Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 October 2020

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

Pendimethalin (ISO)

N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine

EC Number: 254-938-2

CAS Number: 40487-42-1

Index Number: 609-042-00-X

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Version number: 2 **Date: February 2019**

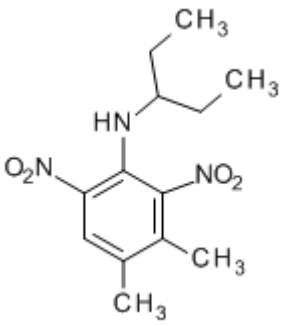
ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON PENDIMETHALIN (ISO); *N*-(1-ETHYLPROPYL)-2,6-DINITRO-3,4-XYLIDENE

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	Pendimethalin
EC number (if available and appropriate)	254-938-2
EC name (if available and appropriate)	Pendimethalin
CAS number (if available)	40487-42-1
Other identity code (if available)	CIPAC No. 357
Molecular formula	$C_{13}H_{19}N_3O_4$
Structural formula	
SMILES notation (if available)	CCC(CC)Nc1c(cc(C)c(C)c1N(=O)(=O))N(=O)(=O)
Molecular weight or molecular weight range	281.3 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not relevant
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant.
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 90%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Pendimethalin	≥ 90%	Skin Sens. 1 (H317)	Acute Tox. 4 (oral)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
CAS 40487-42-1		Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	Skin Sens. 1 (H317) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
1,2-dichloroethane CAS 107-06-2	≤ 1 g/kg	Flam. Liq 2 (H225) Acute Tox. 4 (H302) Skin Irrit. 2 (H315) Eye Irrit. 2 (H319) STOS SE 3 (H335) Carc. 1B (H350)	-	No
Nitroso-pendimethalin	≤ 45 mg/kg	None	-	No

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
None					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Existing and proposed harmonised classification and labelling according to the CLP criteria for pendimethalin

	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 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-xylidine	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-xylidine	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	-	M = 100 M = 10	-
Resulting Annex VI entry if agreed by RAC and COM	609-042-00-X	pendimethalin (ISO); N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine	254-938-2	40487-42-1	Repr. 2 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H361d H317 H400 H410	GHS08 GHS07 GHS09 Wng	H361d H317 H410		M = 100 M = 10	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class assessed in this dossier, Subcategory (1B) added to the current classification.	**Yes**
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Harmonised classification proposed (Cat. 2)	**Yes**
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class assessed in this dossier, No change to existing entry: Aquatic Acute 1 and Aquatic Chronic 1. Proposal for M-factors added.	**Yes**
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

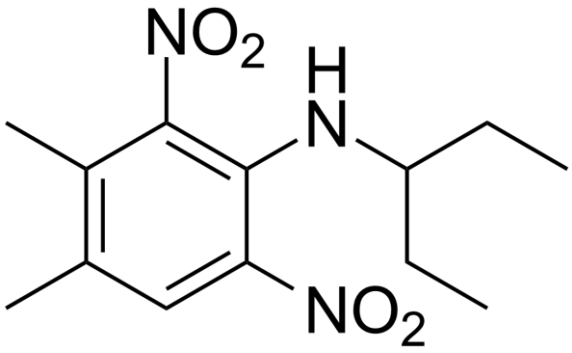
3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Pendimethalin has previously been assessed for harmonised classification by TC C&L. Pendimethalin has an Annex VI entry as Skin Sens. 1 (H317), Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410).

Pendimethalin was previously approved as a plant protection product active substance in 2003. Pendimethalin has recently been re-evaluated and renewed under Regulation (EC) 1107/2009 as of the 1st of September 2017.

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. The EFSA Pesticide Peer Review (PPR) no. 119 of 2015 concluded with a recommendation of classification for developmental toxicity Category 2 based on the Developmental toxicity study in rabbits (Anonymous, 1982).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Change in existing entry due to changes in the criteria/new interpretation of existing data

Further detail on need of action at Community level

After evaluation of the available data in the context of the renewal of pendimethalin a change in the current harmonized classification is proposed. The proposed changes consist of addition of the subcategory 1B to the current classification as skin sensitizer and addition of M-factors to the current classification for aquatic toxicity. In addition, during Pesticide Peer Review Meeting (TC 119) it was concluded that pendimethalin should be classified as Repr. Cat. 2 (H361d) on the basis of a re-evaluation of the existing developmental toxicity studies. Indeed, in the developmental toxicity study in rabbits, increased incidence of less than twelve pairs of ribs and missing/incomplete vertebrae were observed in the absence of maternal toxicity.

5 IDENTIFIED USES

Pendimethalin is used as an herbicide.

6 DATA SOURCES

This CLH report was prepared based on the dossier submitted and the renewal assessment report (RAR) prepared in the context of the renewal evaluation of pendimethalin.

7 PHYSICOCHEMICAL PROPERTIES

The information in Table 8 was derived from the renewal assessment report (RAR) of pendimethalin and the EFSA conclusion. A reference list has been included in Annex I.

