateral microftalmia and internal hydrocephalus observed in a teratology study in rabbit (Giese 1982), and an increased in the occurrence cervical ribs at 500 mg/kg bw/d in a teratology study in rats (Salamon 1985). Besides, the formation of 1,2,4-triazole (metabolite classified as R63, accounting for 15% of administered dose) has also be taken into account. Other relevant information on reproductive toxicity The study results on azole and triazole compounds with the same mode of action and the critical role of several CYP enzymes in reproduction, support the classification of penconazole for fertility (Repr Cat 3; R62) and for development (Repr Cat 3; R63). A hormonal mechanism relevant to humans can not be discarded, based on the fact that azole compounds interact with several enzymes of the P450 system in different species, affecting endocrine systems and inhibiting different steps of steroidogenesis, mainly through the inhibition of the activity of the following enzymes: ▪ Sterol-14α-demethylase (CYP51): the union of azole compounds to this enzyme inhibits its activity, which is an essential step in the transformation of lanosterol into cholesterol and in the production of steroids that activate meiosis (MAS) and modulate germinal cells development in mammalians (human included). Deficient germ cell development may lead to reduced fertility. ▪ Aromatase (CYP19): this enzyme transforms androstenedione into estrone and testosterone into estradiol. The union of azole compounds to this enzyme disturbs the balance between the levels of estrogens, androgens and progesterone, what may potentially affect fertility and embryonic development. ▪ CYP26: this enzyme is involved in the retinoic acid degradation. Its inhibition implies craniofacial/brain malformations during development, especially the neural crest cells, hind brain, cranial nerves and cranio-facial structures. The increased incidence of bilateral microftalmia and internal hydrocephalus observed in rabbit and the increased in the occurrence cervical ribs in rats observed with penconazole could be caused by interaction with this enzyme.		
03/03/2011	Austria / Austrian Agency for Health and Food Safety	Xn, R62 / Repro Cat 2, H361f - There were two multigeneration studies in rat (1st study: 80, 400, 2000 ppm; 2nd study: 25, 250, 2500ppm) - The proposal for R62 is based on death at or after parturition observed in 3 F0 and 3 F1 dams at the high dose (2000 ppm) and 1 F0 and F1 dam at the middle dose (400 ppm) in the 1st, but not in the 2nd study - In the 1st study, in the F0 generation, only two dams died at parturition (one at 400 and		We acknowledge Austria MSCA conclusion about no-classification for fertility

Date	Country/ Person/ Organisation /MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
		one at 2000 ppm), whilst other two at 2000 ppm died at day 4 and 11 p.p - In the 1st study, in the F1 generation, one dam of 400 ppm died at parturition; at 2000 ppm, two dams died at day 2 and one at day 4 p.p - It is stated, that dams died without obvious cause - Dams of F0 at 2000 ppm had a body weigh gain of -8% during pregnancy (-5% food consumption), while F1 dams had -16% body weight gain (-9% food consumption) (compared to control) - The same number of dead dams was observed by -8% (F0 dams) and -16% (F1 dams) body weight gain in the 1st study - In the 2nd study, at 2500 ppm, dams of F0 at 2500 ppm had a body weigh gain of +/- 0% during pregnancy (-7% food consumption), while F1 dams had +/-10% body weight gain (-3% food consumption) (compared to control) - Purity of the first study: 91.7% ; purity of the second study: >98.7% (Inclusion Directive: > 95%) - Other effects in females of 2000 ppm group in the 1st study: increased relative liver weight and hepatocellular hypertrophy (only F1; in F0 no organ was weighed) Conclusion: It is unclear wheather the death of the dams (observed on days 0, 4 and 11 p.p in F0 dams and on days 2, 2 and 4 p.p in F1 dams) observed in the 1st but not in the 2nd study (both studies with comparable dose ranges) is due to dystocia. According to the study author, the dams died without obvious cause. There might be an assumption that the different findings of the 1st and the 2nd study could be assigned to differences in purity grade of batches. Since current specification for penconazole (> 95%) is between the two test batches, no statement can be made about current possible influence of impurities. Indeed, according to Regulation (EC) 1272/2008, effects on parturition belong to "adverse effects on sexual function and fertility". However, it is unclear if the death of the dams after parturition is due to dystocia. It should be kept in mind that the observed toxicity in dams of 2000 ppm in the 1st study was limited reduced body weight gain of -8% and -16% (F0 and F1 dams, respectively) and lower food consumption (-5% and -9% in F0 and F1 dams, respectively), accompanied by increased relative liver weight and hepatocellular hypertrophy. Normally, reduced food consumption should be much higher in order to cause this body weight gain loss. Therefore, there might be some effects, which were not observed, but affected the dams to die in the days following parturition. Taking into account all these information, it seems doubtful to consider Xn, R62/ Repro Cat 2, H361f appropriate for Penconazole, in absence of any other effects on fertility.	The litters found dead shortly after parturition in mid and high dose groups (almost all from dams with a pregnancy duration of more than 21 days) indicate the presence of parturition problems/dystocia even though this term is not used in the study report. Moreover, in the study report the 3 high dose F1 females are noted as having died during delivery and not on days 2	effects but classification for developmental toxicity.

