Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM) to the Opinion proposing harmonised classification and labelling at EU level of

paclobutrazol (ISO); (2*RS*,3*RS*)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-ol

EC Number: -
CAS Number: 76738-62-0

CLH-O-0000001412-86-213/F

Adopted

8 June 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PACLOBUTRAZOL (ISO); (2*RS*,3*RS*)-1-(4-CHLOROPHENYL)-4,4-DIMETHYL-2-(1H-1,2,4-TRIAZOL-1-YL)-PENTAN-3-OL

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: paclobutrazol (ISO); (2*RS*,3*RS*)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)-pentan-3-ol
EC number: -
CAS number: 76738-62-0
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	1
Comment received				
According to the DAR of the substance, the purity of Paclobutrazol is 930g/kg (dry weight basis) and 750g/kg (wet paste).				
Dossier Submitter's Response				
This is correct.				
RAC's response				
Thank you very much. Noted. This purity is within the range considered in the CLH report.				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	2
Comment received				
The German CA agrees with the suggested classification for environmental hazards as Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410) and the acute/chronic M-factor of 10. It must be acknowledged that several of the studies which are used now for classification and labelling were not available when the DAR was prepared in 2006 and were not addressed in the EFSA conclusion 2010.				
Dossier Submitter's Response				
Thank you for your support. Your comment has been noted.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	3
Comment received				
No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Thank you very much. Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	4
Comment received				
Concerning the bone marrow micronucleus tests, the date references given in table 16 on page 42 of the CLH report seem to be reversed. The oral study was performed in 1991 and not in 1983; the IP study was performed in 1983 and not 1991. Could you please correct it?				
Dossier Submitter's Response				
Thank you for your comment. At this stage, we cannot make changes to the CLH report. However, you are correct. There are two micronucleus tests; the oral study was performed in 1991 and the intraperitoneal study was conducted in 1983.				
RAC's response				
Thank you very much. Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	5
Comment received				
The proposal for classification for developmental toxicity is supported. However, the need for a more severe categorisation should be further discussed in light of the developmental findings: - increased incidence of cleft palates in rat which is a clear malformation of concern (even though only observed in at maternotoxic dose) - increased incidences of other skeletal and soft tissues abnormalities in both rat and rabbit teratogenicity studies in the absence of maternal toxicity - common pattern of effects among studies and species (e.g.: rudimentary cervical ribs, supernumerary lumbar ribs) - cleft palates, cervical ribs are abnormalities implying a disturbance in the process of craniofacial morphogenesis commonly observed with triazoles.				
Dossier Submitter's Response				
We agree that further discussion of the appropriate classification for developmental toxicity is necessary. In our opinion, category 2 appears most appropriate, given that cleft palate was only observed in rats at a maternally lethal dose, and no malformations were observed in rats or rabbits at lower doses.				
RAC's response				
Thank you very much. Noted and discussed in the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Spain		MemberState	6

Comment received

Fertility

We agree with the UK CLP Competent Authorities that there is no reason to discount the testicular toxicity observed in the 90-day study in dogs as not being relevant for human health. However, in isolation, they are not considered sufficient to support classification for fertility. No treatment-related adverse effects on fertility were observed in the 2-generation study at doses of up to 100-125 mg/kg/day, the highest dose tested. Similarly, no adverse effects on fertility were observed in the one-generation preliminary study, at doses of up to 150 mg/kg/day, the highest dose tested.

Therefore, the Spanish CA consider not necessary to classify paclobutrazol for effects on fertility.

Developmental toxicity

Paclobutrazol induced cleft palate in rats in 3 foetuses/2 litters at the highest dose (compared to 0 in controls) of 250 mg/kg/day; a dose that caused severe maternal toxicity (1 dam died and 4 sacrificed in extremis). This dose of 250 mg/kg/day was also associated with widespread skeletal variations, mostly delayed ossification and supernumerary ribs (increased 14th bilateral). At lower non-maternally toxic doses, paclobutrazol also induced Cleft palate in 1 foetus at 40 mg/kg/day, retardation of skeletal development, increased supernumerary ribs and visceral variations (kidney and urinary tract) at doses of 40 to 100 mg/kg/day, with only retarded skeletal development noted at a dose of 10 mg/kg/day.