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	orange-yellow solid	Kroehl T., 2011	Measured.
Melting/freezing point	56°C	Kroehl T., 2011	Measured.
Boiling point	246-251°C (overlapped by beginning decomposition in this temperature range)	Walter D., 2002	Measured.
Relative density	-		
Vapour pressure	1.39 x 10^{-3} Pa at 20°C 3.34 x 10^{-3} Pa at 25°C	Schneider V., 2001	Measured.
Surface tension	Not required.		
Water solubility	pH 4: 0.260 mg/L at 20°C pH 6: 0.309 mg / l at 20°C pH 9: 0.265 mg / l at 20°C	Walter D., 2000	Measured.
Partition coefficient n-octanol/water	log Pow = 5.4, at 20°C pH 6.5	Walter D., 2001	Measured.

Property	Value	Reference	Comment (e.g. measured or estimated)
Flash point	175.5°C	Loehr S., 2011	Measured.
Flammability	Non-flammable	Loehr S., 2011	Measured.
Explosive properties	Not explosive	Loehr S., 2011	Measured.
Self-ignition temperature	321°C	Loehr S., 2011	Measured.
Oxidising properties	Not oxidising	Loehr S., 2011	Measured.
Granulometry	No data.		
Stability in organic solvents and identity of relevant degradation products	No data.		
Dissociation constant	pKa = 2.8	American Cyanamid, 1992	Measured.
Viscosity	No data.		

8 EVALUATION OF PHYSICAL HAZARDS

Not addressed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

The mammalian toxicity studies of pendimethalin were assessed in the Renewal Assessment Report (February 2012) in the context of the renewal of the approval (Reg. (EU) No. 2017/1114), under Reg. (EC) 1107/2009. All studies were carried out under GLP unless indicated otherwise. The non-GLP studies were conducted prior to GLP. Generally studies were conducted in accordance with OECD test guideline except for the studies for which no OECD Guideline were available at the time of conduct of the study. All studies were considered acceptable (Klimisch Score 1 or 2) unless indicated otherwise in the remarks.

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
ADME study in rats Non-guideline (not available at time of study), Single dose oral (7.3 and 37 mg/kg bw) Royal Hart Wistar rats, 1 or 2 males per group	70% excreted via feces, 20% via urine 24 hours post-treatment	Study not acceptable. Number of animals too low Metabolite distribution reported in study 2 (Doc ID PM 10-757)	Study 1, IIA 5.1.1/01 DocID PD-M-9-94
ADME study in rats Non-guideline (not available at time of study) Single dose, oral (7.3 and 37 mg/kg bw) Royal Hart Wistar rats, 1 or 2 males per group	Identified metabolites in muscle and blood CL202,347, CL99,900, CL113,072 Identified metabolties in fat CL202,347, CL113,066 and CL99,900	See remarks study 1 (PD-M-9-94)	Study 2, IIA 5.1.1/02 DocID PD-M 10-757
ADME study in rat	Absorption 57% (bile + urine)	-	Study 3, UUA

Method	Results	Remarks	Reference
Non-guideline, Single dose, 37 mg/kg bw. Sprague-Dawley rats, 4/rats per group	Predominatly glucuronide conjugates as metabolites.		5.1.1/04 = Doc ID MET 00-004
ADME study in rats OECD 417 Single dose, 35 mg/kg bw Wistar rats 10 males, 10 females/dose	>58% excreted via faeces, <31% via urine. Main metabolites M455H015, M455H026/M455H027, M455H047 / M455H048 and M455H050.	-	Study 4, KCA 5.1.1/1 DocID 2011/1070049
ADME study in rats OECD 417 7.3 and 37 mg/kg bw (oral); 7.3 mg/kg bw (intravenous) Wistar rats, 4 females per dose group	Rapid metabolism (parent not detected at 1hr after administration). Tmax metabolites: 8 hours, T1/2 metabolites: ~3 hours	-	Study 5, KCA 5.1.1/3 DocID 2009/1102210

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Two new ADME studies were performed for the purpose of the renewal. Different nomenclature was used in the new studies to identify the metabolites compared to the old studies. The following table matches the old nomenclature to the new one.

Old studies	New studies		Common Term
CL code	BASF metabolite	Reg No.	
CL 92,553	BAS 455 H/M455H000	900072	Pendimethalin
CL 99,900	M455H001	4108474	Acid metabolite
CL 113,066	-	4108469	
CL 113,071	M455H048	4108076	
CL 113,072	M455H050	4108077	
CL 202,078	-	4110478	
CL 202,345	M455H047	4110479	
CL 202,347	M455H025	4110480	Alcohol metabolite
-	M455H029	4982164	Goat metabolite 6
CL 94,756	M455H033	4295966	Metabolite 7
CL 113,070	M455H046	4108075	
CL 206,925	M455H049	4110490	
CL 202,078	M455H065	4110478	
CL 113,066	M455H066	4108469	
CL 206,923	M455H067	4110489	

CL 113,529	M455H068	4108078	
CL 113,530	M455H069	4108079	

Absorption

Results from the biliary excretion study showed that a minimum of 57% of the total dose was absorbed by rats 48 hours after a single oral dose of 35 mg/kg of [^{14}C] CL 92553. The absorption was estimated by pooling the percent total administered doses in bile, urine and cage wash. Approximately 7% of the total dose was excreted in urine (including cage wash) and 50% of the total dose was excreted in the bile.

Distribution

After oral administration, maximum residual radioactivity levels in the soft tissues were found in liver and kidney, while other tissue values of radioactivity were low. After 96 hours, the residual radioactivity in tissues was almost inexistent. Comparison of the 24-hours levels of residual radioactivity for the tissues showed that the levels were reasonably proportional to the administered dose.