Date	Country/ Person/ Organisation /MSCA	Comment given during public consultation	Dossier Submitter's response to comment	RAC's response to comment
		Xn, R63 / Repro Cat 2, H361d - R63 was proposed based on increased incidence of bilateral micropthalmia/internal hydocephaus in the 1st rabbit teratogenicity study - In the 2nd rat study (Salamon, 1985) umbilical hernia present in 1 fetus of the highest dose (500 ppm) – no HCD reported - In the 1st rabbit study (Giese, 1982), additionally to micropthalmia/hydocephaus (above HCD) at 150 mg/kg bw also one fetus had cleft palate (no HCD reported) - all other fetal findings in the two rat and two rabbit studies were either delayed ossifications or other variations mostly without any dose response Conclusion: Four findings (malformations) are considered relevant for proposal for R63 / Repro Cat 2, H361d: - a finding of umbilical hernia in one rat fetus in the 2nd rat study (Salamon, 1985) without the report of HCD - increased incidence of bilateral micropthalmia in the 1st rabbit teratogenicity study (Giese, 1982) - internal hydocephaus in the 1st rabbit teratogenicity study (Giese, 1982) above HCD - a finding of cleft palate in one rabbit fetus in the 1st rabbit teratogenicity study (Giese, 1982) without reporting the HCD All these malformation types were either above HCD or no comparison to HCD is reported and all these malformations are considered to be rare. Additionally, malformations per se do not depend on maternal toxicity regarding C&L. In case of penconazole it might be appropriate to consider classification as Repro Cat 2, H361d (suspected of damaging the unborn child).	or 4 post partum. We disagree with a classification as R63 because the effects in rats occur in the maternally lethal dose range and the incidence of microphthalmia in rabbits lies within the historical control range. Single incidences of heterogeneous malformations without a dose-response are not considered evidence for teratogenicity.	

Other hazards and endpoints

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
11/02/2011	Belgium / Denauw Frederic /	we support the environmental classification proposal by Germany : Following dir. 67/548/EC :	Thank you for the support.	We acknowledge the Belgium

