Committee for Risk Assessment

RAC

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: 66063-05-6

CLH-O-0000001412-86-32/F

Adopted

04 December 2014

04 December 2014

CLH-O-0000001412-86-32/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

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

EC number: 266-096-3

CAS number: 66063-05-6

The proposal was submitted by **The Netherlands** and received by the RAC on **9 April 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **29 April 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 June 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Elodie Pasquier**

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

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation; the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 December 2014.** The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

RAC adopted the opinion that **Pencycuron** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	616-220-00-0	Pencycuron (ISO); 1-[(4-chlorophenyl) methyl]-1-cyclopentyl-3-phenylurea	266-096-3	66063-05-6	Aquatic Chronic 1	H410	GHS09	H410		M = 1	
RAC opinion	616-220-00-0	Pencycuron (ISO); 1-[(4-chlorophenyl) methyl]-1-cyclopentyl-3-phenylurea	266-096-3	66063-05-6	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09	H410		M = 1 M = 1	
Resulting Annex VI entry if agreed by COM	616-220-00-0	Pencycuron (ISO); 1-[(4-chlorophenyl) methyl]-1-cyclopentyl-3-phenylurea	266-096-3	66063-05-6	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09	H410		M = 1 M = 1	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal
No classification is proposed by the Dossier Submitter (DS) for physical hazards considering that pencycuron has no explosive properties as shown in an EEC A.14 study. Pencycuron is a solid and has no auto-ignition properties, it is not flammable in contact with water and the molecular structure does not indicate oxidizing properties.

Comments received during public consultation
No specific comments were received.

Assessment and comparison with the classification criteria
RAC supports the proposal of the DS not to classify pencycuron for physical hazards.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal
Acute toxicity: oral
No classification was proposed based on the absence of mortality at the limit dose of 5000 mg/kg in a study on rats compliant with OECD TG 401. Signs of toxicity were observed in 3 males and 1 female (urine and/or anal stain). They recovered within 3 days. One female lost weight between day 7 to 14. In this study, the LD_{50} of pencycuron in rat by oral route exceeded 5000 mg/kg, irrespective of sex.

The DS mentioned that additional oral acute toxicity studies were available on rats, dogs and cats but these studies were not considered acceptable due to deviations from the guidelines and were not further described.

Acute toxicity: inhalation
Rats (5/sex) were exposed (head-nose exposure) to 5.13 mg/L of pencycuron as aerosol (MMAD 5.61 µm) for four hours in a study in accordance to OECD TG 403. No mortality, no clinical signs and no necropsy findings were observed. Decreased body weight gain was observed in males and females on day 3. In this study, the LC_{50} of pencycuron in rat by inhalation exceeded 5.13 mg/L, irrespective of sex.

The DS mentioned that an additional inhalation acute toxicity study was available on rats but this study was not considered acceptable due to limited reporting and was not further described.

Acute toxicity: dermal
Rabbits (5/sex) were exposed to a limit dose of 2000 mg/kg in a study partly compliant with OECD TG 402 (occlusive dressing to maximise the effect). One male died due to a bacterial infection. Lacrimation was observed in one male and one female on day 1. No effects on body weight were observed. In this study, the LD_{50} of pencycuron in rabbit by dermal route exceeded 2000 mg/kg, irrespective of sex.
The DS mentioned that additional dermal acute toxicity studies were available on rats and mice but these studies were not considered acceptable as they were not performed according to guidelines and were not further described.

No classification was proposed by the DS for acute toxicity.

Comments received during public consultation
Industry made some editorial comments on the description of the dermal acute toxicity study.

Assessment and comparison with the classification criteria

Acute toxicity: oral

Based on the data presented, the LD_{50} of pencycuron in rat is above the criteria of 2000 mg/kg, below which classification for acute toxicity by oral route applies according to CLP.

Acute toxicity: inhalation

Although it is noted that the mean particle diameter of the test substance (5.61 µm) is slightly outside the range of OECD TG 403 recommendation (1-4 µm), the study described provides no evidence that the LC_{50} of pencycuron in rats is below the criteria of 5 mg/L triggering classification for acute toxicity by inhalation for aerosols under CLP.

Acute toxicity: dermal

The LD_{50} of pencycuron in rabbit is above the criteria of 2000 mg/kg, below which classification for acute toxicity by dermal route applies according to CLP.

RAC supports no classification for acute toxicity as proposed by the DS.