A study on plasmakinetics in rat showed that a liver first pass effect with a very high level of biotransformation during resorption and liver passage can be assumed.

Metabolism

The near-quantitative recovery of the administered radioactivity in the excreta indicated that conversion to respiratory $^{14}CO_2$ could not be a significant factor in pendimethalin metabolism. The metabolites identified in the metabolism of pendimethalin in rats indicate an oxidative pathway of degradation. The 4-methyl group on the benzene ring and the N-alkyl side chain of the dinitro-substituted aniline appeared as the predominant sites for oxidation

The pathways for metabolism of pendimethalin in the rat are a) oxidation of the alkyl side chains (methyl and/or 1-ethylpropyl group), that results in hydroxyl and/or carboxyl groups, b) reduction of one or two nitro groups to amine groups and c) cyclisation to a benzimidazole heterocycle. Alongside these transformation steps, some phase I metabolites are conjugated with glucuronic acid, glucose and sulphate. Frequently, cyclisation also occurs upon insertion of units with more than one carbon atom (e.g. insertion of C2/acetate and C18/stearic acid). The proposed metabolic pathway is included in figures 1 and 2 below.

Excretion

In the radiobalance study of pendimethalin, rats received 37 mg/kg of the radiotracer, 95.6 % of the radioactivity was found in excreta within 96 hours after treatment. About 75 % of the dose had been excreted in faeces and 20 % in urine. Pendimethalin was the major compound in the extract of faeces. Not withstanding, a structure for a minor metabolite isolated from faeces, accounting for 4 % of the radioactivity, was proposed to be N-(1-ethyl-2-propenyl)-2,6-dinitro-3,4-xylidine, on the basis of chemical ionization mass spectral data. The metabolites isolated and identified in urine are CL 99,900, CL 113,066, CL 113,072, CL 202,078, CL 202,345 and CL202,347, but existing at least 23 metabolites in urine. Most of the radioactivity in the urine was contributed by 8 metabolites. Metabolite-4 was the principal in urine, while metabolites 5-, 6-, 8-, 9-, 10- and 12 were considered as major metabolites. At least 16 metabolites were detected in the 6-hour urine, 23 metabolites in the 12-hour urine and 21 in 24-hour urine.

The new study submitted for the renewal confirm the results of the older study with the majority of radioacitivity excreted via faeces (>58%) and urine (<31%). In urine, the presence of M455H050 (CL 113,072) and M455H047/M455H048 (CL 202,345/CL 113,071) confirm the results of the previous studies. New metabolites in faeces M455H015, M455H026, M455H027 and M455H031 were also identified. The metabolite patterns in faeces extract were comparable for both sexes. In urine the metabolite pattern were different for female and male rats to some extent. Both share the presence of metabolites M455H050, M455H047 and M455H048, but metabolites M455H001, M455H017 (iso) and M455H019 were only identified in females whereas M455H056 was only found in urine of males.