Cleft palate is a very rare malformation (relevant background rate of 0) in rats and should be taken into consideration for classification purposes. The increased incidence of cleft palate, although at a maternally lethal dose, should be regarded as relevant for human health. Besides, cleft palate appeared with lower incidence in the absence of maternal toxicity, this fact speak against the cleft palates being chance findings and support their association with exposure to paclobutrazol. Furthermore, the increased incidence of cleft palates in rat has also been observed in response to exposure to other triazoles (e.g. cyproconazole, propiconazole and epoxiconazole).

An important role of some CYP isoforms (CYP26 isoforms) expressed during mammalian development is the catabolism of retinoic acid. The suggested mechanism for the teratogenic effects of triazoles involves the inhibition of CYP 26, which means increased concentrations of retinoic acid (Menegola et al., 2006). Retinoid acid is a well-known morphogen in vertebrate and invertebrate embryos. Triazole-related abnormalities are confined to structures controlled by retinoic acid, especially the neural crest cells, hind brain, cranial nerves, and craniofacial structures. There is no information showing that the mechanism is not relevant for humans and whether human sensitivity is more similar to rabbits (where no cases were reported) or to rats.

Paclobutrazol not only induced cleft palate at maternally lethal doses in rats, but also there was evidence of cranio-facial malformations at lower doses without maternal toxicity. Support for classification for developmental toxicity comes from an increased incidence of skeletal and visceral variations, and retardations of skeletal development

without maternal toxicity. The Spanish CA opinion is that a classification as Repr. 1B; H360D is more appropriate for paclobutrazole than the dosssier submitter proposal to classificy paclobutrazole with Category 2 H361d.
Dossier Submitter's Response
Fertility We thank Spain for their response, and support for no classification. Developmental toxicity We consider that H361d is more appropriate, as it takes into consideration the fact that malformations were only observed at maternally lethal doses in rats. The observation of a single cleft palate in rats at the lowest dose of 40 mg/kg/day is considered to be a chance finding. This is supported by the lack of craniofacial malformations at the intermediate dose of 100 mg/kg/day in the same study, and an absence of cleft palate in the second rat study, conducted at doses of up to 100 mg/kg/day using the same protocol and rat strain. We note that paclobutrazol could be a CYP 26 inhibitor, which is the suggested Mode of Action for cleft palate induction of other triazole molecules. However, there is no evidence to suggest that paclobutrazol is a CYP 26 inhibitor, other than some structural similarity. Without additional information, it is not possible to conclude on Mode of Action for cleft palate induction.
RAC's response
Thank you very much. Noted. Noted and discussed in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	7
Comment received				
Comment on classification proposal for developmental toxicity: The proposed classification as Repr. 2, H361d is based on cleft palates observed at the highest dose (250 mg/kg bw/d) with severe maternal toxicity (lethality) in rats (Killick M, Pigott G, Banham P et al. (1983)). As stated in the CLH report cleft palate is a very rare malformation and is of high concern for human health. Cleft palate is commonly observed in reproductive studies at maternally toxic levels in mice (Moore et al., 2013) but not in rat or rabbit. Furthermore, in a preliminary study cleft palates were also observed at the highest dose (240 mg/kg bw/d). Thus the result is reproducible. Therefore, we ask for a more detailed rationale why a classification with Repr. 1B, H361D is not warranted. In addition at 100 mg/kg bw/d a significant increase in foetuses with hydroureter was observed in the second rat study (Killick M, Pigott G, Banham P et al. (1984)). Hydroureter is also classified as a malformation according to Moore et al. (2013). For further evaluation we ask for historical control data. Moore, N. P., et al., 2013. Guidance on classification for reproductive toxicity under the globally harmonized system of classification and labelling of chemicals (GHS). Crit Rev Toxicol. 43, 850-91. Comment on classification for fertility: Although the one- and two generation studies in rats did not show any adverse effects on fertility (Wickramaratne 1987a and Hodge 1987b, page 48), it cannot be excluded that				

