Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Pencycuron (ISO);
1-[(4-chlorophenyl)methyl]-1-cyclopentyl-3-phenylurea

EC number: 266-096-3
CAS number: 66069-05-6

CLH-O-0000001412-86-32/F

Adopted

04 December 2014

ANNEX 2 – COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PENCYCURON (ISO); 1-[(4-CHLOROPHENYL)METHYL]-1-CYCLOPENTYL-3-PHENYLUREA

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 attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). 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.

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Substance name: Pencycuron (ISO); 1-[(4-chlorophenyl)methyl]-1-cyclopentyl-3-phenylurea

CAS number: 66063-05-6

EC number: 266-096-3

Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	1
Comment received				
Comments have been provided on part B regarding composition of test material, Physico-chemical properties,toxikokinetics, repeated dose toxicity and bioaccumulation data **Part B 1.2.1 Composition of test material** **Statement from the CLH report:** The studies were performed with technical pencycuron with a purity range of 97.6% to 99.4%. This represents the above mentioned compostition of pencycuron (≥ 980 g/kg). No information regarding the impurities in the batches used for testing is available **BCS comments:** This information was included in the confidential part of the dossier for Annex I inclusion. The detailed description and toxicological assessment of the tested batches were submitted with the dossier for Annex I inclusion (M-345410-01-1 and M-345694-01-1).				
Dossier Submitter's Response				
Noted. However, this confidential information is not available to the dossier submitter.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	2
Comment received				
Part B 1.3 Physico-chemical properties Relative density **Statement from the CLH report:** D^{20}_4: 1.24 **BCS comments:** The unit should be added as g/cm^3				
Dossier Submitter's Response				
Agreed				
RAC's response				

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	3

Comment received

Part B 1.3 Physico-chemical properties Partition coefficient noctanol/ Water
Statement from the CLH report:
Log Kow: 4.0 at 25 °C
HPLC shake
BCS comments: The PH should be added as such : (pH 4; 7; 9)
The method is HPLC **and** shake flask method

Dossier Submitter's Response

noted

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	4

Comment received

Part B 4.1.3 Summary and discussion on toxikokinetics : Table 9

BCS comments: A comment on % oral absorption should be added as such : *) Based on renal excretion, except for the last study where biliary excretion was determined too.
Some values seem to be the wrong ones

Dose (mg/kg bw)	Dose frequency	Label	% oral absorption *)	Strain	Vehicle	Reference
200	single	^{14}C-carbonyl	**19-13** (m-f)	Fischer	N,N-dimethyl-formamide in polyethylene glycol 400 (1:9 v/v)	Oyama *et al.*, 1982
200	single	^{14}C-phenyl	**28-37** (m-f)	Fischer	N,N-dimethyl-formamide in polyethylene glycol 400 (1:9 v/v)	Oyama *et al.*, 1982
40	single	^{14}C-carbonyl	**30-35** (m-f)	Fischer	N,N-dimethyl-formamide in polyethylene glycol 400 (1:9 v/v)	Oyama *et al.*, 1982

Dossier Submitter's Response

We agree with the addition of the proposed comment. In addition, some of the values in the CLH report (and the DAR) are indeed wrong. The values as indicated above (by BCS) are correct based on the summary of this study in the DAR.

RAC's response

Noted. It is not considered however to affect the classification discussion.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	5

Comment received

Part B 4.1.3 Summary and discussion on toxikokinetics : Metabolism summary

ANNEX 2 – COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PENCYCURON (ISO); 1-[(4-CHLOROPHENYL)METHYL]-1-CYCLOPENTYL-3-PHENYLUREA