Figure 1: Proposed Metabolic Pathway (Part 1) Based on Intact Aniline Structure

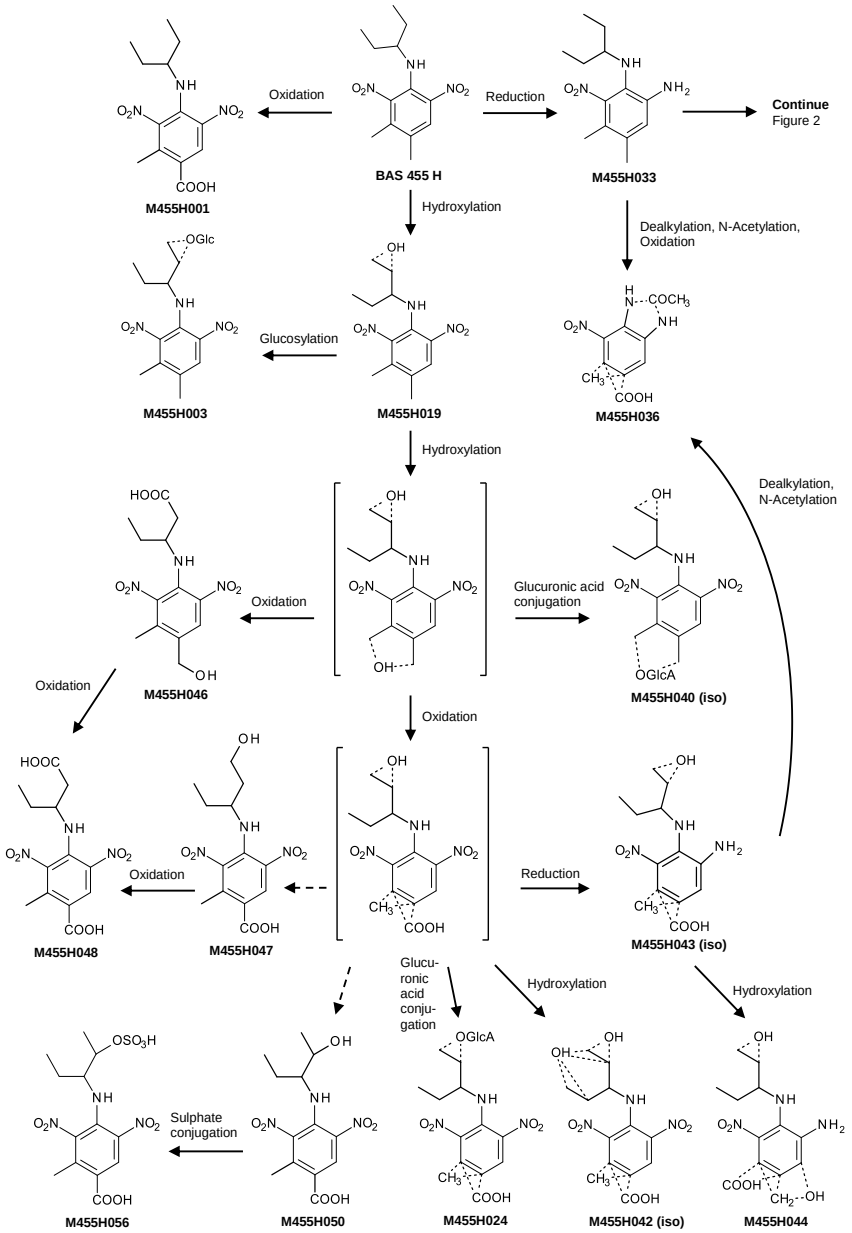
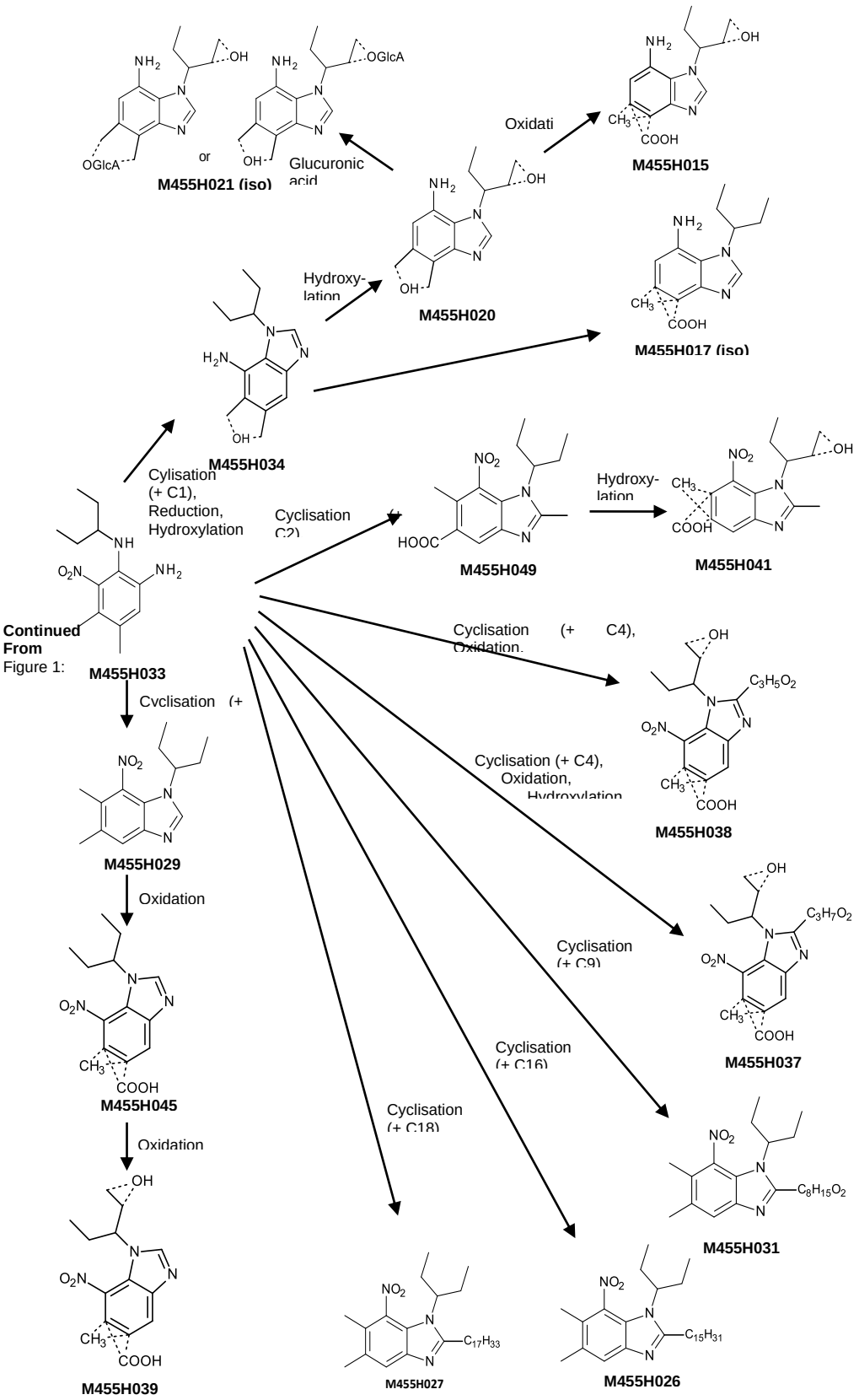


Figure 2: Proposed Metabolic Pathway (Part 2) Based on a Benzimidazole heterocycle



10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

This hazard class has not been evaluated.

10.2 Acute toxicity - dermal route

This hazard class has not been evaluated.