paclobutrazol has adverse effects on fertility. Regarding the fact that rats are less sensitive than dogs concerning fertility the following findings in the 90 day oral dog study (Hodge 1987a) should be discussed:
- 450 mg/kg bw/d: decreased tested weight, giant spermatid cells (3/4 compared to 0/4 in controls), immature testes (4/4 compared to 0/4 in controls), decreased epididymides weight, no spermatozoa present in epididymides (3/4 compared to 0/4 in controls)
These effects are clearly treatment related. Although the DS states that there is "no testicular toxicity in the 1 year dog study", there were in fact degenerative changes in the seminiferous epithelium (1-0-2-2), moderate chronic inflammatory cell infiltration (0-0-0-1), seminiferous debris (1-0-0-2), atrophic prostate (0-0-0-1) and dilated acini of the prostate (0-0-0-1).
The testicular toxicity might be taken into consideration for STOT RE, but it is argued in the CLH dossier that it would rather suggest a delay in sexual maturation. Such an offspring effect would justify classification as Repr. 2; H361f.

General comment:
The section "Fourteen animals died […]" on page 56 does not describe the result of the first study in rabbits (Killick M, Lichtfield M, Banham P et al. (1983b)) but the range-finding study (Hodge, 1987). This should be corrected.

Dossier Submitter's Response

Developmental toxicity

We consider that H361d is more appropriate, as it takes into consideration the fact that malformations were only observed at maternally lethal doses in rats. A single foetus with cleft palate was observed at the lowest dose of 40 mg/kg/day which is considered to be a chance finding. No craniofacial malformations, including cleft palate, were observed in a second rat developmental toxicity study, conducted using an identical protocol with the same rat strain, at doses of up to 100 mg/kg/day; the highest dose tested. In our opinion category 2 is appropriate, as this recognises paclobutrazol is a developmental toxicant, but takes into account that malformations were only induced at maternally toxic doses.

We note that no kidney changes were reported in the first rat study, conducted at higher doses of up to 250 mg/kg/day. This suggests that the observed hydroureter may be a chance finding. However to facilitate interpretation, we contacted the applicant, who provided the following information.

Dilated ureter is used to describe an abnormal distension of the ureter with fluid, hydroureter may be used to describe an extreme dilation of the ureter (Makris et al., (2009)). Within laboratories conducting assessments of developmental toxicity the terminology used to describe findings can change with time and the assignment of severity grades (qualitative measurement) are also very variable between and within laboratories. Therefore the descriptors of hydroureter and dilated ureter (extreme/moderate) have been used to collate additional historical control data (see below):

Historical control data for hydroureter and dilated ureter (extreme) in the Alpk:AP rat at Central Toxicology Laboratory (CTL) 1983 to 1992

Study date	Hydroureter		Dilated ureter (extreme)		Dilated ureter (moderate)	
	Litter incidence	Foetal incidence	Litter incidence	Foetal incidence	Litter incidence	Foetal incidence
Oct 1983					5/23	7/268
Nov 1983	1/24	1/306	1/24	1/312	4/24	5/306

Feb 1984					1/23	1/255
April 1984					10/30	15/335
Nov 1984			1/24	1/312	5/24	6/312
Dec 1984					7/24	10/299
Feb 1985					1/6	1/58
May 1985					6/24	13/304
Jul 1985					1/23	2/305
Nov 1985					1/20	1/202
Nov 1985					2/20	2/220
April 1986					2/20	2/218
Jun 1986					2/24	2/303
June 1986					4/24	6/280
Nov 1986					1/24	1/288
Sept 1987					2/24	6/282
Sept 1987					1/24	1/302
Nov 1987					4/23	5/276
Jan 1988					2/24	3/281
Feb 1988					2/24	2/297
Jul 1988	1/158	1/1877				
Jun 1989	1/24	1/275				
Mar 1990					1/116	1/370
May 1990	2/116	2/1370	1/116	1/1370		
May 1990	1/23	2/278				
Jun 1992	1/21	1/230				

