Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

pendimethalin (ISO);
N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene

EC Number: 254-938-2
CAS Number: 40487-42-1

CLH-O-0000006863-66-01/F

Adopted

8 October 2020

8 October 2020

CLH-O-0000006863-66-01/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 Regulation (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:

Chemical name: **pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene**

EC Number: **254-938-2**

CAS Number: **40487-42-1**

The proposal was submitted by **the Netherlands** and received by RAC on **8 February 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

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 **15 April 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14 June 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Brendan Murray**

Co-Rapporteur, appointed by RAC: **Kostas Andreou**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **8 October 2020** by **consensus**.

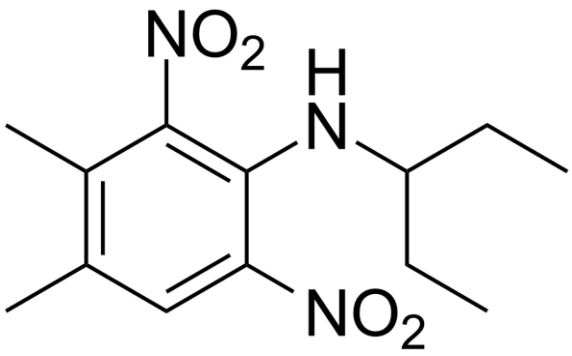
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	609-042-00-X	pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene	254-938-2	40487-42-1	Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H317 H400 H410	GHS07 GHS09 Wng	H317 H410			
Dossier submitters proposal	609-042-00-X	pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene	254-938-2	40487-42-1	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Repr. 2 **Modify** Skin Sens. 1B	**Retain** H317 H400 H410 **Add** H361d	**Retain** GHS07 GHS09 Wng **Add** GHS08	**Retain** H317 H410 **Add** H361d		**Add** M=100 M=10	
RAC opinion	609-042-00-X	pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene	254-938-2	40487-42-1	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Repr. 2 **Remove** Skin Sens. 1	**Retain** H400 H410 **Add** H361d **Remove** H317	**Retain** GSH09 Wng **Add** GHS08 **Remove** GHS07	**Retain** H410 **Add** H361d **Remove** H317		**Add** M=100 M=10	
Resulting Annex VI entry if agreed by COM	609-042-00-X	pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene	254-938-2	40487-42-1	Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H361d H400 H410	GHS08 GSH09 Wng	H361d H410		M=100 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Pendimethalin is a selective herbicide used to control most annual grasses and certain broadleaf weeds in several arable crops. It is registered for various applications which have been evaluated in the context of the Plant Protection Products (PPP) Regulation EC 1107/2009 (EFSA, 2016). Pendimethalin inhibits root and shoot growth and acts by preventing plant cell division and elongation. It is a dinitroaniline herbicide.



Pendimethalin is already in Annex VI of the CLP Regulation (EC) No 1272/2008 with Index Number 609-042-00-X and classified as Skin Sens. 1; H317, Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. The proposed changes to the existing entry are to modify Skin Sens. 1 to Skin Sens. 1B and to add Repr. 2; H361d for developmental effects in rabbits. The proposal for revision is due to the review of existing data presented in the Renewal Assessment Report (RAR) on the renewal of the approval of the active substance in a PPP. The dossier submitter (DS) also proposed to add M-factors.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Summary of data from the dermal sensitisation tests presented in the CLH report

The results of three dermal sensitisation studies were presented by the DS.

Buehler assay (Anonymous, 1985)

In a GLP- and US-EPA Guideline No. 81-6 compliant Buehler study, groups of 12 male Albino Guinea pigs (Hartley) were topically administered pendimethalin (purity 92.2 %). The test substance was applied undiluted. The positive control was 1-chloro-2,4-dinitrobenzene (0.1 % w/v). Pendimethalin was negative for skin sensitisation in this study.

Guinea pig maximisation test 1 (Anonymous, 1995)

In a GLP and OECD TG 406 (1981) compliant study, groups of 15 males were treated with pendimethalin (purity not reported). The test substance was applied at an intradermal induction concentration of 5 % w/v. There was no positive reaction at challenge. Based on this result, technical pendimethalin did not display sensitising capacity in the Guinea pig maximisation test (GPMT) with an intradermal induction using 5 % w/v test material.

Guinea pig maximisation test 2 (Anonymous, 1995)

The final study by Anonymous (1995) was a guideline compliant (US EPA 81-6), GLP, GPMT study using 20 (test) or 10 (control) Dunkin Hartley albino Guinea pigs, treated with pendimethalin (purity not reported). The test substance was applied at an intradermal induction concentration of 10 % w/v. One week later, a 75 % topical induction was applied and on day 21, topical challenge at 10 % and 25 %. Within the 25 % topical challenge group, positive sensitisation reactions (grade 1 erythema) were noted at the challenge sites of eleven animals (55 %), 24 hours after removal of the dressing. Positive dermal reactions were noted to persist in one animal only, 48 hours after removal of dressing. In the case of the 10 % topical challenge dose group, positive sensitisation reactions (grade 1 erythema) were only noted in 2 animals (10 %) 24 hours after patch removal.

Conclusion of the dossier submitter

Based on the results from the two GPMT tests, the DS proposed that pendimethalin should be classified as a skin sensitiser in sub-category 1B.

Comments received during consultation

Comments on the CLH proposal

Three comments in total were provided on skin sensitisation during consultation. No new data was supplied.

All comments were submitted by Member State Competent Authorities (MSCAs). They all supported the proposal to classify pendimethalin as Skin Sens. 1B; H317.

One MSCA noted the choice of a dilution of 5 % for topical induction and topical challenge in the first GPMT study (Study 2, IIA 5.2.6/01 Doc ID 8230) was low considering that pendimethalin is not an irritant to the skin as confirmed by the dilution used for topical induction used in the Buehler test (100 %).

Comments received during ad hoc consultation

As two recent (2005, 2011) mouse local lymph node assay (LLNA) studies had become available after the consultation, and ad hoc consultation was held from 13/07/2020 to 10/08/2020.

Four comments were received; two comments from different industry sources and two from MSCAs.

Both industry comments supported the weight of evidence assessment and agreed that pendimethalin did not warrant classification as a skin sensitiser. In addition, both recognised that the material used in the positive GPMT study from 1995 was of unknown purity with an unknown impurity profile.

The first MSCA acknowledged the new studies but had some reservations around validity. They also noted that the maximum tested concentration in both LLNAs was 50 %. This MSCA was prepared to agree with the removal of skin sensitisation classification if its concerns were

addressed in a final weight of evidence approach. It was clarified by RAC, that there were no validity concerns and that both studies had appropriate positive control tests.

The second MSCA also noted the lack of information regarding the purity or composition of the tested batch in the positive GPMT study. This MSCA noted the higher purity of technical material in both LLNAs compared with the reference specification and concluded that the LLNA studies were not enough to remove the concern for sensitisation. They commented that the difference in outcome of the GPMT study and LLNA studies might be due to a difference in impurity profile and data was lacking regarding the presence of one specific impurity with alerts for skin sensitisation.