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
	MSCA	classification :N, R50-53 (14dErC50 Lemna gibba ≤1mg/l And not readily biodegradable and log Pow ≥ 3, BCF ≥100) Specific concentration limits : C≥25% N; R50-53 2,5%≤C<25% N; R51-53 0.25%≤C<2.5% R52-53 Following reg. 1272/2008 : Aquatic Acute 1, H400 (14dErC50 Lemna gibba ≤ 1 mg/l.) Aquatic chronic 1, H410 (14dErC50 Lemna gibba ≤ 1 mg/l + not rapidly biodegradable) M-factor = 1 =>based on 14dErC50 Lemna gibba =0.22mg/l (0.1 mg/l< L(E)C50 ≤ 1mg/l) Following 3rd revision of GHS : Aquatic Acute 1, H400 (14dErC50 Lemna gibba ≤ 1 mg/l.) Aquatic Chronic 1 (Non-rapidly degradable substances for which there are adequate chronic toxicity data available + NOEC ≤0.1mg/l) Acute M-factor = 1 =>based on 14dErC50 Lemna gibba = 0.22mg/l (0.1 < L(E)C50 ≤ 1) Chronic M-factor = 1 =>based on 21dNOECDaphnia = 0.069mg/l (0,01 < NOEC ≤ 0,1) Some editorial or/and minor comments: 4.1.2.3 simulation test : penultimate paragraph : please refer to Table 4.1-3 instead of Table 1.3-1 4.1.3 Summary and discussion of persistency: please refer to the CLP criterion of rapid degradation instead of ready degradation in this section, there are, besides a readily biodegradability test, also data on simulation tests available. 4.3.3 summary and discussion of bioaccumulation : BCF = 200L/kg : please make a clear distinction, in the last phrase, between the conclusion drawn following the criteria of dir. 67/548/EC (BCF>100 : potential to bioaccumulate) and reg. 1272/2008 (BCF <500 : no significant bioaccumulation potential)	Done. We now refer to the criterion of rapid degradation. Information added.	MSCA support for the environmental classification proposed by DS; as also the key justifications adjustments which we will include in opinion document.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PENCONAZOLE

Date	Country / Person / Organisation / MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
17/02/2011	Netherlands / RIVM / National Authority	p11 – 4.1.1 Photolysis in water The paragraph is unclear; it is not certain whether data are not needed in the DAR or not available. Furthermore, the ZA5519 is not further specified.	The data is not needed AND it is not available in the DAR. The reference to ZA5519 is deleted as it is not relevant for C&L.	Noted
		p18 – 4.3.3 Summary and discussion of bioaccumulation The bioaccumulation criterion is independent of the degradability of the substance. We propose to delete 'for not readily biodegradable substances' in the 4th line of this paragraph.	We agree and deleted as suggested.	Noted
		According to the CLP regulation substances with a BCF < 500 are considered to have no potential to bioconcentrate for classification purposes. This is not in line with the description in the report that penconazole is able to 'significantly bioaccumulate'. We propose to revise the text accordingly.	Information added.	
		p35/36 – 7.1.1.3 Toxicity of penconazole to Lemna gibba 1) A 14-d Lemna gibba study is the key study for classification of the aquatic toxicity of penconazole. We agree with the use of Lemna gibba for the purpose of classification and labeling. However, we have remarks about the use of a 14-day ErC50 value as a basis for an acute toxicity classification. The Lemna testing protocols can be used to derive both an EC50 (acute toxicity) and a NOEC (chronic toxicity). The CLP guidance considers two guidelines as appropriate for testing using Lemna gibba: OECD guideline no 221 and US-EPA 850.4400. The exposure period in the OECD 221 guideline is 7 days. The general exposure period	Based on the raw data we recalculated the ErC_{50}-value for day 7. The CLH-report was changed accordingly.	We agree with the adjustment to 7 days.