In the first developmental toxicity study in rats with paclobutrazol (doses 0, 40, 100 & 250 mg/kg/d) there were no treatment related abnormalities of the kidney or urogenital tract. In the second developmental toxicity study in rats, which utilised lower doses (doses 0, 2.5, 10, 40 & 100 mg/kg/d) hydroureter was observed in 4/24 litters (8/305 foetuses) at 100mg/kg/day. Hydroureter and dilated ureters are frequently seen in control Alpk:AP rats at the conducting laboratory and are very variable in their occurrence and severity between control groups. The inconsistency in the observation of this finding at the same dose levels across the two studies and the failure to detect this change at the highest dose tested in this species falls some way short of constituting 'clear evidence' of an adverse effect on development that is of relevance to classification. The level of uncertainty presented by the two data sets amount to no more than 'some evidence' for a deviation from normal development.

References

Makris S.L; Solomon H.M; Clark R; Shiota K; Barbellion S; Buschmann J; Ema M; Fujiwara M; Grote K; Hazelden K.P; Hew K.W; Horimoto M; Ooshima Y; Parkinson M; Wise L.D (2009). Terminology of developmental abnormalities in common laboratory mammals (version 2). Reproductive Toxicology (28) 371-434.

Reproductive toxicity

Paclobutrazol did not cause any adverse effects on sexual function or fertility in two well-conducted standard fertility studies in rats.

Paclobutrazol caused testicular toxicity and some delay in testicular maturation, at the top dose of 450 mg/kg/day in dogs. Similar effects were not reported in the 1-year study, conducted at equivalent doses of 300 mg/kg/day. That no delay in testicular maturation was observed in the 1-year study suggests that this change in the 90-day study was a transient retardation, and not a treatment-related effect. We agree that some testicular

changes were observed in the 1-year study, but these changes were not dose-related and could easily be chance findings.

Overall, we do not consider that the testicular changes observed in dogs should be used to support classification for adverse effects on sexual function and fertility, as no adverse effects were observed in standard reproductive toxicity studies in rats.

General comment

Thank you for your comment. At this stage, we are unable to make changes to the CLH dossier. However, you are correct. In the range finding study conducted in 1987, groups of 8 presumed pregnant females New Zealand White rabbits were dosed by gavage with 100, 200 or 400 mg paclobutrazol/kg bw/day in corn oil from days 6 to 18 of gestation. Fourteen animals died or were killed *in-extremis* during the study. Seven of these deaths were due to misdosing, two were unrelated to treatment and one was due to abortion. Four deaths at 400 mg/kg /day were considered to be treatment-related. The large number of deaths and the low pregnancy rate in the control and 400 mg/kg /day groups confounds interpretation of this study.

In the first rabbit developmental study described in the CLH dossier, there were difficulties obtaining the required number of preganant females because of poor mating performance. The number of pregnant females at study termination was 9, 12, 13 and 8 in the control, 25, 75 and 125 mg/kg bw/day groups, respectively. In this study, two rabbits each in the control, 75 and 125 mg/kg bw/day groups died. In the 75 mg/kg bw/day group, two animals were killed following abortion. One control animal was killed *in extremis*, and the other mortalities were animals that were found dead. There was no evidence of any differences in the number, growth or survival of the fetuses *in utero* at any dose level, when compared with control values. There was no treatment-related increase in the incidence of minor visceral and skeletal fetal defects. One fetus from the 125 mg/kg bw/day and another from the 75 mg/kg bw/day groups had cardiac anomalies. A concurrent study from the reporting laboratory revealed 2 fetuses with cardiac anomaly in the control group and it was concluded that the incidence in this study should be regarded as spontaneous.

RAC's response

Thank you very much. Noted. The new information supplied in this RCOM was used by RAC in the RAC discussion and opinion.

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2017	Switzerland	Syngenta	Company-Manufacturer	8

Comment received

Syngenta support the proposed Cat 2 classification for developmental toxicity; the attached document provides a summary of all the available data relating to this endpoint.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Paclobutrazol Syngenta CLH response July 2017.docx

Dossier Submitter's Response

We welcome the support from industry.