New studies on Skin Sensitisation

Background

After the consultation, RAC located two new independent mouse LLNA studies dating from 2005 and 2011. The DS did not report these studies in the CLH report, nor were they assessed as part of the mammalian toxicity data pack for PPP Annex I renewal in 2015.

The first LLNA study (Anonymous, 2005) had previously been evaluated in 2007 by the RMS (Spain) who was originally responsible for the DAR leading to Annex I inclusion under Dir 91/414/EEC in 2003. The assessment in 2007 was part of a tier II evaluation on the technical equivalence of pendimethalin from a new production site (India) and comparing this material to that from the primary notifier that was used in the toxicity studies in support of the original Annex I inclusion.

The second LLNA study (Anonymous, 2011) was submitted by one of the two notifiers responsible for supplying updated documents in the pendimethalin dossier presented for PPP Annex I renewal in 2013. This study was similarly submitted as part of the technical equivalence toxicity support pack (under Volume 4: confidential section for the RAR) for technical pendimethalin manufactured at a second new site, this time based in China. This study was also not incorporated into the main toxicity data pack for the renewal dossier and was not assessed by the RMS in the RAR, or by the DS in the CLH report.

It also appears that EFSA has not evaluated or discussed these LLNA studies. At least two MSCAs have been aware of these studies in respect of technical equivalence and issued statements in support of the use of the two new sources of data on pendimethalin.

Summaries and evaluations of each LLNA study are presented below.

LLNA study 1 (Anonymous, 2005)

Pendimethalin was assessed for skin sensitisation potential in a well conducted LLNA study performed according to GLP and OECD TG 429 (2002). Three groups, each with four female CBA/CaOlaHsD mice, were treated with different concentrations of the test substance. A control group of four mice was treated with the vehicle only.

To determine the highest non-irritant and technically applicable test substance concentration, a non-GLP pre-test was performed in two mice with concentrations of 5, 10, 25 and 50 % (w/v). The treated animals did not show any signs of toxicity or irritation.

Pendimethalin (96.8 % (w/w) pure) was administered by topical (epidermal) application to the dorsal surface of each ear lobe (left and right) at concentrations of 10, 25 and 50 % (w/v) in 4:1 (v/v) acetone:olive oil. The application volume, 25 µL, was spread over the entire dorsal surface of each ear lobe once daily for three consecutive days. A further group of mice was treated with an equivalent volume of the relevant vehicle alone (control animals).

Five days after the first topical application, all mice were administered with 250 µL of 80.6 µCi/mL ^{3}H-methyl thymidine (^{3}HTdR) (corresponding to 20.15 µCi ^{3}HTdR per mouse), by intravenous injection via the tail vein. Approximately five hours after treatment with ^{3}HTdR all mice were euthanised by intraperitoneal injection of sodium thiopental, the draining auricular lymph nodes excised and pooled per group.

Single cell suspensions of pooled lymph node cells were prepared and extracted so that the proliferative response of the cells, determined by the level of ^{3}HTdR incorporation, could be measured in a β-scintillation counter.

Results

All treated animals survived the scheduled study period. In this study, stimulation indices (SI) of 2.42, 1.43 and 1. 71 were determined with pendimethalin at concentrations of 10, 25 and 50 % (w/v) in acetone:olive oil (see table below). The EC3 value could not be calculated, since none of the tested concentrations induced an SI value greater than 3. The validity of the test system was confirmed with the positive control substance, α-Hexylcinnamaldehyde in acetone:olive oil (SI of > 3 at ≥ 10 % concentration).

***Table**: Results of the 2005 mouse LLNA test using different induction concentrations of pendimethalin*

Test item concentration % (w/v)	Group	Measurement DPM	Calculation			Result
			DPM-BG [a)]	number of lymph nodes	DPM per lymph node [b)]	S.I.
---	BG I	0.0	---	---	---	---
---	BG II	0.0	---	---	---	---
---	CG 1	4187.8	4187.8	8	523.5	
10	TG 2	10131.3	10131.3	8	1266.4	**2.42**
25	TG 3	5988.0	5988.0	8	748.5	**1.43**
50	TG 4	7181.0	7181.0	8	897.6	**1.71**

BG = Background
CG = Control Group
TG = Test Group
DPM = Disintegrations per minute

Conclusion

A test substance is regarded as a sensitiser in the LLNA if the exposure to one or more test substance concentrations results in a 3-fold or greater increase in incorporation of ^{3}HTdR relative to concurrent controls. This is indicated by the SI value.

Pendimethalin technical was found not to be a skin sensitiser.

LLNA study 2 (Anonymous, 2011)

This study was performed in a different test facility to that used for the 2005 study. The study director and other personnel were also not affiliated with those of the first LLNA study.

Pendimethalin was assessed for skin sensitisation potential in a well conducted LLNA study performed according to GLP and OECD TG 429 (2010). Three groups, each with five female

CBA/CaOlaHsD mice, were treated with different concentrations of the test substance. A control group of five mice was treated with the vehicle only.

Before the initiation of the preliminary test, a solubility test was performed. The maximum technically applicable concentration of the test substance was found to be 50 % in 4:1 (v/v) acetone:olive oil. To determine the highest non-irritant concentration, a non-GLP pre-test was performed in two mice with a pendimethalin concentration of 50 % (w/v). One further animal was treated with 100 % acetone:olive oil and served as the negative control. Immediately before the first application, approximately 48 hours after the first application, and shortly before sacrifice, the thickness of both ears of all animals was measured. There were no significant differences relative to the control animal. The treated animals did not show any signs of systemic toxicity or irritation at the application sites.

Immediately before the first application, the thickness of both ears of all animals was measured. Pendimethalin (97.7 % (w/w) pure) was administered by topical (epidermal) application to the dorsal surface of each ear lobe (left and right) at concentrations of 12.5, 25 and 50 % (w/v) in 4:1 (v/v) acetone:olive oil. The application volume, 25 µL, was spread over the entire dorsal surface of each ear lobe once daily for three consecutive days. A second measurement of the ear thickness of all animals was carried out approximately 48 hours after the first application. A further group of mice was treated with an equivalent volume of the relevant vehicle alone (control animals).

Five days after the first topical application, all mice were administered with 250 µL of 80 µCi/mL ^{3}H-methyl thymidine (^{3}HTdR) (corresponding to 20 µCi ^{3}HTdR per mouse), by intravenous injection via the tail vein. Approximately five hours after treatment with ^{3}HTdR all mice were sacrificed by cervical dislocation. Shortly before sacrificing the thickness of the ears of all animals was measured for a third time, the draining auricular lymph nodes excised and pooled per animal.

Single cell suspensions of pooled lymph node cells were prepared and extracted so that the proliferative response of the cells, determined by the level of ^{3}HTdR incorporation, could be measured in a β-scintillation counter.

Results

All treated animals survived the scheduled study period and did not exhibit any clinical signs. There were no effects on body weight across any of the test groups relative to the control group. In this study, SI values of 2.1, 1.9 and 2.2 were determined with pendimethalin at concentrations of 12.5, 25 and 50 % (w/v) in acetone:olive oil, (see table below). Individual animal responses did not exceed an SI value of 2.5 in any test group. The EC3 value could not be calculated, since none of the tested concentrations induced an SI value greater than 3.