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		according to the EPA guideline is 7 days but the test can be extended for up to 14 days if test solutions are refreshed to prevent test substance and nutrient depletion. In general, a 7-day exposure period is regarded in both protocols as appropriate for the purpose of determining an EC50 and NOEC in Lemna gibba. We consider a 14-day period less appropriate for the purpose of assessing acute toxicity of Lemna due to the difficulty of ensuring that the growth of control cultures is not unintentionally inhibited e.g. due to overcrowding or nutrient depletion, which would lead to derivation of an erroneous EC50 value. We therefore propose to use the EC50 value determined after 7 days.In addition, the CLP Guidance does not discuss in detail the most appropriate exposure period for Lemna for the purpose of classification and labelling. Therefore, we welcome a further discussion on this issue as Lemna is commonly used as the key species for deriving the classification and labeling of plant protection products. 2) Furthermore we also would like to note that the 2nd ATP to the CLP will be published in the foreseeable future. The 2nd ATP will come into force on the 1st of December 2012. The harmonised classification for penconazole will not be mandatory before the 1st of December 2012. The 2nd ATP will implement the 3rd revised edition of GHS in which classification and assignment of M-factors can also be based on chronic aquatic toxicity. We therefore recommend including the NOEC value for Lemna and identify the NOEC value which is most appropriate for classification of chronic aquatic toxicity based on chronic hazards. We propose to evaluate the need for a chronic classification for penconazole based on the available chronic data.	Besides criteria for fish and crustacea the third level states criteria for "algae or other aquatic plants". Hence, Lemna can be used equally. For completeness we included the NOEC (14d) for Lemna. However, as the C&L dossier was written when the enforcement of the 2nd ATP was not yet foreseeable, we prefer to complete the current proposal. We	RAC opinion follows the criteria of the 2nd ATP.

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
			are not aware of an agreed approach how to deal with the situation that the legal basis and/ or criteria change after the CLH-procedure of a certain substance has already started.	
01/03/2011	France / MSCA	☐ Identity of the substance and physical and chemical properties P 7, point 1.2: composition of the substance: The minimum purity should be mentioned as ≥ 950 g/kg and not > 950 g/kg. ☐ Environmental fate properties P 11, point 4.1.1 Photolysis in water: Please specify what ZA 5519 is. P 12, point 4.1.1 Photolysis in soil: It is currently indicated that "This results in half-lives of penconazole of 269 and 271 at latitude 30 and 40 °N, respectively". Please could you specify that the half-lives values are expressed in days. ☐ Other human health hazards P25, point 5.6.5 Summary and discussion of repeated dose toxicity: The liver changes observed in the repeated dose studies are considered mainly as adaptative responses. However some severe liver changes are noted at 500 ppm in dog studies (necrosis in 1 male out of 4 in the 90-day study and fibrosis in the 1-year study). Hepatic degeneration is also observed in one rat 90-day study at 1000 ppm (72 mg/kg bw/d). The effective dose level of 500 ppm (16.9-18 mg/kg bw/d) is below the guidance value. These changes could support a STOT RE. 2 H373 (Xn; R48/22) classification.	Correct. Reference is deleted as not relevant for C&L. Specification added. Liver toxicity that resulted in changes of clinical chemistry endpoints was present at 5000/2500 ppm but not at 500 ppm in the dog studies.	We acknowledge the modifications in the environmental fate section. RAC discussed this and did not see classification for STOT RE2 warranted.

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		☐ Physical hazards P 28, point 6.1 – explosivity, 6.2 – flammability and 6.3- oxidising potential: For classification, it should be useful to give details and explanation regarding these points. P 8, point 7.10 P 28, point 6.2 – flammability: Could you please give some details to be able to classify penconazole as not flammable and not only not highly flammable. ☐ Environmental hazards P 33, table 7.1-1: Acute toxicity of penconazole to fish and P 39 conclusion point 7.6: According to the last version of the List of Endpoints of the 03-07-2008, the LC50 for Oncorhynchus mykiss should be indicated to be 1.13 mg/L instead of 1.3 mg/L to taking into account the low purity of the test material. P 34, table 7.1-2: Long-term toxicity of penconazole to fish: According to the last version of the List of Endpoints of the 03-07-2008, the NOEC for Pimephales promelas should be indicated to be 0.32 mg/L instead of 0.36 mg/L to taking into account the low purity of the test material. P 35, table 7.1-4: Long-term toxicity of penconazole to invertebrates: According to the last version of the List of Endpoints of the 03-07-2008, the NOEC for Daphnia magna should be indicated to be 0.060 mg/L instead of 0.069 mg/L to taking into account the low purity of the test material. P 39, table 7.1-5: Long-term toxicity of penconazole to algae and P 35, aquatic plants and P 39 conclusion point 7.6: According to the last version of the List of Endpoints of the 03-07-2008, the ErC50 for Lemna gibba should be indicated to be 0.19 mg/L instead of 0.22 mg/L to taking into account the low purity of the test material. P 37, toxicity to Lemna gibba, conclusion: "Based on nominal concentrations, the 14-day EC50 values for frond number and dry weight were 0.22 and 0.11 mg/L, respectively. The test concentration was not analytically confirmed." and P 39	All relevant information can be found in the draft assessment report. Corrected value taking impurity into account added. See comment above. See comment above. See comment above. See comment above.	Noted