Statement from the CLH report: No apparent explanation can be offered for main quantitative and qualitative difference between the metabolism of pencycuron after administration of [N-^{14}C-methylene] pencycuron on the one hand and of [UL-^{14}Cphenyl] pencycuron or [^{14}C-carbonyl] pencycuron on the other: the presence of M932 (=M08) as glucuronide or sulphate conjugate. **BCS comments:** The non apparent explanation could be the following one ; it could be due to different strains of rats (Wistars SPF Cpb versus Fisher)
Dossier Submitter's Response
The use of different strains indeed could be an explanation
RAC's response
Noted. It is not considered however to affect the classification discussion.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	6
Comment received				
Part B 4.1.3 Summary and discussion on toxikokinetics : Dermal absorption **Statement from the CLH report:** The potential absorption for pencycuron as 23.2% formulation by rat membranes accounts for ca. 2% at concentrations <1 mg/cm2 and for ca. 0.5% at concentrations of ca. 3 mg/cm2. In all experiments with both rat and hyman membranes, the absorption **BCS comments:** The type of formulation should be mentioned : The potential absorption for pencycuron as 23.2% **suspensible concentrate** formulation by rat membranes accounts for ca. 2% at concentrations <1 mg/cm2 and for ca. 0.5% at concentrations of ca. 3 mg/cm^2. It should be **human** and not hyman				
Dossier Submitter's Response				
Agreed				
RAC's response				
Noted. It is not considered however to affect the classification discussion.				

Date	Country	Organisation	Type of Organisation	Comment number
12.06.2014	France		MemberState	7
Comment received				
FR supports the classification proposal for environmental hazards. No comment on human health hazards.				
Dossier Submitter's Response				
Thank you for the support				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2014	Sweden		MemberState	8
Comment received				
The Swedish CA support the conclusion by the Netherland CA that classification of Pencycuron as Aquatic Chronic 1(H410) with an M-factor of 1 is warranted based on data showing long-term toxicity to Daphnia magna and the fact that Pencycuron is not rapidly biodegradable.				
Dossier Submitter's Response				

Thank you for the support
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2014	Germany		MemberState	9
Comment received				
The German CA supports the proposed environmental classification and labeling as Aquatic chronic 1 (H410) and chronic M-factor of 1. Furthermore, we would suggest addition of Aquatic acute 1 (H400) and acute M-factor of 1, because of additional data for acute aquatic toxicity. ***(ECHA note: The following attachment was provided [Attachment 1])*** Akute Daphnien Toxizität von Pencycuron.pdf				
Dossier Submitter's Response				
Thank you for the information. We agree that Aquatic Acute 1 should be added to the classification. Furthermore, the test concentrations of the above mentioned study are nominal. This means that the analytical EC50 values could be much lower, which may lead to a higher M-factor. However, as the actual concentrations are unknown we agree with an M-factor of 1 based on the available data.				
RAC's response				
RAC agrees with Aquatic acute 1, M-factor 1, based on the additional Daphnia study results.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	10
Comment received				
Part B 4.9.4 Summary and discussion of mutagenicity **Statement from the CLH report:** Three studies in vitro studies on *Salmonella typhimurium* (two point mutations and one point mutation/frame shift/ transition) were all negative **BCS comments:** It is not useful to repeat studies: Three in vitro studies on *Salmonella typhimurium* (two point mutations and one point mutation/frame shift/transition) were all negative.				
Dossier Submitter's Response				
Agreed				
RAC's response				
Noted. It is not considered however to affect the classification discussion.				

REPRODUCTIVE TOXICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	11
Comment received				
Part B 4.11 Toxicity for Reproduction **Statement from the CLH report:** Developmental oral gavage study, rat, dosing during gestation from day 6 to 20. Table 30 -Langrand-Lercher				

Part B 4.11.2.1 Non human Information **Statement from the CLH report:** In a study of Langrand-Lercher (2008), **BCS comments:** The correct author name is Langrand Lerche
Dossier Submitter's Response
Noted.
RAC's response
Noted. It is not considered however to affect the classification discussion.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	12
Comment received				
Part B 4.2.1.3 : Acute toxicity : dermal **Statement from the CLH report:** Acute toxicity: In one study (Ono and Lyatomi, 1978) rats were dermal exposed to pencycuron (purity 99.0%). The study was not performed in accordance with OECD 402, however, the guideline was not available at the time the study was conducted. The study report was very consice and was lacking essential information such as: **BCS comments:** The correct Author names are Ono and Iyatomi The study report was very c**oncise** and was lacking essential information such as **Part B 4.2.1.4 Acute toxicity : other routes** **Statement from the CLH report:** Ono and Lyatomi, 1978 **BCS comments:** The correct Author names are Ono and Iyatomi				
Dossier Submitter's Response				
noted				
RAC's response				
Noted. It is not considered however to affect the classification discussion.				