The validity of the test system was confirmed with the positive control substance, 1 % phenylenediamine in acetone:olive oil. An SI of > 7 and < 15 was reported at several time points throughout the second half of 2011. The most recent reliability check with respect to the main study (December 2011) was in October 2011.

The results of the radioactivity determination were supported by the means of the ear thickness per group, which showed no significant difference compared to the negative control group.

***Table**: Results of the 2011 mouse LLNA test using different induction concentrations of pendimethalin.*

Concentration % (w/v)	Group	Measurement DPM	Data			Result
			DPM-BG	lymph nodes	DPM per lymph node	S.I.
--	BG	14.8	0	--		
0	Control	1 040.8	1 026	10	513	1.0
12.5	TG 01	2 191.8	2 177	10	1 089	2.1
25	TG 02	1 919.4	1 904.6	10	952	1.9
50	TG 03	2 250.8	2 236	10	1 118	2.2

BG = Background
CG = Control Group
TG = Test Group
DPM = Disintegrations per minute

Conclusion of the dossier submitter

A test substance is regarded as a sensitiser in the LLNA if the exposure to one or more test concentrations results in a 3-fold or greater increase in incorporation of ^{3}HTdR relative to concurrent controls. This is indicated by the SI.

Pendimethalin technical was found not to be a skin sensitiser.

Assessment and comparison with the classification criteria

Overall assessment of Skin Sensitisation

The skin sensitisation potential of pendimethalin has been investigated in a total of five studies (see table below), three of which were reported in the RAR of 2015 and in the CLH report by the DS. RAC obtained two newer studies based on the mouse LLNA and performed according to GLP and OECD TG 429. RAC considers the two LLNA studies as acceptable and important in the weight of evidence assessment of the skin sensitising potential of pendimethalin.

***Table**: Summary of all available skin sensitisation studies*

Test material	Type of study	Test system	Dose range	Result	Reference
Pendimethalin 92.2 % (w/w)	Buehler, EPA Guideline No. 81-6 GLP	Dunkin Hartley albino Guinea pigs (males) 12/group	100 % topical induction	Not sensitising Positive control = yes, 1-chloro-2,4-dinitrobenzene (DNCB)	Anonymous, 1985 Annex IIA 5.2.6
Pendimethalin (purity not reported)	GPMT, OECD TG 406 (1981). GLP	Dunkin Hartley albino Guinea pigs (males) 20/group	10 % (w/v) 10, 25 % challenge	**Positive: 25 % challenge (55 % responding, 24 h; 5 % responding, 48 h)**	Anonymous, 1995 Annex IIA 5.2.6

Pendimethalin (purity not reported)	GPMT, OECD TG 406 (1981). GLP	Dunkin Hartley albino Guinea pigs (males) 15/group	5 % (w/v)	Not sensitising	Anonymous, 1995 Annex IIA 5.2.6
Pendimethalin 96.8 % (w/w)	LLNA, OECD TG 429, 2002 GLP	CBA/CaOlaHsD mice 4/group	10, 25, 50 % (w/v) in acetone:olive oil, 4:1 (v/v)	Not sensitising Positive control = yes, α-Hexylcinnamaldehyde (α-HCA)	Anonymous, 2005 Annex IIA 5.2.6
97.7 % (w/w)	LLNA, OECD TG 429, 2010 GLP	CBA/CaOlaHsD mice 5/group	12.5, 25, 50 % (w/v) in acetone:olive oil, 4:1 (v/v)	Not sensitising Positive control = yes, p-phenylenediamine (PPD)	Anonymous, 2011 Annex IIA 5.2.6

Treated animals did not show any signs of toxicity or irritation.

The two LLNA studies (2005, 2011) tested pendimethalin up to 50 % and were both negative. These studies have not been evaluated as part of the main toxicity data pack for Annex I inclusion or renewal of the active substance under the PPP legislation. They were, however, included as supplementary toxicity studies under Volume 4: Confidential section of the DAR/RAR, in support of the technical equivalence of pendimethalin from two new production sources, one based in India, the other in China. A more complete data package for skin sensitisation is now available. The two newer studies are GLP and OECD TG 429 compliant and are validated with appropriate positive controls. The results do not indicate a potential for skin sensitisation of pendimethalin when tested at concentrations ranging from 10, 12.5, 25 and up to 50 % (w/w). The single positive test was in an old GPMT which tested a maximum 10 % concentration of pendimethalin for intradermal induction.

RAC considers that the newer LLNA studies should have a greater weighting than the single positive GPMT study. Both were well conducted with appropriate control data and guideline compliant. The LLNA tests were run up to the maximum solubility limits of pendimethalin in acetone:olive oil. The GPMT from 2005, using an intradermal induction of 10 % is only positive at the 24-hour time point for the 25 % dermal challenge. A single negative LLNA would add uncertainty to the DS proposal for classification. However, taking into account the fact that there are two independent negative LLNA studies carried out in different years by different research laboratories and personnel, RAC considers the studies to support no classification.

Based on the inclusion of the LLNA studies and taking all studies into account in a weight of evidence approach, RAC proposed removal of the existing classification on pendimethalin and concluded that **no classification is warranted for skin sensitisation**

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

A single rat two-generation study (Anonymous, 1990) was briefly described. Limited details were available. Altogether, four generations of litters (F1a, F1b, F2a, F2b) were produced because a

second mating was introduced in each generation. Though the study was performed according to OECD TG 416 (1981), and EPA 83-4 and both were valid at that time, there are several deficiencies to note, including:

- No assessment of sperm parameters.
- No clinical chemistry and haematology.
- Limited oestrous cyclicity data (daily vaginal smear, during mating).
- No sexual maturation parameters were investigated.
- No organ weights from F0 and F1 animals.

Limited data was available for dosing of the active substance. There was no data for females to distinguish between pre-mating, gestation and lactation exposures. Animals (25/sex) were fed pendimethalin (92.6 %) in the diet at concentrations of 0, 500, 2 500, and 5 000 ppm, which corresponded to:

- 0, 30, 150, 296 mg/kg bw/day for males; and
- 0, 39, 195, 388 mg/kg bw/day for females.

General toxicity

There were no significant mortalities related to treatment. Clinical observations were limited to discoloured yellow urine, observed in all treated animals at all dose levels. Maternal toxicity was evident in body weight and feeding parameters when compared with controls:

- Lower bw gain, significant, top dose group (max -20 %).
- Body weight significantly reduced, mid dose (max -9 %) and top dose (max -15 %).
- Reduction in food consumption, mid dose (max -12 %) and top dose (max -17 %).

There were no significant adverse effects at any dose level or in any generation on vaginal smear pattern, time course of mating, performance of mating (males and females), fecundity, or gestation duration. The DS noted a slight non-statistical decrease of the number of pups in the high dose group in both litter groups of both generations.

Conclusion of the dossier submitter

The DS proposed no classification for adverse effects on sexual function and fertility.