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		conclusion point: According to the last version of the List of Endpoints of the 03-07-2008, the ErC50 and the EbC50 for Lemna gibba should be indicated to be 0.19 mg/L and 0.096 mg/L instead of 0.22 mg/L and 0.11 mg/L, respectively, to taking into account the low purity of the test material.		
02/03/2011	UK / MSCA	Page 20. Acute toxicity. We agree with the proposal to classify for acute oral toxicity as Xn; R22 / Acute Tox. 4; H302. Pages 21 and 22. Irritation and sensitisation. We agree that these end-points do not meet the criteria for classification. Since slight responses were obtained in the eye irritation and skin sensitisation assays, it might aid transparency if the results obtained were compared against the criteria. For example, penconazole induced sensitisation in fewer than the 30% of animals that are required in an adjuvant assay for the result to be regarded as positive. Pages 23 and 24. Repeated dose toxicity. The most significant finding was hepatoxicity in dogs and rats at doses that seemed to be below the guidance values for classification; however, from the data presented in Table 5.6-1, it is not always apparent which effects occurred at which doses, so this should be clarified. The 1-year dog study included a recovery period, but the results of this phase were not reported; inclusion of this information would help with the interpretation of the results. Overall, the report concludes that the liver changes are mainly a response to the increased metabolic load. However, the degeneration and necrosis that were observed are not suggestive of adaptive changes, and in some studies they appeared to occur at doses below the guidance values for classification. We therefore propose that a more thorough discussion of the results and justification of the classification decision are required. Section 7.1.1.1: We think further detail is needed for the description for the chronic fish test. What is meant by "internal method"? For example is this a DE guideline, what does the NOEC represent? We note that section 7.6 refers to the test as an early life stage, so it would be helpful to make this clearer in 7.1.1.1. Section 7.1.1.1 & 7.6: We appreciate the issues for potential endocrine disrupting properties, however as there are no classification criteria for ED at present, we think only a brief description is needed in the Annex IV dossier. We do not feel the present	Penconazole has been reviewed in the programme covered by Commission Regulation (EC) No 1490/2002. Therefore, detailed information on these studies can be found in the Draft Assessment Report. Further information included in section 7.1.1.1 Section deleted as not relevant for C&L (p. 33)	We will express it in opinion in the manner suggested by UK. We will consider the arguments that the degeneration and necrosis are not suggestive of adaptive changes and even may occur at doses below the guidance values. We also found uncomfortable the description "internal method" and