OTHER HAZARDS AND ENDPOINTS – Specific target organ toxicity – Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	13
Comment received				
Part B 4.7.1.1 Repeated dose toxicity oral **Statement from the CLH report:** The changes in (female) body weight and in liver weight observed at doses below 10000 are relatively small, and considered to be not (yet) adverse. **BCS comments:** The unit should be added : The changes in (female) body weight and in liver weight observed at doses below 10000 **mg/kg food** are relatively small, and considered to be not (yet) adverse.				
Dossier Submitter's Response				

noted
RAC's response
Noted. It is not considered however to affect the classification discussion.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	14
Comment received				
Part B 4.7.1.1 Repeated dose toxicity oral **Statement from the CLH report:** Table 19 *Submxillary glands* **BCS comments:** It should read *Subm**a**xillary glands*				
Dossier Submitter's Response				
noted				
RAC's response				
Noted. It is not considered however to affect the classification discussion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	15
Comment received				
Part B 4.7.1.3 Repeated dose toxicity dermal **Statement from the CLH report:** Table 23 Microscopy *Liver* - slight pigmentation in Kupffer cells **BCS comments:** Incidences in males should read 1/5, **1**/5, **1**/5, 0/5 at 0, 250, 500, 1000 mg/kg bw, respectively.				
Dossier Submitter's Response				
Agreed. However, these different incidences do not affect the conclusion on the study or the conclusion regarding the STOT RE classification.				
RAC's response				
Noted. It is not considered however to affect the classification discussion.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	16
Comment received				
Comments are provided on the aquatic bioaccumulation: the BCF study and values have been accepted by the EU Rapporteur evaluation (The Netherlands) and by EFSA: Pencycuron has no bioaccumulative potential **Part B 5.3.1.2 Measured bioaccumulation data** **Statement from the CLH report:** This study has deficiencies: lethal and sublethal effects were not recorded **BCS comments:** BCF studies are performed at concentrations that are not toxic, i.e. at nonlethal and non-sublethal concentrations. The BCF study has been conducted at a concentration of 0.084 ppm (nominal) which is in the range of the $NOEC_{fish}$ = 0.0832 mg/L derived from the ELS test. Consequently, no lethal and no sublethal effects are expected and, as stated in the study report, no abnormal signs of general appearance and behavior for test carp were observed in the aquarium during the experiment.				
Dossier Submitter's Response				

Noted
Please keep in mind that the guideline recommends test concentrations lower than the chronic effect level (factor 10 below the NOEC) or a factor 100 below the asymptotic LC50. The NOEC mentioned is for Oncorhynchus mykiss (rainbow trout) and the BCF study is carried out with carp, a different species with a different sensitivity.
Furthermore, a nominal NOEC means that the actual NOEC could be lower and such values should be used with care.
Finally, the BCF value is not lipid corrected, lipid corrected (4%) this gives a BCF of (see OECD 305, 226 x 0.05/0.04 =) **283**.

RAC's response

The question was discussed in RAC and RAC members have an unanimous opinion: the bioaccumulation study is reasonably reliable and acceptable. Based on the measured fish bioaccumulation pencycuron has no bioaccumulative potential.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	17

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: The growth of fish during the study was not taken into account

BCS comments: The fish weight was measured in the study (see Table 2). As the weight of the fish is not changing much neither during the 28 day exposure period nor during the 14 day elimination period, there is no need to correct the BCF value for growth dilution. Thus, growth is not affecting the validity of the study.