Adverse effects on development

The DS described effects from the two-generation rat dietary study (Anonymous, 1990), a rat developmental toxicity study (Anonymous, 1979) and a rabbit developmental toxicity study (Anonymous, 1982).

Two-generation rat study (Anonymous, 1990)

The DS described two effects from a developmental point of view:

i. Relative to controls, there was a slight statistically non-significant decrease in the number of pups in the top dose groups from both litters of both generations (see table below; F1a, F1b, F2a, F2b).

ii. Pup weight was significantly decreased in the mid dose (max -14.26 %) and at the top dose (max -21.3 %) from day 7 in the F1a generation and from day 4 in the F1b generation. In the F2a and F2b generations a decrease in body weight was also observed in the mid- and in the high dose groups, but only at 388 mg/kg bw/day did the reduction exceed 10 %.

***Table**: Mean number of pups from each treatment group (mg/kg bw/day)*

Maternal dose	0	39	195	388
P1 (F1a litter)	15.6	16.1	15.7	14.5
P1 (F1b litter)	15.9	15.1	15.0	14.6
F1 (F2a litter)	14.9	14.5	13.9	11.8
F1 (F2b litter)	15.0	14.2	13.3	12.7

Rat developmental toxicity study (Anonymous, 1979)

A single rat developmental study was briefly described. Limited details were available. Four groups of 33 Sprague-Dawley female rats were mated and dosed with pendimethalin (94.2 % purity) using corn oil as a vehicle. The study was pre-guideline. There are several deficiencies to note including:

- Treatment only during days 6-15 of gestation.
- Uterus weight not reported.
- Foetal sex not determined.
- Individual pup necropsy data incomplete.
- No litter incidence reported.

The dose groups were 0 (controls, pure corn oil only), 125, 250 and 500 mg/kg bw/day. Treatment was by gavage from day 6 through to day 15 of gestation.

There was no significant maternal toxicity.

There was no significant difference in pregnancy rate, mean number of implantations, implantation efficiency, incidence of resorption, mean number of live and dead foetuses, incidence of foetal death, foetal viability, and the mean foetal length and weight of the treated groups when compared to controls. A higher number of corpora lutea were observed when the high dose group (500 mg/kg bw/day) was compared to the control group (15.3 vs 13.76).

Offspring effects

External anomalies

No treatment related external malformations were observed in either the control or treated groups.

Visceral anomalies

Visceral examination revealed hydronephrosis in one mid dose foetus and this was within the historical control data (HCD) from the testing facility. The DS did not consider this isolated incidence to be treatment related. Visceral variations observed in this study included slightly dilated kidneys and ureters but not at the top dose. There was no dose response or treatment related effect.

Skeletal anomalies

Several types of delayed ossification were observed in the study (see table below). Apart from delayed ossification of the extremities, all these ossification variations were comparable to controls. The DS noted there was no HCD available for the incidence of delayed ossification in extremities.

***Table**: Incidence of delayed ossification in extremities*

Concentration (mg/kg bw/day)	**0**	**125**	**250**	**500**
Number of Live foetuses examined	234	242	232	254
Number of litters examined	29	29	28	30
Delayed ossification in extremities Foetal incidence Litter incidence	 6 (2.6 %) 3 (10.3 %)	 3 (1.2 %) 3 (10.3 %)	 13 (5.6 %) 7 (25 %)	 13 (5.1 %) 7 (23.3 %)

The DS concluded there were no significant developmental abnormalities, or signs of maternal toxicity up to the top dose level of 500 mg/kg bw/day.

Rabbit developmental toxicity study (Anonymous, 1982)

In a developmental toxicity study in New Zealand White rabbits, groups of 20 mated females were exposed to pendimethalin at doses of 0, 15, 30 and 60 mg/kg bw/day. The test substance was administered daily by gavage, as a suspension in corn oil from day 6 through 18 of gestation. The dose levels were based on a pilot study using groups exposed to pendimethalin at 31.25, 62.5, 125, 250 and 500 mg/kg bw/day. Doses above 62.5 mg/kg bw/day resulted in unacceptable rabbit mortality (3/5, 5/5, 4/5 at 125, 250 and 500 mg/kg bw/day respectively). The Maximum tolerable dose was established as being less than 125 mg/kg bw/day. There were some deficiencies to note in the main study including:

- Pre-OECD TG 414 study.
- Treatment only during days 6-18 of gestation.
- Food consumption was not reported (only maternal adipsia and anorexia recorded).
- Lack of individual/litter data in the study report.
- Only Alizarin Red staining was performed for skeletal investigations (which only stains the ossified parts of the bones) and no staining for cartilage was conducted.

As regards maternal toxicity, there were no deaths or premature sacrifices that were attributed to treatment. The only clinical signs that were credited to treatment were an increase in the incidence of anorexia and adipsia at 60 mg/kg/day (see table below). Although the incidence of anorexia (based on visual inspection of food hoppers and water bottles) at 60 mg/kg bw/d was twice as high compared to the control it was still below the control incidence in the pilot study. There was no other evidence of maternal toxicity, no effect on maternal body weight for example. There were no necropsy findings among surviving animals attributable to treatment, except for a vague description of a compound-like material found in chest/thoracic cavity, thymus, diaphragm, and/or adipose tissue of the mid- and high dose groups.

***Table:** Summary of maternal findings*

Dose (mg/kg bw/day)	**0**	**15**	**30**	**60**
Anorexia	4/20	4/20	6/20	8/20
Adipsia*	2/20	3/20	2/20	6/20

* lack of thirst

Pregnancy rate, corpora lutea, implantations as well as foetal weights, lengths and size were similar in the control and treated groups, even though a lower incidence of resorptions and higher incidence (statistically non-significant) of foetal viability was observed in the high dose group.

Examination of the rabbit foetuses indicated a slightly greater number of foetal skeletal anomalies. These consisted of:

- "Ribs – less than 12 pairs", which was seen in one foetus from litter 27923 and 3 foetuses from litter 27928, both from the high dose group (60 mg/kg bw/day). It was also observed in one foetus from one litter in the mid dose group (30 mg/kg bw/day). None were observed at 15 mg/kg bw/day nor in the concurrent control group.
- Missing/incomplete vertebrae in the lumbar, sacral and caudal regions; most of the affected foetuses were from litter 27928 from the high dose group.
- A slightly higher foetal incidence of fused/forked ribs at 60 mg/kg bw/day compared with the concurrent controls or the lower dose groups (8 in the high dose, compared with 3, 1 and 1 at 0, 15 and 30 mg/kg bw/day, respectively). The litter incidences of this finding were 2, 1, 1, 3 at 0, 15, 30 and 60 mg/kg bw/day, respectively.
- The foetal incidence of misaligned thoracic vertebral arches and centra was also marginally higher at 60 mg/kg bw/day compared with the concurrent control and lower dose groups. The litter incidences were 9 from 3 litters in the top dose group compared with 6, 2, 3 foetuses from 4, 2 and 3 litters at 0, 15 and 30 mg/kg bw/day, respectively.