10.3 Acute toxicity - inhalation route

This hazard class has not been evaluated.

10.4 Skin corrosion/irritation

This hazard class has not been evaluated.

10.5 Serious eye damage/eye irritation

This hazard class has not been evaluated.

10.6 Respiratory sensitisation

This hazard class has not been evaluated.

10.7 Skin sensitisation

Table 9: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
EPA 81-6 (Buehler) Deviations: 12 animals were included in the test group instead of 20.	Guinea pigs (Hartley), males, 12/group	Pendimethalin, batch AC 3528-129-1, purity 92.2%	100%, 4x6 cm area, Induction: 3x times per week for 3 weeks (total of 9 treatments), 6 hour exposure Challenge: 6-hr exposure	Negative	Study 1, IIA 5.2.6/01 Doc ID 84-4639A
OECD 406 (Maximisation) Deviations: None	Dunkin Hartey albino Guinea pigs, males,	Pendimethalin, batch MN/05 (purity not reported)	5% (w/v) Intradermal induction followed by epidermal	Negative	Study 2, IIA 5.2.6/01 Doc ID 8230

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results**	**Reference**
	15/group		booster and challenge.		
EPA 81-6 (Maximisation) Deviations: None	Dunkin Hartley Guinea pigs, 20/test group, 10 control	Pendimethalin, batch AO 86/87, purity not reported.	Intradermal induction : 10% Topical induction: 75% Topical challenge: 25% and 10%.	10% challenge: positive 2/20 animals (24 hours) and 0/20 (48 hours). 25% challenge: positive 11/20 animals (24 hours) and 1/20 animals (48 hours).	Study 3, IIA 5.2.6/01 Doc ID PRO 705

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

In a Buehler study groups of 12 male albino Guinea pigs (Hartley) were topically administered the test substance: pendimethalin AC 92,553, Batch No. AC 3528-129-1, purity 92.2% (Doc ID 84-4639A). The test substance was applied undiluted. The positive control was 1-chloro-2,4-dinitrobenzene (0.1% w/v). Animals treated with AC 92,553 were observed to have yellow stained hair around test side. There were no other effects and pendimethalin was conluded not to be a skin sensitiser.

In a Guinea pig Maximisation test groups of 15 males were treated with pendimethalin (batch MN/05, purity not reported) (Doc ID 8230). All animals were observed for clinical signs daily during the entire study period. No toxic symptoms were evident in the guinea pigs of either the control or test group. No death occurred. No animals showed positives reactions at the challenge (5% w/v).

In a second Guinea pig Maximisation test groups of 20 (test) or 10 (control) were treated with pendimethaling (batch AO-86/87) (Doc ID PRO 705). Three intradermal injections using: (a) Freund´s complete adjuvant plus distilled water 1:1; (b) A 10% w/v dilution of the test material (Pendimethalin Technical, lot nº AO-86/87, purity not reported) in arachis oil B.P.; c) A 10% w/v dilution of the test material in a 1:1 preparation of Freund´s complete adjuvant plus distilled water. One week later a 75% topical induction was applied and on day 21 topical challenge at 10% and 25%. For 25% challenge positive sensitization reactions (grade 1 erythema) were noted at the challenge sites of eleven animals (55%) 24 hours after removal of dressing, and persisting in one animal 48 hours after removal of dressing. For the 10% challenge dose positive sensitization reactions (grade 1 erythema) were noted in 2 animals 24 hours after removal of patch. No skin reactions were noted in any of the animals for all the test.

10.7.2 Comparison with the CLP criteria

Pendimethalin was negative in a Buehler assay, but was found to be positive in one of the Guinea pig Maximisation test at a 10% intradermal induction dose in 55% of the animals. In addition, another maximisation test, using a lower induction dose of 5% was negative.

According to Regulation EC No 1272/2008 (CLP) Table 3.4.2.2.3.2 substance should be classified for skin sensitisation (Guinea pig maximisation test) when:

Category 1A:

≥ 30 % responding at ≤ 0,1 % intradermal induction dose or

≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose

Categroy 1B:

≥ 30 % to < 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose or

≥ 30 % responding at > 1 % intradermal induction dose

Based on the response of 55% at 10% intradermal induction pendimethalin should be classified as a skin sensitiser sub-category 1B. The negative results in the other maximisation study at a lower induction dose exclude sub-category 1A.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the results of the studies pendimethalin should be classified as skin sensitiser, cat. 1B (hazard statement H317 - May cause an allergic skin reaction).

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	GPMT, OECD TG 406	Dunkin Hartley albino Guinea pigs	10 % (w/v) 10, 25 %	**Positive: 25 % challenge (55 % responding, 24 h; 5 % responding,**	Anonymous, 1995 Annex IIA

reported)	(1981). GLP	(males) 20/group	challenge	**48 h)**	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**.

10.8 Germ cell mutagenicity

This hazard class has not been evaluated.