Dossier Submitter's Response

noted

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	18

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: There is a great difference between the concentration of pencycuron found in the two fish for the same time points

BCS comments: The factor between the two BCF values, calculated from the two concentrations, was 1.4 on day 3, 1.3 on day 7, 1.4 on day 14, 1.7 on day 21, and 2.8 on day 28. We do not consider these factors as exceptionally high, especially up to day 21. Even a factor of 2.8 is acceptable, given the high analytical recoveries, indicating that there is no issue in the concentration measurement ("Analytical recoveries of Pencycuron from water and fish were 98% and 80% respectively"). In addition, differences in the concentrations were taken into account by selecting the highest BCF resulting from the concentration measurements. This represents a worst case and fair interpretation of the results. Differences in concentrations do not justify invalidating the study.

B.9.2.5.1a. Residues in carp during 28 days exposure to Pencycuron (Table taken from the DAR).

Day of experiment	3	7	14	21	28	28 + 3	28 + 7	28 +14
BCF individual	136/94	171/136	186/130	192/112	80/226	7/18	< 1	<1
BCF average	115	154	158	152	153	13	< 1	< 1

Dossier Submitter's Response

Thank you for the clarification. We agree that it is good that the highest BCF was chosen to reflect the BCF of this study. It is not clear whether residual values are corrected for recovery (80%). If this, as well as the lipid correction for 4%, is taken into account the **BCF = 339**. And please also see response to comment nr 16.

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	19

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: Identification of metabolites was not performed.

BCS comments: This statement does not seem correct. The study report states that "by cochromatography, 1-(p-chlorobenzyl)-3-(p-hydroxyphenyl) urea as metabolite was detected from carp body (0.07 ppm), but other metabolites were not found". The metabolite identified is metabolite M08 that is also present in the rat (13.4% of oral dose found in urine). However, since the concentration of this metabolite was low, it has a negligible effect on the BCF.

Dossier Submitter's Response

noted

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	20

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: The GC-chromatogram of the standard stock solution shows several degradation products (all hydrophilic).

BCS comments: This statement refers to the GC-chromatogram on the left hand side of Figure 1 of the BCF report. However, this is not a GC-chromatogram of the stock solution used for the BCF test. It is a GC-chromatogram of a reference standard that was used to identify the minor metabolite in fish via co-chromatography (according to the 4th paragraph under Results and Discussion).

Dossier Submitter's Response

noted

RAC's response

Thank you for the clarification

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	21

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: In the chromatogram of the fish, only pencycuron and one (minor) metabolite is

BCS comments: Because the metabolite is minor, it has a negligible effect on the BCF.

Dossier Submitter's Response
noted
RAC's response
Thank you for the clarification.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	22

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: It is not clearly described in the report which concentration for pencycuron in water was taken into account for the calculation of the BCF.

BCS comments: Table 2 of the report shows the measured water concentrations. These measured concentrations were taken into account for BCF calculations for each time point. BCF values were correctly calculated.