According to the RMS and DS, the data presented in the original report was not very detailed. Industry also argued that it was not clear if the "missing" vertebrae were merely unossified or were actually absent; the absence of cartilage staining (staining for cartilage was not common at the time of conduct of the 1982 study) may mean that some of the missing vertebrae were only unossified. The DS acknowledged it was difficult to conclude if the less than twelve pairs of ribs truly reflect rib agenesis as was reported in the HCD, or if it may reflect a lack of ossification. However, there were no other indications of a treatment related effect on foetal skeletal ossification in the study.

No visceral or external effects were noted by the DS.

Conclusion of the dossier submitter

Although the skeletal findings in the top dose mainly occurred in one litter, they were also observed in the mid dose as well as in another litter in the top dose. The findings were considered biologically significant by the DS and the lack of appropriate HCD as well as the limitations of the study together with developmental effects in the absence of clear maternal toxicity only served to reinforce a proposal for classification for developmental toxicity. The DS proposed to classify pendimethalin with **Repr. 2; H361d** (Suspected of damaging the unborn child).

Adverse effects on or via lactation

In the rat two-generation study (Anonymous, 1990), an effect on pup body weight occurred during the lactation period starting from day 7. However, the effect only occurred in the presence of maternal toxicity in the form of reduced body weight (-9 % mid dose, -15 % high dose) reduced body weight gain (-12 % mid dose, -20 % high dose) and reduced food consumption (-12 % mid dose, -17 % high dose). The DS did not consider this effect on pup weight to be sufficient for classification and labelling.

Comments received during consultation

Comments on the CLH proposal

Four comments in total were provided on reproductive toxicity during consultation. No new data was supplied.

Three MSCAs in total commented. They all supported the proposal to classify pendimethalin as Repr. 2; H361d for effects on development citing skeletal anomalies (missing or incomplete vertebrae and/or a decrease in pairs of ribs) as their primary concern.

One MSCA noted that the slight decrease in the number of pups (F1 and F2) at 5 000 ppm in the two-generation study should also be considered in respect of developmental toxicity. The DS elaborated that a slight (statistically non-significant) decrease in the mean number of pups was indeed observed at the high dose level but that there was some maternal toxicity at this dose that also needed to be considered.

There was one comment from a company-manufacturer; they disagreed with classification for reproductive toxicity. The notifier pointed out that the main developmental abnormalities were largely seen in a single high dose litter (rabbit #27928). It was their contention that this litter was clearly an outlier since it displayed multiple malformations and skeletal variations. If the data from this 'atypical' litter were to be excluded, then the foetal and litter incidences of these observations would be similar in all groups. Hence, in their view, there was no treatment related teratogenic effect and classification was not warranted. There was no new information included in their comment. It was previously available and discussed by the RMS in the RAR (2015) on the renewal of the approval of the active substance pendimethalin as a plant protection product. The DS concluded that there was insufficient evidence to exclude the findings in the litter at the top dose level and proposed classification in Category 2.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

There were no indicators of a substance related effect on any of the recorded sexual function and fertility parameters (see table below). There was a slight, statistically non-significant decrease in the number of pups in the top dose group in both litters of both generations, as compared to the control group.

***Table**: Pregnancy and litter data from the rat two-generation study (Anonymous, 1990)*

Dose (mg/kg bw/day)		**0**	**30/39**	**150/195**	**296/388**
P1 (F1a litter)					
Mating index					
Males [%]		92	88	96	88
Females [%]		96	100	100	100
Fertility index [%]					
Males [%]		100	86.4	91.7	95.5
Fecundity index					
Females [%]		100	80	92	92
Number pregnant	[n]	24	20	23	23
Gestation index	[%]	100	100	100	100
Duration of gestation	[days]	22.0	22.1	22.0	22.0
Mean number of pups	[n]	15.6	16.1	15.7	14.5
Mean viability index	[%]	91.1	92.1	94.0	96.1
Sex ratio	[M/F]	47/53	47/53	48/52	48/52

P1 (F1b litter)					
Mating index [%]					
	Males [%]	84	88	100	100
	Females [%]	100	96	100	100
Fertility index [%]					
	Males [%]	95.2	72.7	92.0	100
Fecundity index					
	Females [%]	92	75	92	100
Number pregnant	[n]	23	18	23	25
Gestation index	[%]	100	100	100	100
Duration of gestation	[days]	22.3	22.1	22.0	22.0
Mean number of pups	[n]	15.9	15.1	15.0	14.6
Mean viability index	[%]	94.7	94.1	97.1	97.8
Sex ratio	[M/F]	49/51	53/47	52/48	52/48
F1 (F2a litter)					
Mating index [%]					
	Males [%]	76.0	60.0	70.8	76.0
	Females [%]	100	96	95.8	100
Fertility index [%]					
	Males [%]	94.7	93.3	76.5	84.2
Fecundity index					
	Females [%]	96.0	95.8	87.0	92.0
Number pregnant	[n]				
Gestation index	[%]	95.8	100	100	100
Duration of gestation	[days]	22.0	22.1	22.1	22.3
Mean number of pups	[n]	14.9	14.5	13.9	11.8
Mean viability index	[%]	80.9	76.5	88.5	96.5
Sex ratio	[M/F]	50/50	53/47	52/48	45/55
F1 (F2b litter)					
Mating index [%]					
	Males [%]	91.7	76.0	95.8	96.0
	Females [%]	100	88	100	100
Fertility index [%]					
	Males [%]	95.5	94.7	91.3	95.8
Fecundity index					
	Females [%]	95.8	90.9	91.7	96.0
Number pregnant	[n]				
Gestation index	[%]	95.7	90.0	95.5	95.8
Duration of gestation	[days]	22.1	22.2	22.1	21.9
Mean number of pups	[n]	15.0	14.2	13.3	12.7
Mean viability index	[%]	71.2	67.1	85.3	93.7
Sex ratio	[M/F]	52/48	49/51	50/50	55/45

The DS did not propose classification for adverse effects on sexual function and fertility. RAC supported the DS proposal and **concluded that no classification is warranted for effects on sexual function and fertility**.

Adverse effects on development

Rat developmental toxicity study (Anonymous, 1979)

There was no significant difference in pregnancy rate, mean number of implantations, implantation efficiency, incidence of resorption, mean number of live and dead foetuses, incidence of foetal death, foetal viability, or the mean foetal length and weight of the treated

groups when compared to controls (see table below). A higher number of corpora lutea were observed in the high dose group (500 mg/kg bw/day) relative to controls.

***Table**: Summary of ovarian, uterine and litter data*

Concentration (mg/kg bw/day)		**0**	**125**	**250**	**500**
Pregnancy rate		88	85	88	91
Corpora lutea	[n]	13.76	14.0	14.04	15.13*
Implantations	[n]	12.24	12.86	12.28	12.83
Resorptions	[n]	0.62	0.69	0.39	0.6
Live foetuses	[n]	11.52	12.17	11.89	12.23
Foetal body weight	[g]	4.00	4.08	4.02	4.01

External anomalies

No external malformations were observed in the control or treated groups.

Visceral anomalies

Some visceral effects were noted but they did not exceed the HCD. The incidence of hydronephrosis is considered not to be treatment-related and likewise the incidences of dilated kidneys and ureters was similar to concurrent controls.