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

Summary of the Dossier submitter's proposal

None of the findings reported further to single exposure following administration by oral, dermal and inhalation routes indicated a concern for specific target organ toxicity.
No classification was proposed by the DS for STOT SE.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

No acute human data are reported and experimental data on animals do not indicate a target organ toxicity following acute exposure. RAC supports no classification for STOT SE, as proposed by the DS.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

In a study compliant with OECD TG 404, pencycuron (as powder moistened with water) was applied to the skin of three rabbits for 4 hours under semi-occlusive conditions. No irritation was observed at any time point (up to 7 days of observation) in any animal (scores of 0). Pencycuron was not irritating to the rabbit skin.
The DS mentioned that an additional dermal irritation study was available with a 24-hour exposure, but this study was not considered acceptable due to limited reporting and was not further described.
No classification was proposed by the DS for skin corrosion/irritation.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

In the absence of any signs of irritation in a guideline study, pencycuron does not fulfil the criteria for skin irritation under CLP neither in terms of severity of scores nor in terms of irreversibility.
RAC supports no classification for skin corrosion/irritation, as proposed by the DS.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal
In a study compliant with OECD TG 405, pencycuron was instilled into the conjunctival sac of three rabbits. No irritation was observed at any time point (up to 7 days of observation) in any animal (scores of 0). Pencycuron was not irritating to the rabbit eye.
The DS mentioned that an additional eye irritation study was available but this study was not considered acceptable due to limited reporting and was not further described.
No classification was proposed by the DS for eye irritation.

Comments received during public consultation
No specific comments were received.

Assessment and comparison with the classification criteria
In the absence of any signs of irritation in a guideline study, pencycuron does not fulfil the criteria for eye irritation under CLP neither in terms of severity of scores nor in terms of irreversibility.

RAC supports no classification for eye corrosion/irritation, as proposed by the DS.

RAC evaluation of respiratory sensitisation

Summary of the Dossier submitter's proposal
No human or experimental data were available to assess respiratory sensitisation potential and no classification was proposed by the DS for respiratory sensitisation.

Comments received during public consultation
No specific comments were received.

Assessment and comparison with the classification criteria
In the absence of any relevant data, RAC considers that it is not possible to classify pencycuron for respiratory sensitization.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal
In a Guinea Pig Maximization Test (GPMT) compliant with OECD TG 406, pencycuron was injected intradermally to 20 animals at a concentration of 1%. For both topical induction and challenge phases, the test article was dosed at a 25% concentration. Vehicle used was Cremophor EL (a polyethoxylated castor oil) and physiological saline solution. 10% sodium lauryl sulfate (SLS) was used before the dermal induction. Dermal responses were observed in 2/20 (10%) of the test animals. Challenge with vehicle only on the opposite flank of the test animals resulted in dermal responses in 1/20 (5%) of animals. No reaction was observed in control animals (0%).

The DS also mentioned a Buehler test performed using a concentration of 50% pencycuron in ethanol: water (80:20) for both topical induction and challenge. No dermal response was observed in the test animals. The study was however considered unacceptable by the DS due to deviations from the guideline (small number of animals, unclear justification for the choice of vehicle and dose, 24h challenge exposure, no induction exposure in controls).
Based on the negative GPMT, no classification was proposed by the DS for skin sensitisation.

Comments received during public consultation
No specific comments were received.

Assessment and comparison with the classification criteria

Although it is noted that the use of higher topical concentrations should have been investigated, the result of the GPMT test does not fulfil the criteria of 30% of animals with a positive reaction that would indicate a skin sensitisation potential at the doses tested.
Although of limited quality, the Buehler test does not raise a concern regarding a skin sensitising potential.

On the basis of the available information, RAC therefore supports no classification for skin sensitisation.

RAC evaluation of specific target organ toxicity–repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

Subchronic dietary toxicity studies in rats and mice and a 1-year chronic dietary toxicity study in dogs were available. In the oral toxicity studies, the main target organ for pencycuron seen in both rats and mice was the liver. Relative liver weights in male and female rats and mice were significantly increased. This was accompanied by microscopic findings in the liver of males and females consisting of abnormal distribution of chromatin in the nucleus and irregular nucleus size. These histopathological findings were clearly increased at the highest dose in both rats and mice. In the 1-year study in dogs, no histopathological changes were observed in the liver and the differences in liver weight were small and not significant. In the 2-generation study, an effect on the liver (liver weight) in the parents (P0) and an increase in kidney weight in females (P0) were observed.