Dossier Submitter's Response
noted
RAC's response
Noted

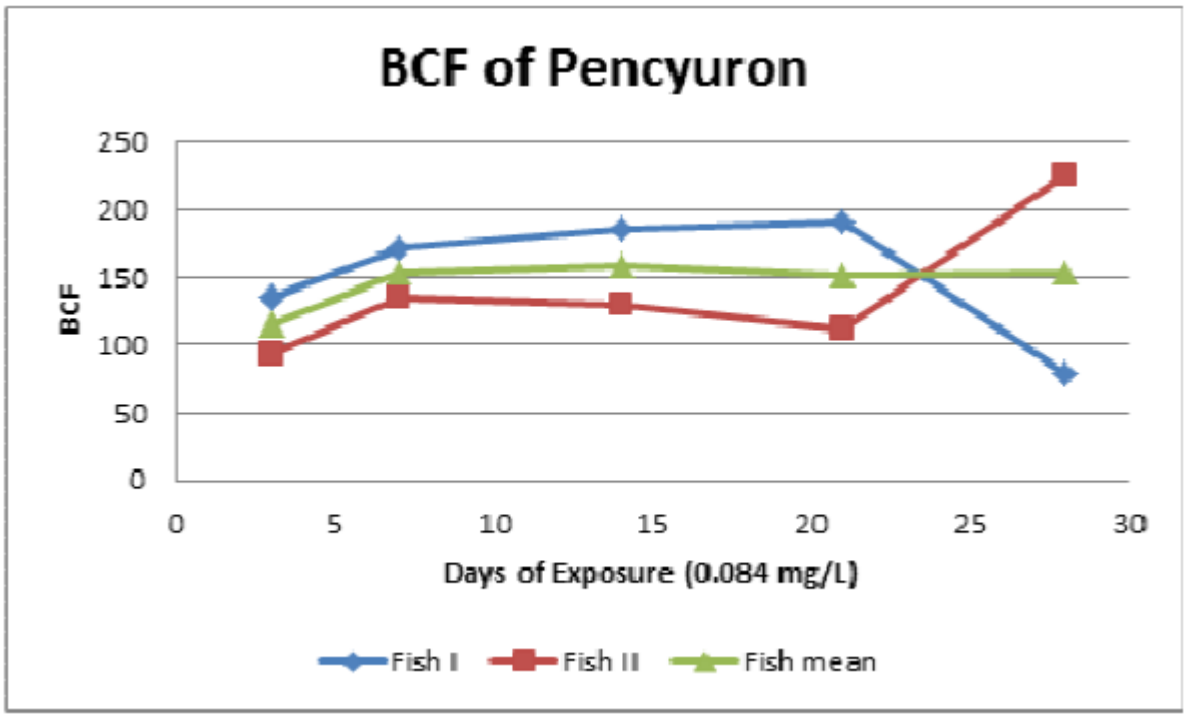
Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	23

Comment received

Part B 5.3.1.2 Measured bioaccumulation data

Statement from the CLH report: Therefore, although the study was well conducted at the time it was performed (1982), the resulting BCF is questionable and the study quality is such that it cannot be used for classification and labelling purposes.

BCS comments: In the opinion of Bayer CropScience, there is no reason to invalidate the study as such. The low BCF value (maximum 226 L/kg) fits well to the fast depuration time. Furthermore, the BCF value of 226 L/kg is a worst case as it refers to the amount of residues found in one single fish, while the BCF in steady state over the last four time points would be around 150 L/kg (see figure below). Thus the BCF of 226 L/kg covers any uncertainties of the study. Repeating the study would not make sense for animal welfare reasons.



It is also possible to standardize the BCF value (226 L/kg) from the study to a lipid content considered to be representative for a broad variety of fish species. The lipid content is given as a % value or as kg/kg bw fish. A 5% lipid content as the basement for standardization was suggested under the REACH Directive. The BCF calculated to a 5% lipid content equals 226 L/kg × 5/4 = 283 L/kg.
The RMS concluded in the DAR that the study and the BCF value are valid ("There are no reasons to consider the BCF factor as not reliable"). The study was also accepted by EFSA. EFSA explicitly stated that "the risk of bioaccumulation in the food chain was considered to be low because pencycuron was rapidly excreted (about 90 % of pencycuron was excreted within 3 days), and after 7 days of depuration the concentration in fish was below the limit of detection (0.01 mg/L)" (EFSA Journal 2010;8(10):1828). Therefore, it is justified to consider that pencycuron does not fulfil the criterion for bioaccumulation potential.

Dossier Submitter's Response

noted

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	24

Comment received

Part B 5.3.2 Summary and discussion of aquatic bioaccumulation

Statement from the CLH report: However, due to significant methodological deficiencies in this study, the BCF value for pencycuron derived in this study is considered not reliable and cannot be used for classification purposes. Pencycuron is considered to fulfil the criterion for bioaccumulation potential according to Regulation EC1272/2008, 2nd ATP, since the log Kow is value is ≥ 4.

BCS comments: In the comments above, BCS addressed the methodological questions and explained that methodological deficiencies are insignificant and do not justify to invalidate the study. This is in agreement with the RMS and EFSA evaluations that accepted the study and the BCF value.
The BCF value can be used for classification purposes, and it is not necessary to use the log Kow criterion. The BCF value supports the EFSA conclusion that "the risk of bioaccumulation in the food chain was considered to be low because pencycuron was rapidly excreted" (EFSA Journal 2010; 8(10):1828).