Skeletal anomalies

There was no treatment-related decrease in group mean ossification of the forelimbs or hindlimbs in any dose group as compared to controls.

Rat two-generation dietary study (Anonymous, 1990)

The DS noted two effects: (1) a decrease in the number of pups in the top dose groups across two matings of both generations, and (2) decreased post-natal pup weight in the mid and high dose groups.

(i) Decrease in the number of pups

There was no significant effect on the number of pups in the top dose groups. The mean viability index was not affected by treatment and there were no further details available. RAC concludes there is insufficient information to propose classification based on this parameter.

(2) Decreased post-natal pup weight

Parental toxicity manifested itself as lower body weight, lower body weight gain during lactation and lower food consumption compared to controls. Body weight for example was significantly reduced at the mid dose (max -9 %) and top dose (max -15 %) as compared to controls. The decrease in pup body weight was generally between 10-21 % that of the control groups and this can be assumed to be a developmental delay in the presence of some maternal toxicity.

Rabbit developmental toxicity study (Anonymous, 1982)

The results of the main rabbit developmental toxicity study (Anonymous, 1982) indicated an increase in the mean incidence of skeletal anomalies in foetuses in the mid- and high dose groups, consisting of less than twelve pairs of ribs and or missing/incomplete vertebral column.

Table: *Summary of foetal (litter) vertebral and rib findings*

Anomaly	Dose level (mg/kg bw/day)			
	0	**15**	**30**	**60**
No. foetuses examined (litters)	111 (17)	106 (17)	118 (17)	107 (17)
Foetuses (litters) with less than twelve pairs of ribs	0	0	1 (1)	4 (2)[1]
Fused/forked ribs	3 (2)	1 (1)	1 (1)	8 (3)
Malaligned thoracic arches and centra	6 (4)	2(2)	3 (3)	9 (3)
Missing/incomplete vertebrae: F (L) - caudal vertebrae - sacral (incomplete) - lumbar	 0 0 0	 0 0 0	 0 0 1 (1)	 3 (1)[1] 2 (1)[1] 2 (1)[1]

[1] 3/4 foetuses came from one litter (#27928). The observed foetuses with missing/incomplete vertebrae also come from this litter.
F (L): foetal (litter) incidence

As pointed out by the notifier, the main developmental abnormalities were largely seen in a single high dose litter (rabbit #27928). Three of the foetuses with less than twelve pairs of ribs were observed in this one litter. The 2 foetuses with missing/incomplete vertebrae also occurred in this litter. It was the contention by the notifier that this litter was clearly an outlier since it displayed multiple malformations and skeletal variations. If the data from this 'atypical' litter were to be excluded, then the foetal and litter incidences of these observations would be similar in all groups. However, there was a lack of evidence to suggest that this female responded more severely to treatment with pendimethalin than others in the study. In fact, examination of the maternal and litter data for female #27928 showed that maternal body weight, food consumption and water intake were comparable with those of the control females, as were foetal body weights and survival *in utero*. Furthermore, it was noted that the effect was also observed in another litter in the mid dose and not solely confined to the top dose group. Other anomalies of note (incidences increased in the top dose group), included fused/forked ribs and misaligned thoracic vertebral arches and centra.

RAC notes that the developmental toxicity studies are old, and no new data is available. This was recognised back during the first assessments of the first pendimethalin dossier, as admitted by the 67th ECCO meeting of 1998, where it was concluded that a new rabbit study may be required. However, no new study has been performed since the original one; hence, further clarifications of the observed effects are not possible. During the latest EFSA technical peer review (TC 119, 2015) some HCD was discussed that was previously provided for the increased incidence of less than twelve pairs of ribs from the performing laboratory. The HCD described rib agenesis in 4/8 studies, each with a single litter affected. The 2 litters affected in the top dose group (and one in the mid dose group), indicated that the Anonymous (1982) study incidence was outside of the HCD range. The HCD came from 8 studies with New Zealand White rabbits carried out in the same laboratory between 1982-1985. No HCD were provided for missing/incomplete vertebrae. The RMS at the time was not convinced of the robustness of the HCD. The experts concluded there was insufficient evidence to exclude the findings in the litters at the top dose level and RAC concurs with this finding.

As regards co-occurring maternal toxicity, an increased, non-significant incidence of anorexia and adipsia at 60 mg/kg bw/day was noted. However, other general indicators of maternal toxicity, such as effects on body weight parameters or feed intake were not associated with pendimethalin treatment. In fact, there was no clear indication of maternal toxicity even at the

top dose level (60 mg/kg bw/day). There are uncertainties associated with the rabbit developmental toxicity study such as the clustering of effects within litter #27928 or the method of skeletal examination. The skeletons were investigated using a method which only stains the ossified (mineralised) parts of the bones, but not the precursor cartilage model of the bones. The notifier contended that evaluators should be wary of terms indicating agenesis of the skeletal structure. They pointed out that it may in fact be present, just not recognisable due to a lack of staining evidence because of incomplete ossification. This is conjecture. There were no other indications of a treatment related effect on foetal skeletal ossification in the study. RAC recognises the difficulty with interpreting the limited detail that was available to the DS but agrees with the conclusion of the DS that these effects cannot be ignored. **The *classification proposal of Repr. 2 for development is supported by RAC.***

Adverse effects on or via lactation

In the two-generation study in rats an effect on pup body weight occurred during the lactation period starting from day 7. However, the effect only occurred in the presence of maternal toxicity. RAC supports the assessment of the DS noting that clear evidence of an adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk could not be demonstrated. There was a study that showed limited transfer into rat milk but only at low levels of up to 7 mg/kg. It is considered unlikely that rat milk could deliver sufficient quantities of pendimethalin via the lactational route to be responsible for the effect on pup body weight. Classification is therefore not warranted.

In agreement with the DS, RAC concluded that **classification of pendimethalin as Repr. 2; H361d (Suspected of damaging the unborn child) is warranted**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Pendimethalin is a dinitroaniline herbicide used for controlling weeds in urban residential areas and crop fields. Pendimethalin has a current entry in Annex VI of the CLP regulation as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410.

All studies presented in the subsequent sections were carried out according to GLP unless indicated otherwise. For the key studies, references to the study summary are provided as in CLH Report. Reliability indexes (RI) as the Klimisch Score are also presented.

Biodegradation

A valid study (RI = 1) on ready degradability is available according to OECD TG 301B (1992) (CA 7.2.2.1/1). The theoretical carbon dioxide ($ThCO_2$) values were below 10 % $CO_2/ThCO_2$ at the end of the exposure (28 days, 22 ± 2 °C) (CA 7.2.2.1/1).

Three simulation tests in water/sediment systems were available and considered reliable (RI 1 or 2) for classification by the DS. The DT_{50} (20 ± 1 °C) for the whole system ranged from 4.5 to 103 days. Four simulation tests in aerobic soil were also presented and considered reliable (RI 1 or 2) for classification by the DS. The DT_{50} (20 ± 2 °C) for soil ranged from 53.6 to 177.7 days. One simulation study for surface water was presented but was not considered for classification. This was due to uncertainties related to the potential sorption of pendimethalin to the test apparatus and so it was questionable whether ultimate degradation was correctly determined.