10.9 Carcinogenicity

This hazard class has not been evaluated.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 10: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Two generation reproduction study OECD 416 Deviations from current guideline: – No assessment of sperm parameters – No clinical chemistry and hematology – Estrous cyclicity only during mating (daily vaginal smear) – No organ weights of P1 and F1 – Histologic evaluation was performed on F0 and F1 animals: • Males: testis, epididymides, seminal vesicles prostate, pituitary • Females: uterus (both horns entire structure), ovaries, vagina, pituitary – No sexual maturation parameters were investigated but evaluation of developmental hallmarks as eye opening, tooth eruption etc. in single animal data)	Pendimethalin (purity 92.6%) 0, 500, 2500 and 5000 ppm (30, 150, 296 mg/kg bw/day for males and 39, 195 and 388 mg/kg bw/day for females) Start exposure 60 days pre-mating till LD 21	<u>NOAEL:</u> Parental: 30 mg/kg bw/day Reproductive: 150 mg/kg bw/day Offspring: 30 mg/kg bw/day <u>Critical effects:</u> <u>Parental:</u> Reduced body weight gain and food consumption at 2500 ppm and 5000 ppm. <u>Reproductive:</u> No effect on vaginal smear pattern, mating performance, fecundity and fertility. <u>Fetal:</u> Reduced pup weight from day 7 at 2500 ppm and 5000 ppm.	IIA 5.6.1/01 Doc ID CBG/2/90

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Sprague Dawley rats, 25/ sex/dose			

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

One hundred Sprague-Dawley rats of each sex were computer randomized into groups of 25 males and 25 females. The study was conducted in accordance with the OECD Guideline 416 (data 1981) which was valid at the time of the study. For two generations the animals were fed AC 92,553 (92.6 % content) in the diet at concentrations 0, 500, 2500, and 5000 ppm, which correspond to 30, 150, 296 mg/kg bw/day for males (M) and 39, 195, 388 mg/kg bw/day for females (F). Following 60 days of treatment, males and females of P1 generation were paired for mating (within dose groups) to produce F1a generation. After 10 days of rest, mating was repeated again to produce F1b generation. At one-hundred days of age males and females of F1 generation were paired to produce F2a generation, and week later were paired again to produce F2b generation. Pairings were always within dose level groups and the females of generation were allowed to litter and rear the next generation to weaning.

There were no significant mortalities either in the P1 and F1 generation related to treatment. Discoloured yellow urine was observed in all treated animals at all dose levels. Yellow fur staining was also observed, mainly in the F1 generation animals in the 296(M)-388(F) mg/kg bw/day dose level (fed 5000 ppm), and to a lesser degree in those of the 150(M)-195(F) mg/kg bw/day dose level (fed 2500 ppm). There were no other treatment-related changes in clinical condition. Lower body weight gain was statistically significant in the animals fed 5000 ppm [296(M)-388(F) mg/kg bw/day] (max-20%), and to a lesser degree in those of 2500 ppm group [150(M)-195(F) mg/kg bw/day] (max -12%). Body weight was significantly reduced at 2500 ppm (max -9%) and 5000 ppm (max -15%).Reduction in food consumption was also related to dose level, being more remarkable in the 5000 ppm group (max -17%) than in the 2500 ppm dose level (max -12%).

There were no significant adverse effect at any dose level on vaginal smear pattern, time-course of mating, performance of mating (males and females), fecundity and fertility in either generation, neither on gestation duration, or outcome of pregnancy.

10.10.3 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2, classification for effects on fertility is based on:

Category 1A:
Known human reproductive toxicant
Category 1B:
Presumed human reproductive toxicant largely based on data from animal studies
— clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or
— the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects
Category 2:
Suspected human reproductive toxicant

— some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility and
— where the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).
— the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

No effects on vaginal smear pattern, time-course of mating, performance of mating (males and females), fecundity and fertility was observed and therefore no classification is needed.

10.10.4 Adverse effects on development

Table 11: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Two generation reproduction study OECD 416 Deviations from current guideline: – No assessment of sperm parameters – No clinical chemistry and hematology – Estrous cyclicity only during mating (daily vaginal smear) – No organ weights of P1 and F1 – Histologic evaluation was performed on F0 and F1 animals: • Males: testis, epididymides, seminal vesicles prostate, pituitary • Females: uterus (both horns entire structure), ovaries, vagina, pituitary – No sexual maturation parameters were investigated but evaluation of developmental hallmarks as eye opening, tooth eruption etc. in single animal	Pendimethalin (purity 92.6%) 0, 500, 2500 and 5000 ppm (30, 150, 296 mg/kg bw/day for males and 39, 195 and 388 mg/kg bw/day for females) Start exposure 60 days pre-mating till LD 21	<u>NOAEL:</u> Parental: 30 mg/kg bw/day Reproductive: 150 mg/kg bw/day Offspring: 30 mg/kg bw/day <u>Critical effects:</u> <u>Parental:</u> Reduced body weight gain and food consumption at 2500 ppm and 5000 ppm. <u>Fetal:</u> Reduced pup weight from day 7 at 2500 ppm and 5000 ppm. Slight non-statistical decrease in the number of pups (F1 and F2) at 5000 ppm.	IIA 5.6.1/01 Doc ID CBG/2/90