RAC's response

Thank you very much. Noted.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	9
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Spain		MemberState	10
Comment received				
In the oral acute toxicity studies, the LD50 values ranged from 490 - 1219 in mice to 1336 - >2000 mg/kg in rats. Therefore, the Spanish CA supports the proposed classification of paclobutazol as Acute Acute Tox 4, H302 - Harmful if swallowed, because LD50 are within the limits 300< ATE ≤ 2000 (oral, mg/kg bw). Following single inhalation exposure, a 4-hour LC50 of 3.13-4.79 mg/l was identified in rats for a dust aerosol. Therefore, we agree with the dossier submitter that the criteria for classification with Acute Tox 4, H332 – Harmful if inhaled are met (LC50 is ≥1≤ 5 mg/l for dusts and mists).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	11
Comment received				
Acute Toxicity (oral): The proposed classification as Acute Tox. 4, H302 is based on acute oral toxicity studies using a solubilizer (Lissatan AC: sodium naphthalene sulfonate formaldehyde condensate (CAS: 9084-06-4)) in the vehicle. The water solubility of paclobutrazol is low and the use of a solubilizer increases the bioavailability. Based on the study by Durando (2006a) using a suspension in distilled water no classification for acute oral toxicity is warranted. Paclobutrazol may be dissolved in various solvents and some of them may enhance toxicity. However, this should be taken into account in the classification of mixtures. The relevance of acute oral toxicity studies using a solubilizer in the vehicle for the classification of paclobutrazol should be discussed in more detail. Acute Toxicity (inhalation): The proposed classification as Acute Tox. 4, H332 is based on an acute inhalation toxicity study (Hext, 1988) which exceeds the recommended limit concentration of 2 mg/L for aerosols according to OECD 403. Furthermore, treatment related clinical signs as increased breathing depth and reduced breathing rate, gasping and abnormal respiratory				

noise were observed. It should also be noted that some animals were sacrificed in extremis. Therefore, it should be considered whether the effects are caused by non-specific toxicity due to high dust concentration rather than substance-specific toxicity. No mortalities or clinical signs were observed up to 2 mg/L in the study of Pinto (2006).
Dossier Submitter's Response
Acute Oral Toxicity We welcome further discussion on this point. Acute Inhalation Toxicity There is no information to indicate why the animals sacrificed *in extremis* were experiencing severe effects. It is possible that these were secondary non-specific effects of exposure to high concentrations of a low toxicity dust. However, without further information they should be regarded as treatment-related deaths supporting classification for acute inhalation toxicity. We note that the current maximium concentration for classification is 5 mg/l, not the 2 mg/l advised in OECD TG 403 as a limit concentration. Therefore at present, adverse effects occurring above 2 mg/l, but below 5 mg/l should be regarded as relevant for classification.
RAC's response
Thank you very much. Noted. Your considerations were incorporated into the RAC discussion and opinion.

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2017	Finland		MemberState	12
Comment received				
FI CA supports the proposed classification of Acute Tox. 4; Harmful if swallowed for paclobutrazol. FI CA supports the proposed classification of Acute Tox. 4; Harmful if inhaled for paclobutrazol.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Spain		MemberState	13
Comment received				
The results of the standard eye irritation study, 2/3 animals with a corneal opacity score of 1, indicate that placlobutrazol meets the criteria for classification with Eye Irrit 2; H319 – Causes serious eye irritation.				
Dossier Submitter's Response				
In our opinion, H319 is appropriate.				

RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	14
Comment received				
The German CA agrees with the proposed classification as Eye Irrit. 2, H319 based on corneal opacity observed in the irritation/corrosion study (Durando, 2006d).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2017	Finland		MemberState	15
Comment received				
FI CA supports the proposed classification of Eye Irrit. 2; Causes serious eye irritation for paclobutrazol.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	16
Comment received				
The German CA proposes classification as STOT RE 2 for liver toxicity, as there were significant toxic effects between 10 and 100 mg/kg bw/day: - Clapp 1984, 1 year oral dog study: increases in hepatic aminpyrine-N-demethylase at lowest dose of 15 mg/kg bw/d up to highest dose. Further changes were increased liver weights in males and females, hepatocellular swelling in males and focal hepatocyte ballooning in females. - Shaw 1986b, 2year rat study: hepatic steatosis in 8/50 male rats at 11 mg/kg bw/d, hepatic steatosis and increased absolute and relative liver weight in 35/50 male animals at 54 mg/kg bw/d, increased relative liver weight and hepatic steatosis in 34/50 animals in female rats at 72 mg/kg bw/d - Shaw 1986a, 2 year mice study: hepatic hypertrophy and steatosis at 14 mg/kg bw/d in 34/52 male mice, hepatic hypertrophy and steatosis as well as increased absolute and relative liver weight in 37/52 male mice at 81 mg/kg bw/d - Litchfield 1983 a, 90 day rat study: increased relative and absolute liver weight and increased aminopyrene-N-demethylase activity in female rats at 22 and 107 mg/kg bw/d, increased liver weight and ALT and aminopyrene-N-demethylase activity at 93 mg/kg bw/d In contrast to the DS, the German CA considers the liver effects severe enough to				