Hydrolysis

The hydrolysis of pendimethalin was evaluated in three studies of which two were carried out with the formulations of the active ingredient. No indication on the nature of the substance in the third study was given. Two of the three studies were not carried out under GLP and no guideline is mentioned in any of the studies. However, all studies showed that pendimethalin was stable under hydrolytic conditions at pH levels of 4, 5, 7 and 9 and temperatures of 20, 22, 37 and 50 °C. No limitations were reported for these studies and thus DS considers them reliable but with RI = 2 for classification purposes.

The DS, taking into account the above-mentioned studies, concluded that pendimethalin is considered not rapidly degradable for classification purposes.

Photolysis

Four photolysis studies available and were considered reliable (RI 1 or 2) for assessment by the DS. Photodegradation of pendimethalin expressed as DT_{50} ranged from 1.5 to 3.4 days.

Adsorption to soil

The sorption of pendimethalin to soil was investigated in a study (RI = 2) with four different soils. Freundlich adsorption coefficients K_F of 124 to 367 mL/g were determined corresponding to K_{FOC} values ranging from approximately 9 000 to 12 600 mL/g. The values show that pendimethalin was sorbed very strongly to the soils.

Bioaccumulation

A reliable (RI = 1) laboratory study was available and it was carried out in accordance with OECD TG 305 (1996) (CA 8.2.2.3/05). The study investigated the bioaccumulation potential of pendimethalin to Rainbow trout (*Oncorhynchus mykiss*). All validity criteria specified in OECD TG 305 (1996) were satisfied. The BCF_{KLG} (growth and lipid corrected) was found to be 931 L/kg. A reliable, no guideline mesocosm study (RI = 1) was also available, investigating the bioaccumulation of pendimethalin in fish under realistic exposure conditions in outdoor mesocosm. The mean BCF based on initial nominal concentration in water was 97.3 L/kg.

A third study (RI = 2) was also available and carried out in accordance with OECD TG 305 (1996) on Zebra fish (*Danio rerio*). Due to some deviations from OECD TG 305, the BCF_{KL} (whole fish, lipid corrected) was measured to be 1 179 L/kg wwt and can be considered for acceptable as weight of evidence. Also, a BCF value for the whole fish was reported to be 1 810 L/kg as part of a full life cycle toxicity test (288 d) in a fourth study (CA 8.2.2.2/01). Based on the above-mentioned studies, the DS agrees that there is a potential for species specificity in the bioaccumulation of pendimethalin, but this does not affect classification.

Pendimethalin has a log P_{ow}=5.4, at 20 °C at pH 6.5 (Walter D., 2001), which shows a potential for bioaccumulation.

The DS concluded that pendimethalin has potential to bioaccumulate based on a BCF_{KLG} = 931 L/kg which is greater than 500 L/kg which is the criterion for bioaccumulative substances.

Aquatic Toxicity

Aquatic toxicity tests for both acute and chronic aquatic toxicity are available for all three trophic levels. For acute toxicity, 2 fish studies, 2 invertebrate studies and 7 studies on algae and aquatic plants were available. For chronic toxicity, 3 fish studies, 5 studies on invertebrates and other aquatic organisms and 6 studies on algae and aquatic plants were available. Studies are summarised in the table below for acute and chronic aquatic toxicity.

Table: *Summary of the aquatic toxicity studies taken into consideration for classification purposes (key data are highlighted in* ***bold****).*

Acute toxicity					
Species	**Method**	**Endpoint**	**Toxicity value (mg a.s./L)**	**Klimisch Score (as presented in CLH Report) (RI)**	**Reference**
Fish					
Pimephales promelas	OECD TG 203	LC_{50} (96 h)	> 0.240 mm (Mortality)	1	CA 8.2.1/04
Oncorhynchus mykiss	None guideline	LC_{50} (96 h)	0.196 mm (Mortality)	2	CA 8.2.1/03
Lepomis macrochirus (1)	APHA guideline	LC_{50} (96 h)	0.138 nm	Not assessed by DS	CA 8.2.1/01 & 02
Oncorhynchus mykiss (1)	APHA guideline	LC_{50} (96 h)	0.199 nm	Not assessed by DS	CA 8.2.1/01 & 02
Ictalurus punctatus (1)	APHA guideline	LC_{50} (96 h)	0.418 nm	Not assessed by DS	CA 8.2.1/01 & 02
Cyprinodon Variegatus (1)	APHA guideline	LC_{50} (96 h)	0.707 nm	Not assessed by DS	CA 8.2.1/01 & 02
Invertebrates					
Daphnia magna	OECD TG 202	EC_{50} (48 h)	0.147 mm (Immobility)	1	CA 8.2.4.1-02
Daphnia magna	EEC method C.2.	EC_{50} (48 h)	> 0.701 mg as/L mm (Immobility)	1	CA 8.2.4.1-05/
Algae and aquatic plants					
Selenastrum capricornutum	OECD TG 201 (2006)	E_rC_{50} (72 h)	**0.0093 mm (Growth rate)**	1	CA 8.2.6-02& CA 8.2.6/07
Selenastrum capricornutum	OECD TG 201	E_rC_{50} (72 h)	0.0243 mm (Growth rate)	1	CA, 8.2.6/11
Selenastrum capricornutum	EPA, 1971	E_rC_{50} (72 h)	> 55 µg/L mm	1	CA 8.2.6-03 & 08
Anabaena flos-aquae	EPA 1971	E_yC_{50} (120 h)	> 0.174 mm	1	CA 8.2.6-04
Lemna gibba	OECD TG 221	E_rC_{50} (14 d)	0.022 mm (frond number)	1	CA 8.2.7/01
Lemna gibba	OECD TG 221	E_rC_{50} (7 d)	0.0156 mm (frond number)	1	CA 8.2.8/01
Lemna gibba	Public literature	E_rC_{50} (7 d)	177 µg/L (frond number)	2	CA 8.2.7/03