According to the CLP criteria, for classification as STOT RE, the effects should clearly indicate functional disturbance or morphological changes which are toxicologically relevant. The liver was clearly the main target organ, but the effects seen in both the 90-day toxicity studies in rats and mice were not considered of sufficient severity to justify classification.

A sub-acute dermal toxicity study in rabbits was also available showing no local or systemic effects up to 1000 mg/kg bw/d. There was no information on repeated dose toxicity via inhalation.

No classification was proposed by the DS for STOT RE.

Comments received during public consultation

Bayer had editorial comments on the description of the repeated dose toxicity study that were agreed by DS and were not considered to have an impact on classification decision.

Assessment and comparison with the classification criteria

The main target organ for pencycuron is the liver with effects observed in rabbit by the dermal route and in rat, mouse and dog by the oral route. The effects generally consisted of an increase in liver weights (with males being more sensitive) that was accompanied in some cases by biochemical changes (increase in liver triglyceride content in rabbit or in cytochrome P450 content in dog) and/or by some histopathological changes. At the doses relevant for classification, the effects were as follows:

- In the 21-day rabbit dermal study - increase in triglyceride content in liver in males and brown pigment in hepatocytes in some animals of all exposed groups (from 250 mg/kg bw/d). No clear dose-response was observed for the latter effect and relation to treatment was considered uncertain.
- In the 28-day rat oral study - increase in relative liver weight (magnitude not given) at 100 mg/kg bw/d in males only without histopathological changes.
- In the 28-day mouse oral study - increase in relative liver weight (magnitude not given) in males at 154 mg/kg bw/d. Histopathological changes consisted of foci of cell infiltration and irregular nucleus size but no clear dose-response was observed.

- In both the 90-day rat and mouse oral studies - increase in relative liver weight (magnitude not given) in males only without histopathological changes (minimal change of nuclear polymorphism and abnormal chromatin distribution clearly elevated at doses above classification threshold only).
- In the rat 2-generation study - increase in relative liver weight at 32/49 mg/kg bw/d without histopathological changes.
- No effects in dogs (1-year oral study) or in the 2-year oral studies in rats and mice at doses relevant for classification.

Overall, although the magnitude of the increase in liver weight is not known, the absence of clear and/or severe histopathological findings at doses relevant for classification does not indicate an effect of sufficient severity to justify a classification.

Some effects were also identified in the kidney in rabbit by dermal route and in rat and mouse by oral route. At the doses relevant for classification, the effects were as follows:
- In the 28-day rat oral study - moderate to marked epithelial proliferation of pelvis of one/a few males at 100 mg/kg bw/d (and not at the highest dose) and in one/a few females from 102 mg/kg bw/d.
- In the 28-day mouse oral study - a decrease in relative kidney weight in males and females at the low and the high doses but not at mid-dose (14.5/15.6, 1559/1758, 154/165 mg/kg bw/d, respectively). The low incidence of epithelial proliferation of pelvis at the doses relevant for classification did not clearly indicate a treatment-related effect.
- In the rat 2-generation study, increase in relative kidney weight in F0 females from 4.6 mg/kg bw/d without histopathological changes.
- No effect in rabbit (21-day dermal study), dog (1-year oral study), rat (90-day and 2-year studies) or mouse (90-day and 2-year studies).

Overall, considering the absence of dose-response, the uncertainties of whether the effects were treatment related and the absence of effects at doses relevant for classification in studies with exposure longer than 28 days, kidney effects were not considered as sufficient to justify a classification.

Finally, isolated findings were observed in the following organs at doses relevant for classification:
- Focal distension in testicular tubules in the 21-day rabbit dermal study but incidences did not reveal a clear dose-response. In addition, this finding is considered to be relevant for the discussion of reproductive toxicity classification and not for STOT-RE.
- Increase in relative brain weight in males in the 28-day oral rat study but an effect on brain was not identified in the other studies available and was not accompanied by microscopic findings.
- Decrease in relative weight of thymus and submaxillary glands in the 90-day mouse oral study but no effect was identified in these organs in the other studies available and the effects on weight were not accompanied by microscopic findings.
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Overall, RAC agrees with the DS that these effects are not considered as sufficient to justify a classification as STOT RE.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Pencycuron was negative in all *in vitro* and *in vivo* mutagenicity studies.