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
data) Sprague Dawly rats, 25/ sex/dose			
Developmental toxicity study No guideline reported (generally in line with OECD 414) Deviations from the current OECD guideline were: - Treatment during day 6-15 of gestation - Uterus weight not reported - Foetal sex not determined - 1/3 visceral, 2/3 skeletal - No special skull investigations - Individual pup necropsy data incomplete - No litter incidence reported in study report, but was included in an addendum (Doc ID PN-902-007 (1996)). Sprague-Dawley female rats 25 pregnant females/group	Pendimethalin (batch 1984-79-3, purity 94.2%) 0, 125, 250 and 500 mg/kg bw/day GD6-15	NOAEL: Maternal toxicity: 500 mg/kg bw/day Developmental toxicity: 500 mg/kg bw Critical effects: Maternal: No adverse effects up to 500 mg/kg bw/day. Developmental: No adverse effects up to 500 mg/kg bw/day. Slight non-statistical increase in delayed ossification was not considered treatment related.	IIA 5.6.2/01 Doc ID 362-115
Developmental toxicity study No guideline reported (generally in line with OECD 414) Deviations from current guideline: - Treatment during GD6-18 - Age of animals missing - Food consumption not reported (only mention of maternal adipsia and	Pendimethalin (92.3%) 0, 15, 30 and 60 mg/kg bw/day. GD6-18	NOAEL: Maternal: 60 mg/kg bw/day Developmental: 30 mg/kg bw/day Critical effects: Maternal: No adverse findings up to 60 mg/kg bw/day Developmental:	IIA 5.6.2/02 Doc ID 362-164

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
anorexia) - 1/3 visceral, 2/3 skeletal evaluation - lack of individual/litter data New Zealand White rabbits 20/group		Increased incidence of less than twelve pairs of ribs and missing/incomplete vertebrae at 60 mg/kg bw/day.	

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

In the two-generation study one hundred Sprague-Dawley rats of each sex were computer randomized into groups of 25 males and 25 females (Doc ID CBG/2/90. The study was conducted in accordance with the OECD Guideline 416 (data 1981) which was valid at the time of the study. For two generations the animals were fed AC 92,553 (92.6 % content) in the diet at concentrations 0, 500, 2500, and 5000 ppm, which correspond to 30, 150, 296 mg/kg bw/day for males (M) and 39, 195, 388 mg/kg bw/day for females (F). Following 60 days of treatment, males and females of P1 generation were paired for mating (within dose groups) to produce F1a generation. After 10 days of rest, mating was repeated again to produce F1b generation. At one-hundred days of age males and females of F1 generation were paired to produce F2a generation, and week later were paired again to produce F2b generation. Pairings were always within dose level groups and the females of generation were allowed to litter and rear the next generation to weaning.

There were no significant mortalities either in the P1 and F1 generation related to treatment. Discoloured yellow urine was observed in all treated animals at all dose levels. Yellow fur staining was also observed, mainly in the F1 generation animals in the 296(M)-388(F) mg/kg bw/day dose level (fed 5000 ppm), and to a lesser degree in those of the 150(M)-195(F) mg/kg bw/day dose level (fed 2500 ppm). There were no other treatment-related changes in clinical condition. Lower body weight gain was statistically significant in the animals fed 5000 ppm [296(M)-388(F) mg/kg bw/day] (max-20%), and to a lesser degree in those of 2500 ppm group [150(M)-195(F) mg/kg bw/day] (max -12%). Body weight was significantly reduced at 2500 ppm (max -9%) and 5000 ppm (max -15%). Reduction in food consumption was also related to dose level, being more remarkable in the 5000 ppm group (max -17%) than in the 2500 ppm dose level (max -12%).

There was a slight non-statistical decrease of the number of pups in the group administered 5000 ppm in both litters of both generations, as compared to the control [Table 10.10.5-1]. This effect only occurred in the presence of maternal toxicity.

Pup weight was significantly decreased at 2500 ppm (max -14.26%) and at 5000 ppm (max -21.3%) from day 7 in the F1a generation and from day 4 in the F1b generation. In the F2a

and F2b generation a decrease in body weight was also observed at 2500 ppm and at 5000 ppm, but only at 5000 ppm did the reduction exceed 10%.

Table 10.10.5-1: Number of pups

Generation	0	500	2500	5000
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

In a rat developmental toxicity study four group of 33 Sprague-Dawley female rats were mated with males (Doc ID 362-115). The test product (94.2 % purity, lot nº 1984-79-3) was orally administered by intubation, using corn oil as a vehicle for the suspension, at dosage levels of 0 (controls, pure corn oil only), 125, 250 and 500 mg/kg bw/day, respectively, from day 6 through day 15 of gestation. The study was carried prio to an OECD guideline. The main deviations from the current OECD Guideline were: treatment during GD6-15, uterus weight was not reported, foetal sex was not determined, 1/3 of the pups were used for visceral examination and 2/3 for skeletal examination and no special skull invesigations were conducted.

There were no significant differences when maternal body weight. There was a significantly higher maternal food consumption on day 20. Increased incidences of urine staining were observed during the treatment (GD6-15, 12.5% at 250 mg/kg bw/day and 39.4% at 500 mg/kg bw/day) and post-treatment (GD16-20, 15.6% at 250 mg/kg bw/day and 54.6% at 500 mg/kg bw/day). Increased incidence of yellow body fat was observed at all dose levels. These effects can be attributed to the physical properties of the test material.

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 were compared to controls. A higher number of corpora lutea was observed when the high dose group (500 mg/kg bw/day) was compared to the control group (15.3 vs 13.76).