Chronic toxicity					
Species	**Method**	**Endpoint**	**Toxicity value (mg a.s./L)**	**Klimisch Score (as presented in CLH Report) (R)**	**Reference (as in CLH Report)**
Fish					
Pimephales promelas	US EPA 1971, US EPA 1975	NOEC (288 d)	0.0063 mm (Mortality)	1	CA 8.2.2.2/01
		EC_{10} (288 d)	0.0072 mm (Mortality)		
Danio rerio	OECD TG 210	NOEC (172 d)	0.020 nm (Mortality)	1	CA 8.2.2.2/02
		EC_{10} (172 d)	0.053 nm (Mortality)		
Danio rerio	OECD TG 210	NOEC (184 d)	0.050 nm (Survival, growth and reproduction)	1	CA 8.2.2.2/03
Invertebrates and other aquatic organisms					
Daphnia magna	No Guideline	NOEC (21 d)	0.0145 mm (Reproduction)	2	CA 8.2.5.1-01
Daphnia magna	OECD TG 211 (1998)	NOEC (21 d)	0.0173 mm (Reproduction)	1	CA 8.2.5/01
Chironomus riparius	Draft BBA guideline	NOEC (30 d)	0.082 mm (Emergence)	2	CA 8.2.5.4-01/
Chironomus riparius	BBA guideline proposal (Streloke & Köpp, 1995)	NOEC (28 d)	≥ 0.0011 mm (Emergence)	1	CA 8.2.7/1
Chironomus riparius	OECD TG 218 (draft, Feb. 2004)	NOEC (28 d)	≥173.5 [(2)] sed dw mm (Emergence)	1	CA 8.2.5.4-02
Algae and aquatic plants					
Selenastrum capricornutum	OECD TG 201 (2006)	NOE_rC (72 h)	0.00759 mm (Growth rate)	1	CA 8.2.6-02 & CA 8.2.6/07
		E_rC_{10} (72 h)	0.0028 mm (Growth rate)		
Selenastrum capricornutum	EPA, 1971	NOEC (72 h)	0.003 mm (Growth rate)	1	CA 8.2.6-03 & CA 8.2.6/08
		E_rC_{10} (72 h)	**0.0018 mm (Growth rate)**		
Selenastrum capricornutum	OECD TG 201 (2006)	NOEC (72 h)	0.0041 mm (Growth rate)	1	CA, 8.2.6/11
Anabaena flos-aquae	EPA 1971	NOEC (72 h)	0.174 mm	1	CA 8.2.6-04
Lemna gibba	OECD TG 221 (2006)	E_rC_{10} (14 d)	0.00415 mm (frond number)	1	CA 8.2.7/01 & CA 8.2.7/02
Lemna gibba	OECD TG 221 (draft 2002)	NOEC (7 d)	0.0037 mm (frond number)	1	CA 8.2.8/01
		E_rC_{10} (7 d)	0.0029 mm (frond number)		

1. Studies were available in DAR (1998) and RAR (2015) but were not included in CLH Report. Data from these studies do not impact classification, they were shown in the table for completeness.
2. This is the mean measured concentration value that corresponds to the NOEC value presented by the DS in the CLH Report.

nm= nominal concentrations
mm=measured concentrations

Acute toxicity for fish, invertebrates, algae and aquatic plants were reported. The most conservative endpoints for each trophic level were:

- LC_{50}(96 h) = 0.196 mg a.s./L mean measured concentration for *Oncorhynchus mykiss*,
- EC_{50}(48 h) = 0.147 mg a.s./L nominal concentration for *Daphnia magna,*
- E_rC_{50}(72 h) = 0.0093 mg a.s./L mean measured concentration for *Selenastrium carpricornutum*

and

- E_rC_{50}(7 d) = 0.0156 mg/L mean measured concentration for *Lemna gibba*.

Based on the endpoint for *Selenastrium carpricornutum*, E_rC_{50}(72 h) = 0.0093 mg/L mean measured concentration, the DS proposed that pendimethalin should be classified as Category Acute 1; H400 with an M-factor of 100.

Chronic toxicity for fish, invertebrates (and other aquatic organisms), algae and aquatic plants were reported. The most conservative endpoints for each trophic level were:

- EC_{10} = 0.0072 mg/L mean measured concentration for *Pimephales promelas*,
- NOEC(21 d) = 0.0145 mg/L mean measured concentration for *Daphnia magna,*
- E_rC_{10}(72 h) = 0.0018 mg/L mean measured concentration for *Selenastrum capriconutum*

and

- E_rC_{10}(7 d) = 0.0029 mg/L mean measured concentration for *Lemna gibba*.

Based on the endpoint for *Selenastrium carpricornutum*s, E_rC_{10}(72 h) = 0.0018 mg/L mean measured concentration, the DS proposed that pendimethalin should be classified as Category Chronic 1; H410 with an M-factor of 10, for a not rapidly degradable substance.

Comments received during consultation

Comments were received from three MSs. One of the MSs explicitly supported the DS on the classification proposal. One MS requested some clarifications on certain studies regarding bioaccumulation and BCF values. The other MS requested some clarifications on one chronic fish study, one aquatic plant study and on a fish BCF study. The MS also requested for an assessment of the validity criteria for the algal growth inhibition studies as these were the key studies for classification. Clarifications were provided by the DS for all the points raised by the MSs and can be found in the RCOM document. The validity assessment was performed by the DS, confirming the validity of the studies and thus their reliability for classification purposes. There was no impact on classification from the comments received.

Assessment and comparison with the classification criteria

Degradation

Pendimethalin is considered by the DS to be not readily biodegradable based on a valid study (RI = 1) on ready degradability following OECD TG 301B (1992). The theoretical carbon dioxide ($ThCO_2$) values was < 10 % $CO_2/ThCO_2$ at the end of the exposure (28 days, 22 ± 2 °C). Pendimethalin does not fulfil the criterion for carbon dioxide generation of 60 % of the theoretical maximum. Half-lives (DT_{50}) from simulation tests in water/sediment systems and in aerobic soils were ranges from 4.5 to 103 days and from 53. 6 to 177.7 days, respectively. Pendimethalin was also shown to be stable under hydrolytic conditions at pH levels up to 9 and temperatures up to 50 °C. Consequently, RAC agrees that pendimethalin is to be considered as not rapidly degradable for the purpose of classification and labelling.

Bioaccumulation

Pendimethalin has a lipid-normalised kinetic bioconcentration factor BCF_{KL}= 931 L/kg which is well above the CLP criterion of BCF of ≥ 500 L/kg. It also has a log P_{OW} = 5.4, which is also above the Log K_{ow} ≥ 4 criterion for substances with bioaccumulation potential. Thus, RAC agrees that pendimethalin is bioaccumulative.

Aquatic Toxicity

The most sensitive overall species for **acute** toxicity is algae, *Selenastrium carpricornutum* with an E_rC_{50} (72 h) = 0.0093 mg/L mean measured concentration. RAC agrees with the DS on the use of this value as the basis for the acute classification. Based on this E_rC_{50} value, which is below the 72 or 96 h E_rC_{50} ≤ 1 mg/L CLP criterion, RAC agreed that pendimethalin warrants **classification as Aquatic Acute 1; H400, M = 100** (0.001 < $L(E)C_{50}$ ≤ 0.01 mg/L).

The most sensitive overall species for **chronic** toxicity is also algae, *Selenastrum capriconutum* with an E_rC_{10} (72 h) = 0.0018 mg/L mean measured concentration. RAC agrees with the DS on the use of this value as the basis for the chronic classification. Based on this chronic value, which is below the NOEC or EC_X is ≤ 0.1 mg/L criterion, and the fact that pendimethalin is not rapidly degradable, RAC agreed that pendimethalin warrants **classification as Aquatic Chronic 1; H410, M = 10** (0.001 < NOEC ≤ 0.01 mg/L).

Additional references

Anonymous (2005), Local lymph node assay in mice (LLNA) in mice with Pendimethalin technical

Anonymous (2011), Test for skin sensitization (local lymph node assay - LLNA) with Pendimethalin technical.

ANNEXES:

Annex 1 The 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 RAC (excluding confidential information).

Annex 3 Records of the targeted public consultation following the submission of additional studies on the skin sensitising properties of pendimethalin (ISO).