Dossier Submitter's Response
noted
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
26.05.2014	Germany	Bayer CropScience AG	Company-Manufacturer	25

Comment received

Part B 5.5 Comparison with criteria for environmental hazards (section 5.1-5.4)

Statement from the CLH report:

Aquatic Chronic hazards

it [Pencycuron] fulfils the criterion for bioaccumulation based on a log Kow ≥ 4.

BCS comments: As Pencycuron has a log Kow ≥ 4 a bioconcentration study in fish was triggered. This bioconcentration study has been evaluated by the RMS and EFSA and was considered valid. The BCF value derived from this study is 226 L/kg. As described above this value is reliable and represents a worst case. Thus the trigger of 2000 L/kg is clearly not met and Pencycuron should therefore not be classified as bioaccumulative. In addition, the study also demonstrated a rapid elimination time of the active substance which also underlines the conclusion that Pencycuron has no bioaccumulative potential.

Dossier Submitter's Response
Noted and please remember that the trigger value is not 2000 but 500 L/kg (Regulation EC no 1272/2008).
RAC's response
The measured BCF is under the criterion (283/339 < 500) and the value of Kow=4.0 is the threshold. As the bioaccumulation study looks acceptable after the clarifications, RAC agrees with the statement that pencycuron has no bioaccumulative potential.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2014	Belgium		MemberState	26

Comment received

No aquatic acute toxicity was observed up to the water solubility (L(E)C50>0.3 mg/l). The most sensitive species in chronic studies were fish and invertebrates, with a NOEC in the same order of magnitude (94d NOEC Oncorhynchus mykiss = 0.0832mg/l, 21dNOEC Daphnia magna=0.099.2mg/l). The substance should be considered as not rapidly degradable, so it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic chronic 1, H410. Furthermore, the substance shows potential to bioaccumulate.

In view of the proposed classification and toxicity band for chronic toxicity between 0.01 and 0.1 mg/l, an M-factor for acute toxicity of 1 could be assigned for this non-rapidly degradable substance.

In conclusion: we agree with the proposed environmental classification by RIVM.

Some editorial or/and minor comments:

General remark: if tests are performed according to a guideline or other method, please indicate the method or guideline (number of the guideline).

5.4.1 Acute toxicity to fish:
Rainbow trout study (Dorgerloh, 2001) and Bluegill fish (Dorgerloh, 2001): is there also a control group used? Are validity criteria of the study met?
In the penultimate paragraph another static 96 h acute toxicity with Bluegill sunfish is described. Please, even if it is considered non-reliable, mention the reference of the study, guideline and study

regime.

Chronic toxicity in fish :
The 21 day chronic toxicity study (Grau, 1989) is not the key study but nevertheless it is a bit strange that in this study with Oncorhynchus mykiss (renewal after 7d, mean measured concentrations between 18-157% of nominal) where dosing is almost similar to the acute toxicity study (Grau, 1990), no adverse effects were observed at or below the water solubility, while in the acute study on the same species sublethal effects like irregular swimming, apathy or swimming at the bottom of the vessel were observed at a concentration just below the water solubility. One would therefore have expected that the NOEC would be less than the WS.

Dossier Submitter's Response

Thank you for your support. The replies to the general remarks are addressed below.

1. Hereby the requested information in relation to the acute aquatic toxicity studies

Study performed with	**Guideline study**
Oncorhynchus mykiss (2001)	EPA-FIFRA, 72-1, 1982/1985; OPPTS 850.1075, 1996; EC C.1, 1992; OECD 203
Lepomis macrochirus (2001)	EPA-FIFRA, 72-1, 1982/1985; OPPTS 850.1075, 1996; EC C.1, 1992; OECD 203
Oncorhynchus mykiss (1990)	EPA, 72.1, 1982
Oncorhynchus mykiss (1983)	not reported

2. Acute toxicity to fish

Limit tests at the water solubility of pencycuron of 0.3 mg/L were carried out for both the rainbow trout and bluegill fish studies with the following exposure concentrations: 0, 0 (solvent) and 0.30 mg/L. Substance was dissolved in acetone. It was not specified in the text if validity criteria were met yet both studies were considered acceptable for risk assessment by the DAR rapporteur.