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		text is helpful in the dossier for the classification of the substance. Section 7.1.1.3: We note the Lemna study is a 14-d test, whereas the current OECD guideline is for a 7-d study. Has the German CA considered this issue - we think it may be interesting to explore it further in the dossier. We think it would also be helpful to consider the test substance stability in the long-term fish and Daphnia studies to provide support for the likely substance stability in the Lemna test. Section 7.1.1.4: We think it would be helpful to differentiate between water spiking and sediment spiking for the sediment toxicity tests. Whilst we appreciate that tests using sediment spiking are ecotoxicity data, we do not think they need to be included in CLP dossiers as these data are not used for classification.	See comment above to the Netherland. Test media and conditions are not comparable so we think this is not useful. The summarized data in table 7.1-7 differentiates between water and sediment spiking methods.	this is still in for example table 7.1.2.
02/03/2011	Sweden / Ing-Maria Olsson / MSCA	Acute toxicity: SE supports classification of penconazole (Cas No 66246-88-6) as specified in the proposal. SE agrees with the rationale for classification. In 5.2.5 (page 21), please note that classification should refer to Reg. (EC) No 1272/2008 instead of GHS. Environment: In general we agree with the proposed classification of Penconazole and the M factor. In addition we have some specific comments: Biodegradation The guidance document on the application of the CLP criteria provides in Annex II, part II decision logic for assessment of biodegradation (section II.4). This decision logic identifies the key data relevant for arriving at a correct assessment of biodegradation. We appreciate that all data available on degradation of the substance have been presented and summarized, however when it comes to the decision on whether a substance is or is not ready biodegradable only the he relevant data should be	Field dissipation studies are deleted.	We agree with Swedish MSCA.

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		referred to (see the decision logic). Therefore we propose to delete field dissipation studies as they do not provide any data on mineralization of the substance. The data set provided indicates that in water/sediment study metabolites are formed. Theoretically, if the metabolites are formed quickly enough and if data on metabolites are available to show whether or not the metabolites are classifiable; this may be used in further assessment of the biodegradation of the substance. If the metabolites are not classifiable the substance can be regarded as readily biodegradable. Bioaccumulation We agree that the substance meets the criteria for being regarded as bioaccumulative both in accordance to DSD (BCF>100) and CLP (BCF>500). We do however not agree with the statement that the criterion of BCF>500 is applicable only to not readily biodegradable substances. Both degradation and bioaccumulation are two separate criteria and should be assessed independently. Therefore we propose to amend the text in section 4.3.3 to: 4.3.3 Summary and discussion of bioaccumulation Penconazole has a log Kow of 3.72. The experimentally derived steady state BCF of 200 (based on total radioactive residue for whole fish) is above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) but lower then 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008). This comment applies also to section 7.6 on conclusion on the environmental classification and labeling. Toxicity What is the relevance of long-term sediment studies for classification? In its section 4.2.1 on scope of the aquatic classification, the guidance document on application of classification criteria states that: "For most substances, the majority of data available addresses this environmental compartment. The classification scheme is limited in scope in that it does not, as yet, include aquatic sediments, nor higher organisms at the top end of the aquatic food-chain, although these may to some extent be covered by the criteria selected". It could be argued that some short-term sediment studies may have relevance for the classification (i.e. when the exposure is waterborne and thus comparable with other aquatic studies testing). *ECHA's comment: ECHA has copied the comment below from the attachment*	We agree to the explanation, this is conform to CLP. We agree and "for not readily biodegradable substances" is deleted. The test substance in the 1st study contained a major impurity	We acknowledge these discussions which will be compiled with arguments of other MSCAs and of Syngenta.