Three *in vitro* studies on *Salmonella typimurium* (two point mutation tests and one point mutation/ frame shift/ transition test) were all negative. Three indicator tests: Rec-assays on the bacteria *Bacillus subtilis* and *E. coli* were negative. A point mutation test (reverse mutation assay) and two mitotic gene conversion tests in yeast *Saccharomyces cer.* D777 were negative. Pencycuron did not induce chromosome aberrations in an *in vitro* mammalian chromosome aberration test with human lymphocytes or in an *in vitro* mammalian chromosome aberration test with Chinese hamster lung cell. In an UDS assay in rat hepatocytes, induction of unscheduled DNA

synthesis was not observed and a mammalian gene mutation test at the HGPRT locus in Chinese hamster ovary cells was negative. The three *in vivo* studies, a micronucleus study according to OECD TG 474, and two dominant lethal studies on different mouse strains following the recommendations of the ad hoc chemogenetic committee because OECD TG was not yet available, were all negative.

No classification was proposed by the DS for germ cell mutagenicity.

Comments received during public consultation

The DS agreed with Bayer's comments on the description of the data; however, the comments were not considered to have an impact on classification decision.

Assessment and comparison with the classification criteria

Negative results were obtained in all available mutagenicity tests performed, both *in vitro* and *in vivo* up to the limit dose.

RAC agrees with the DS that classification for mutagenicity is not warranted.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

Two oral chronic toxicity and carcinogenicity studies were available, one in rats and one in mice. In both studies, pencycuron was administrated orally for 104 weeks at doses of 0, 50, 500, and 5000 mg/kg food. The main target organ in rats was the liver . At the highest dose, hepatocellular hypertrophy, nodular hepatocellular hyperplasia and diffuse hepatocellular fatty change were noted and were associated with increased liver weight (relative and absolute). There was no increase in neoplastic lesions, therefore the substance did not show carcinogenic potential in rats. In the mouse study, the liver was also the main target organ. At the highest dose of 5000 mg/kg food, diffuse hepatocellular swelling and degeneration of the liver in males were observed that were significantly increased compared to controls. The body weight gain of males at 5000 mg/kg food was significantly decreased. No increases of neoplastic lesions were found.
No classification was proposed by the DS for carcinogenicity.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

No evidence of carcinogenicity was reported in the rat and mouse 2-year dietary studies.
In particular, no elevation (significant or not) of the incidences in liver tumours (main target organ) were observed in either rat or mouse.
RAC agrees with DS that classification for carcinogenicity is not warranted.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

One extensively described 2-generation study in rats was available, in which no indication of reproduction toxicity was found. In the 21-day dermal repeated dose toxicity study in rats, an increase in focal distension of the tubules of the testes was observed at the highest dose. However, no clear pattern was observed. In addition, such effects were not observed in other repeated dose studies or in the 2-generation study.

Two developmental/teratogenicity studies were available, one performed in rats and the other in rabbits. No treatment-related effects on maternal or litter parameters, including external fetal observations, were found in either of these studies,. No indication of a teratogenic potential of

pencycuron in rats or rabbits was observed. In the 2-generation study, some developmental effects were observed at the highest dose level in the form of reduced body weights. However, the maternal body weight was also reduced at this dose level.
No classification was proposed by the DS for fertility or developmental toxicity.

Comments received during public consultation

Industry provided editorial comments on the description of the rat prenatal development toxicity study.

Assessment and comparison with the classification criteria

Fertility

In a 2-generation guideline study in rats, no effects on fertility were observed.
The decrease in absolute testicular weight in high-dose males was not significant when the relative weight was considered. It was not accompanied by histopathological or functional findings and it was not observed in the the F1 and F2 generations.

In the repeated dose toxicity studies, focal distension in testicular tubules was observed in the 21-day rabbit dermal study in all test groups (0/5, 2/5, 2/5 and 3/5 males exposed to 0, 250, 500 or 1000 mg/kg bw/d with unilateral or bilateral tubular distension). However, incidences did not reveal a clear dose-response and relation to treatment is uncertain. Repeated-dose toxicity performed in the rat, mouse and dog did not reveal effects on the testis or in any male or female reproductive organs.

In the 2-generation study, a significant decrease in absolute and relative ovarian weight was reported in F0 females exposed to 49 and 999 mg/kg bw/d. It was not accompanied by histopathological or functional findings and it was not observed in the the F1 and F2 generations. Besides, no clear dose-response was observed.

Overall, RAC considers that data do not provide evidence that pencycuron induces adverse effects on the reproductive organs or on fertility and no classification is supported for fertility.

Developmental toxicity

No developmental effects were observed in a rabbit prenatal developmental toxicity study.