Additional information on the 96-h acute toxicity with bluegill sunfish (from the DAR).

Characteristics of the study

reference	:	Carlisle J.C. and D.J. Roney, 1983	exposure duration	:	96h
year of execution	:	1983	nominal concentrations	:	0, 0 (solvent), 10, 32, 47, 69, 100, 150, 220, 320, 470, and 690 mg./L
GLP statement	:	included, but not signed by auditor	measured concentration	:	Chemical analyses were not performed
guideline	:	not reported	dosing method	:	acetone as solvent
test substance	:	Pencycuron (MONCEREN) Technical, CAS no.66063-05-6, batch no. 2030183	acceptability	:	not acceptable
purity	:	98%	96h-LC50	:	not reliable
species	:	bluegill sunfish	96h-NOEC	:	not reliable

The most important deviations of the study are:

- The acclimation period was very short (5 d instead of 12 d prescribed by the guideline).
- The dissolved oxygen concentration was far below 60% (lowest concentration 1.2 mg/L)
- Actual concentrations of the test substance were not measured.
- Test concentrations were above the water solubility of the test substance.
- There was no clear dose-response relationship between mortality and test concentration

The lowest measured dissolved oxygen concentration was 1.2 mg/L; pH values varied between 6.5 and 7.6, the test temperature was between 17.2°C and 20.9°C and the alkalinity 30 - 32 mg/L. In all dose groups fish showed signs of intoxication with a nonlinear dose-response relationship, which was relatively flat at higher test concentrations indicating that no additional test substance was dissolved at higher test concentrations. The test concentrations are above the water solubility of the test substance (0.3 mg/L). The authors state that the 96h-LC50 and the 96h-NOEC are 127 mg/L and < 10 mg/L, respectively.

3. Chronic toxicity in fish (Grau, 1989)

We sympathise with the comments by the Belgium CA.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2014	Sweden		MemberState	27
Comment received				
We note that the ErC50 and NOErC for algae toxicity of the hydrolytically stable degradation product Pencycuron-BB-amine are expressed as being greater than (>) 8.92 ug/L and we wonder whether there is information to be more specific and to give an exact value or a more precise range for the effect levels. Based on the current data it is uncertain if Pencycuron gives an effect above 8.92 ug/ml that would fulfill the criteria for Acute tox 1 (72 or 96 hr ErC 50 (for algae or other aquatic plants) ≤ 1 mg/l).				
Dossier Submitter's Response				
Noted. The only other threshold values provided in the DAR are (additional to the EC50 values): 72h-E_bC90 and 72h-E_rC90 > 8.92 µg/L. 8.92 ug/L is the highest measured concentration that was tested and at this concentration no EC50 was obtained. 72h-E_bC10 = 2.64 µg/L (1.4 – 4.41) and 72h-E_rC10 = 8.05 µg/L (5.32 – 18.0) We agree that this does not rule out the criteria Acute tox 1, however, based on these results it is not confirmed either.				
RAC's response				
RAC also noted the uncertainty due to the stabile metabolite of M 16 (pencycuron-amine). In addition to the uncertainty of the real ErC values, the ratio of M 16 was only 3.5% based on the applied radioactivity in the water/sediment simulation study, included in the dossier. The newly presented acute toxicity result of Daphnia supports classification for Aquatic Acute 1.				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2014	Germany		MemberState	28
Comment received				
p.79 chapter 5.4 Aquatic toxicity, point 5.4.2.1 Short term toxicity to aquatic invertebrates: additional study not considered in the dossier: reference : Heimbach, F., 1986 year of execution : 1986 GLP statement : yes guideline : OECD 202, 1984 test substance : Pencycuron (tech.), batch no.: 233596031 purity : 96.0% species : water flea (Daphnia magna) water solubility : 0.3 mg a.s./L exposure duration : 48h nominal concentrations : 0, 0 (solvent), 0.032, 0.056, 0.1, 0.18 and 0.32 mg a.s./L dosing method : via acetone as solvent acceptability : acceptable 48h-EC50 (mobility) : 0.27 mg a.s./L 48h-NOEC (mobility) : 0.032 mg a.s./L The following study design was applicable: species : water flea (Daphnia magna) age : < 24h exposure regime : static exposure duration : 48h exposure temperature : 20 ± 1°C				