warrant classification.
Dossier Submitter's Response
Clapp 1984 We estimate the guidance value for STOT RE 2 to be 2.5-25 mg/kg/day, therefore effects observed at 15 mg/kg/day are relevant for consideration. At this dose, the effects observed were slight hepatocyte ballooning and elevated N-demethylase activity. Shaw 1986b We estimate the guidance value for STOT RE 2 to be 1.25-12.5 mg/kg/day, therefore effects observed above 12.5 mg/kg/day are not relevant. Hepatic steatosis was observed in males administered 2.2 (1/50) and 11 mg/kg/day (8/50). No other changes were observed which might indicate that liver function was compromised. Shaw 1986b We estimate the guidance value for STOT RE 2 to be 1.25-12.5 mg/kg/day, therefore effects observed above 12.5 mg/kg/dayare not relevant. We agree that hepatic steatosis was observed at a dose of 2.6 mg/kg/day and above in males. However, only the changes at the lowest dose of 2.6 mg/kg/day occurred within the relevant guidance band for STOT RE 2. These changes are not considered to indicate significant liver toxicity or impairment of liver function. Litchfield 1983 The guidance value for STOT-RE 2, for a 90-day rat study, is 10-100 mg/kg/day. All dose levels in this study are within, or just outside this guidance value. The increase in ALT, N-demethylase activity and elevated liver weight all occurred at doses relevant for classification. However, other toxicological parameters related to liver structure and function were also investigated and no supportive evidence of liver toxicity or impairment of liver function was observed. Although there are some liver changes in rats, mice and dogs, at doses relevant for classification these are not sufficient to support classification with STOT-RE 2 as there is no evidence of significant liver toxicity or impairment of liver function.
RAC's response
Thank you very much. Noted. Nevertheless, RAC supports the DS's estimations regarding the cut-off points for triggering classification.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	France		MemberState	17
Comment received				
FR agrees with the classification for environmental hazards and with the acute and chronic M factor values proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	Germany		MemberState	18
Comment received				
Page 58 point 5.1 Degradation: For the water sediment simulation by Simmons (1987) the DT50 total system should be 167 to > 1000 days instead of 167 to 1378 days as no degradation values could be calculated in the Virginia Water (14C-triazole-labelled) test system because of the very little degradation of paclobutrazol in this test system. Page 58 point 5.1 Degradation: For the Water/sediment kinetic evaluation according to FOCUS Guidance by Harvey (2009a) the DT50 total system should be 193 to > 1000 as no acceptable fit was found for the degradation of paclobutrazol in the water/sediment system Virginia due to slow degradation and fluctuating levels of the compound. It can lead to a misunderstanding of the degradation behavior of paclobutrazol if only the (shorter) DT50 total system value is stated. Page 62 point 5.1.2.3 Simulation test: Please state that for the triazole-label no DT50 total system in the Virginia Water system could be calculated due to the very little degradation of paclobutrazol in this system.				
Dossier Submitter's Response				
At this stage, we are unable to make changes to the CLH dossier. Your comments have been noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2017	Finland		MemberState	19
Comment received				
FI CA supports the proposed classification of Aquatic Acute 1 with M-factor of 10 and Aquatic Chronic 1 with M-factor of 10 for paclobutrazol.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS

1. Paclobutrazol Syngenta CLH response July 2017.docx [Please refer to comment No. 8]