Visceral and skeletal findings were observed in the rat prenatal developmental toxicity study in the absence of maternal toxicity. Incidences of unossified 7th cervical centrum, incomplete ossification of the 5th metacarpals, delayed ossification of sacrocaudal vertebrae and dilated ureters were within the historical control data (HCD) ranges both on a litter and on a foetal basis and were not considered related to treatment.

The incidence of discontinuous costal cartilage was slightly above the HCD at the high dose on a litter basis only and no dose-response is observed. Because the high dose incidence was only slightly above the incidence in the controls and low dose incidence was also near the upper limit of historical controls, RAC did not consider this finding as treatment-related.

The incidence of renal pelvis dilatation was slightly but clearly above the HCD at the high dose on a litter basis only. Solecki *et al.* (2003) noted that the incidence of dilated renal pelvis was generally greater in fetuses than in pups supporting the idea that these changes are likely to be transient and should be considered as variation. Solecki *et al.* (2003) also concluded with a good agreement score (75%) that it was a variation and not a malformation. The slight increase in incidence of dilated renal pelvis is therefore not considered by RAC as sufficient to justify classification.

The incidence of incomplete ossification of hyoid centrum was at the upper range of historical controls from 200 mg/kg bw/d both on a litter and on a foetal basis and exceeded the HCD at the high dose on a foetal basis. This finding was unanimously considered as a variation in the report of the third workshop on the terminology in developmental toxicology (Solecki, 2001).

Makris *et al.* (2009[1]) confirmed that this finding relates to the ossification status and does not involve an abnormality of the structure. Although it is noted that this delay in ossification is observed without a significant effect on body weight development, this finding is not considered by RAC as sufficiently severe to justify a classification.

An effect on pup weight was observed in the 2-generation study in rats. Whereas there was either no effect on pup body weight at birth (F2b) or a decrease of similar magnitude than maternal body weight decrease (F1a, F1b, F2a), the effect was more pronounced at the end of the lactation period except for F1b.

In F1a, although the decrease in pup body weight on postnatal day (PND) 21 was of higher magnitude that the decrease in maternal body weight (-10% in dams vs. -19/20% in pups), the decrease in maternal body weight indicated some maternal toxicity and it could not be excluded that the effect on pup weight may be secondary to maternal toxicity.

In F2a and F2b, no effect on maternal body weight was observed at the end of the lactation period. The decrease in pup body weight was observed from mid-dose in females and increased with dose, it was also observed at high dose in males. It was noted that the weight of control F2 pups at the end of the lactation period was high compared to control F1 pups. Compared to F1b control pups, there was no decrease in F2 female mid-dose pup weight and the decrease in high dose pups was still present but reduced to 7 to 12%. Historical control data were not available to confirm that F2 control pup weight was unusual high at the end of the lactation period.

No data is available on a possible presence of pencycuron in milk or on a possible impairment of milk quality or quantity. Overal during the lactation period, a progressive decrease in pup body weight (no or slightly decreased body weight at birth, an effect that worsened towards the end of the lactation period) was observed. This suggests that the effect was likely a consequence of a direct exposure of pups via food. The effect therefore indicated that pups were more sensitive to body weight impairment than dams in terms of magnitude of the observed effect. However, the results of the studies did not indicate that the effect on pup body weight occurred at lower doses than the doses also inducing body weight impairment in dams although to a lesser extent.

Overall, RAC considers that the effect of pencycuron on the impairment of pup body weight development during lactation at the highest dose does not justify a classification of pencycuron for developmental toxicity. RAC supports no classification for developmental toxicity.

RAC evaluation of aspiration toxicity

Summary of the Dossier submitter's proposal

The DS did not address classification for aspiration toxicity in the CLH dossier.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

Pencycuron is a solid and classification for aspiration toxicity is not relevant for solid substances according to section 3.10.1.6.2 *bis* of the CLP regulation.
RAC considers that no classification for aspiration toxicity is justified.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Pencycuron is currently not listed in Annex VI of CLP. The DS's proposal for harmonised classification and labelling was Aquatic Chronic 1 (H410) with an M-factor of 1.

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[1] Makris S. *et al*. (2009) Terminology of developmental abnormalities in common laboratory mammals (Version 2). *Reprod Toxicol* **86**(4):227–327

Hydrolytic stability was tested in three studies. The studies showed variable half-life values in the range of 30–289 days at pH 5–9 at environmentally relevant temperatures.