photoperiod : 8h dark/16h light
type of dilution water : synthetic, prepared by adding salt solutions and vitamins to deionised water

type of test vessel and content: glass beakers; 50 mL
number of replicate test vessels: three
number of animals per test vessel: 10
aeration : no
dosing : 0.1 mL acetone/L as solvent
exposure concentrations : 0, 0 (solvent), 0.032, 0.056, 0.10, 0.18 and 0.32 mg a.s./L
type of observations : daily for immobility and other adverse effects
type of measurements : water temperature, pH, dissolved oxygen
chemical analysis : no

sampling times : at start and end of test (0h and 48h)

Results
All reported concentrations of the test substance are nominal values, because there is no demand for chemical analysis of concentrations according OECD guideline 202 (1984).
The lowest measured dissolved oxygen concentration was 97.5%; pH values varied between 7.9 and 8.0.
In the control and solvent control groups, the number of immobilised animals was ≤ 10%. At 0.056 mg a.s./L and the higher concentrations tested, adverse effects with respect to condition were observed after 48h of exposure. The author stated that the 24h and 48h-EC50 are > 0.32 mg a.s./L and 0.27 mg a.s./L (95% confidence limits 0.2 0.46 mg a.s./L), respectively and that the 48h-NOEC is 0.032 mg a.s./L.

Remark
The reported values for the LC50 and NOEC are based on nominal concentrations. Related to the water solubility of the active ingredient (0.3 mg a.s./L at 20°C) and confirmed by no precipitation of the test substance reported at any test concentration, it must be concluded that the test substance is toxic to Daphnia magna at a level of its aqueous solubility and slightly below.

Acceptability of the test
The test is acceptable. There are several studies for aquatic toxicity with chemical analysis of pencycuron concentrations in the same range (0.032 – 0.32 mg a.s./L), which confirms the stability and bioavailability of the test substance.

Under consideration of this additional acute toxicity study for Daphnia magna with EC50(48h) = 0.27 mg a.s./L, Pencycuron should be classified and labeled as Aquatic acute 1 (H400) and acute M-factor of 1, additionally.

(ECHA note: The following attachment was provided [Attachment 1])

Akute Daphnien Toxizität von Pencycuron.pdf

Dossier Submitter's Response

Thank you for providing us with this additional study.
We agree with the German CA regarding the acceptability of *Daphna magna* study mentioned above.

Regarding the concentrations tested for the two available acute toxicity tests in Dapnia:
Reported in CLH
Hendel, B (2001): 0, 0 (solvent), 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6, and 10.0 mg a.s./L [nominal concentrations] chemical analysis performed,
New study
Heimbach, F (1986): 0, 0 (solvent), 0.032, 0.056, 0.10, 0.18 and 0.32 mg a.s./L [nominal concentrations]

We agree with the proposed classification Acute Toxicity category 1 and M-factor of 1 although a

higher M-factor cannot be excluded because of the absence of information on the actual concentration (see also comment nr. 9).
RAC's response
RAC agrees with the acceptance and inclusion of the newly submitted Daphnia study and with the resulting classification of Aquatic Acute 1 with an M-factor of 1.

ATTACHMENTS RECEIVED:

1. Akute Daphnien Toxizität von Pencycuron, Submitted by Germany on 13.06.2014 [*Please refer to comments 9 and 28*]

2. CLP_Pencycuron_BCS Comments_ECHA, Submitted by Bayer CropScience AG on 26.05.2014 [*The contents of this attachment were copied in comments table above, under the respective hazard categories. Please refer to comment numbers 1-6, 10-25*]