Date	Country / Person / Organisation / MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		COM_CLH_PC_Penconazole_SE Appendix.doc Appendix to Swedish Comments on Annex XV dossiers proposing harmonised Classification & Labelling for Penconazole (CAS Number: 66246-88-6 EC Number: 266-275-6) March 2, 2011 "Reproductive toxicity Penconazole" Description of the effects in Annex B-6: Toxicology and metabolism the DAR for Penconazole • 2-generation rat (1st study, considered supplementary) dystocia, as shown by the live litter pregnancy index, even though not significant, showing a dose dependent decrease (F0 95-79 %, F1 100-84 %, Table B6.6-8, page 278), the same goes for the live birth index (F0 93-73 %, F1100-81 %, Table B6.6-9, page 279). It should also be noted that there was maternal mortality at 400 and 2000 ppm in both F0 [1 (0 days p.p.) + 3 (0, 4, 11 days p.p.) animals] and F1 [1 (0 days p.p.) + 3 (2, 2, 4 days p.p.) animals], one female died in the control group 19 days p.p. • 2-generation rat (2nd study, considered acceptable) table B.6.6-21 (page 286) reporting small (uni- or bilateral) testes occur in animals exposed to 250 and 2500 ppm both in the F0 (1+1 animal) and F1 generation (3+2 animals). Epididymidis aspermia of varying grade is also reported in both F0 and F1 (dosing 0, 25, 250 and 2500 ppm resulted in 1, 1, 5, and 7 animals in each dose group). Testis with tubular atrophy and aspermatogenesis is reported in 2, 0, 4, and 5 animals respectively. This can be considered as an indication of the substances potential to harm spermproduction. Further support is added by the results in the B.6.5.1 Mouse life-time study table B.5.6-11 (page 256) – occurence of selected non-neoplastic microscopic changes that reports inflammation with fibrosis in the epididymidis. And the histopathological findings from the 1 yr oral study in dogs where testis tubular atrophy was found in 3 animals (at the dose levels 500 and 5000/2500 ppm) and reduced spermatogenesis in 2 animals in the high dose group (Table B.6.3-66, page 206). • Prenatal toxicity in rat (1st study) a dose dependent increase in early resorption can be seen(not significant) (dose 0, 30, 100, and 300 mg/kg bw/day – 4.8, 5.9, 8,1 and 9.0 % of implantation respectively, Table B6.6-26, page 294). • Prenatal toxicity rat (2nd study) resorptions were higher in the dosed animals with significance for the low and high dose (0, 5, 100, and 500 mg/kg bw/day – % of	which could be responsible for the dystocia. Table B.6.6-21 of the DAR reports a total of 2, 0, 4, and 3 males (F0 + F1) with any grade of tubular atrophy and aspermato-genesis in the testis, out of the 60 F1 and F2 males examined per group. This is not indicative of testicular toxicity in the rat. Testicular changes in 90-d and 1-yr dog studies are considered a likely consequence of the immaturity of the males at start of the study in combination with the	

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		implantations 2.2, 4.4, 3.6, and 18.9 respectively, Table B.6.6-34, page 301) • Based on the prenatal toxicity rabbit (1st study) developmental toxicity could also be considered as there were 1 fetus with microphtalmia and 1 with microphtalmia and hydrocephalus. The report states that a weak teratogenic activity cannot be excluded, however it is confined to a dose level (150 mg/kg bw/d) which was also toxic to the does (page 308). • Prenatal toxicity rabbit (2nd study) reports dystocia in the form of premature delivery in 5 animals (in 2, 2, and 1animal at dose levels 10, 50, and 200 mg/kg bw/d respectively Table B6.6-42, page 311).	reduction in food consumption at the high dose. A higher number of dams with increased resorptions in the rat prenatal toxicity studies was only seen in the dose range that was lethal for the mothers. This is not indicative of developmental toxicity. Regarding microphthalmia in rabbits, see response to France. Premature births in rabbits are not dystocia and not dose-related.	
03/03/2011	Spain / Elina Valcarce/ MSCA	p. 21 Summary and discussion on acute oral toxicity The Spanish CA supports the proposed classification of Penconazol as Xn, R22: Harmful if swallowed according to Directive 67/548/EC and as Acute Tox 4 (oral)	Thank you	We acknowledge the Spain

Date	Country / Person / Organisation/ MSCA	Comment given during public consultation	Dossier Submitter's response to comments	RAC's response to comment
		(H302: Harmful if swallowed) according to Regulation EC 1272/2008. This classification is based on the LD50 value in male rats (LD50 < 2000 mg/kg) and the combined male and female rabbits (LD50 = 971mg/kg) obtained in the acute oral toxicity studies with penconazol.		MSCA support for acute tox 4 classification.