Only one of the studies followed the stability of the degradation products and concluded that the only degradation product (pencycuron-PB-amine, M16) was stable at pH 5 and pH 7. No studies on direct photodegradation in water were available. The potential for photodegradation of pencycuron was investigated by testing light absorption at >295 nm. The DS concluded that photodegradation is not expected for pencycuron therefore photolysis test was not performed.

Ready biodegradability tests were not reported for pencycuron. However, one water/sediment simulation study with two types of aerobic water–sediment systems was included in the CLH report. Average DT_{50} values in the simulation tests – for the whole system covering water and sediment – were 139.0 and 82.6 days and therefore the DS concluded that pencycuron is not rapidly degradable in the aquatic environment according to the CLP regulation as it failed to meet the criterion of >70% degradation in 28 days. Mineralization based on radioactivity was 12% and 22% (after 91 days) in the two systems respectively. The metabolite M16 reached 3.5% of the applied radioactivity in water.

One bioaccumulation test was reported but the DS considered it as not reliable. In lack of experimental results the DS concluded that pencycuron fulfils the criterion for bioaccumulative potential, based on a HPLC-shake flask method test which resulted log K_{ow} values of 4.0 at 25 °C and 4.7 at 20 °C.

All acute toxicity studies of pencycuron on fish (four studies reported), invertebrates (one study) and algae (one study) showed relatively low toxicity and did not lead to classification, because the LC_{50} /L_rC_{50} values are estimated to be higher than 0.3 mg/L, which is the water solubility limit of pencycuron.

The degradation product M16 showed low acute toxicity for the tested fish and crustacean species, but the 72-h static, algae test gave an E_rC_{50} >0.00892 mg/L value (highest nominal concentration).

Based on these results the DS proposed no classification for aquatic acute toxicity.

Chronic toxicity of pencycuron was tested in fish (one sub-chronic study), crustacean (two studies) and algae (one study). The lowest observed NOEC values were in the same range for fish and crustaceans: NOEC (94d) = 0.0832 mg/L for *Oncorhynchus mykiss* (based on swim-up and growth, measured concentrations) and NOEC (21d) = 0.067 mg/L for *Daphnia magna* (based on parental immobility and mean measured concentrations). No toxic effects of pencycuron were observed in the algae study.

Based on these results the DS proposed to classify pencycuron as Aquatic Chronic category 1 with an M-factor of 1.

Comments received during public consultation

Three member states agreed with the proposed environmental classification.

One member state asked for further clarification which was provided by the DS in the RCOM.

One MSCA submitted an additional acute toxicity study on *Daphnia magna*. The study from 1986 showed higher toxicity than the studies included in the report (EC_{50}: 0.20–0.46 mg/L). The DS agreed with the German CA that this study is valid and leads to classification Aquatic Acute 1 with an M-factor 1.

Another MSCA raised a concern about the stabile metabolite M16 and its possible acute toxicity. M16 may be acutely toxic, but not certainly known. since no measured data are available to justify it. On the other hand, new data on Daphnia acute toxicity provided evidence for classification pencycuron as an acutely toxic substance.

One company submitted 10 comments on the bioaccumulation study carried out in fish in 1982. The DS did not take this study into consideration in their original CLH proposal, since it was considered as a non-valid study. The company provided arguments for the acceptable quality of

the study, explaining some of the details, which partly were not agreed by, partly not clear to the DS. After these clarifications, the DS accepted the study as valid. Acceptance and inclusion of the fish bioaccumulation study did not impact the CLH proposal, given that classification of chronic toxicity is not dependent on the bioaccumulation potential if adequate long term toxicity and degradation data are present, as is the case for pencycuron.

Additional references

Heimbach, F. 1986. Akute Toxizität von Pencycuron (techn.) für Wasserflöhe. English title: Acute toxicity of pencycuron to waterflea (Daphnia magna). Bayer AG, Leverkusen. Study No E 320 0016-2.

Makris S. et al. (2009) Terminology of developmental abnormalities in common laboratory mammals (Version 2). Reprod Toxicol 86(4): 227–327.

Solecki R. et al. (2001) Harmonization of rat fetal skeletal terminology and classification. Report of the Third Workshop on the Terminology in Developmental Toxicology. Berlin, 14–16 September 2000. Reprod Toxicol 15: 713–721.

Solecki R. et al. (2003) Harmonization of rat fetal external and visceral terminology and classification. Report of the Fourth Workshop on the Terminology in Developmental Toxicology. Berlin, 18–20 April 2002. Reprod Toxicol 17: 625–637.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excl. confidential information).