No external malformations were observed in the control or treated groups. Visceral examination revealed hydronephrosis in one mid-dose fetus which was within historical control range and the effect did not occur in the high dose group. Historicol control data from the testing facility indicate that the fetal incidence of hydronephrosis (renal pelvic cavitation) in control litters ranges from 0.0% to 1.8% (mean 0.76%) and the litter incidence ranges from 0.0% to 8.0% (mean 4.08%). The historical control data was obtained from 5 studies with Sprague-Dawley rats carried out between 1981-1983 in the same laboratory.

Slight dilated kidney was increased at 125 mg/kg bw/day but did not occur in the mid and high dose group and thereofore was not considered treatment related. An increase in delayed ossification of the extremities was observed in mid and high dose group compared to controls (Table 12). Statistical comparison of the fetal and litter incidences indicate however that the differences from control were not statistically significant. Moreover, no statistically significant linear trend was observed when the data were analyzed by the Cochran-Armitage test, indicating the lack of a dose-response. In addition, there was no treatment-related decrease in group mean ossification of the forelimbs or hindlimbs in any dose group as compared to controls. The mean numbers of ossifications centers in the forelimb were 11.2, 11.4, 11.1 and 11.2 centers at 0, 125, 250 and 500 mg/kg bw/day, respectively. Similarly, the mean ossification sites in the hindlimb were 9.0, 9.0, 8.9 and 9.1 centers, respectively. The historical control data indicate a number of ossification centers in the forelimb in the range of 5.67 to 11.9 (mean 7.86) and in the hindlimb

of 5.62-10.67 (mean 7.67). The number of ossification centers in controls was obtained from a total of 3978 Sprague-Dawley foetuses from 479 litters. The dates of these historical control studies was not reported. No historical control data is available for the lagging ossicifcation in extremities.

Overall, it was concluded that the slight increase in the incidence of delayed ossification were not treatment-related.

Table 12:**:** 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				
Fetal incidence	6 (2.6%)	3 (1.2%)	13 (5.6%)	13 (5.1%)
Litter incidence	3 (10.3%)	3 (10.3%)	7 (25%)	7 (23.3%)

In a developmental toxicity study in New Zealand White rabbits groups of 20 females were exposed to 0, 15, 30 and 60 mg/kg bw/day (Doc ID 362-164). The test product was administered daily by gavage, at the aforementioned dose levels, as a suspension in corn oil from day 6 through 18 of the gestation. The dose levels were based on a pilot study using dose levels of 31.25, 62.5, 125, 250 and 500 mg/kg bw/day.

The only maternal finding that was observed in the study was an increased incidence of anorexia at 60 mg/kg bw/day (Table 13). However, the incidence was still below the control incidence of the pilot study (3/5, 60%). In addition, there was no significant effect on mean maternal body weight. It was therefore concluded that there was no sign of maternal toxicity in the study.

Table 13: Summary of maternal findings

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

Pregnancy rate, corpora lutea, implantations as well as foetal weights, lengths and size were similar in the control and treated groups. An increase in the mean incidence of skeletal anomalies unique to foetuses in the mid- and high- dose groups, consisting of less than twelve pairs of ribs and or missing/incomplete vertebral column, was observed [Table 14]. The observed increase in missing/incomplete vertebrae at 60 mg/kg bw/day all occurred in one litter group. The observed increase of less than twelve pairs of ribs occurred in 2 litters at the high dose, which included the litter with missing/incomplete vertebrae.

The terminology used in the study report and the available historical control data differ. There appears to be no historical control data available for missing/incomplete nor missing/incomplete vertebrae. The term less than twelve ribs is not used in the historical control data base, but it does report and incidence of rib agenesis in 1 foetus in four out of eight studies, indicating that the incidence is outside of the historical control range. The historical control data came from 8 studies with New-Zealand White rabbits carried out in the same lab between 1982-1985. Additional historical control data was provided from literature on the fetal incidence of missing

ribs which is shown in Table 15. These historical control data are from 1994 to 2010 and are therefore much more recent than when the study was carried out in 1981. No information is available in the public literature data on litter incidence. In the pendimethalin study the fetal incidence of 4 out of 107 examined (3.7%), which is above the HCD.

Three of the foetuses with less than twelve pairs of ribs were observed in one litter (litter 27928). The 2 foetuses with missing/incomplete vertebrae also occurred in this litter. It was argued by the applicant that if this litter would be excluded that the remaining incidence of less than twelve pairs of ribs would be within historical control data and that the effect was therefore not treatment related. However, during the pesticide peer review meeting if was considered that if the effect was incidential due to a genetic aetiology than it is expected that this would have been reflected in the historical control data as well. Furthermore, it was noted that the effect was also observed in another litter in the mid-dose as well as in the top-dose. Therefore it was concluded that there was not sufficient evidence to exclude the finding and that it should be considered as treatment related.

The study was conducted prior to an OECD guideline, but was mainly in accordance with OECD 414. The main deviations were the exposure duration (GD6-18), the age of animals was missing and food consumption was not reported. In addition, there was a lack of individual/litter data in the study report although the litter incidences have been provided seperataly (doc. no. PN-902-007). One other limitation of the study was that only Alizarin Red staining was performed (which only stains the ossified parts of the bones) and no staining for cartilage was included. Therefore, it is difficult to conclude if the less than twelve pairs of ribs trully reflect rib agenesis as was reported in the HCD or may reflect a lack of ossification. However, there were no other indications of a treatment related effect on foetal skeletal ossification in the study.

The foetuses with less than four ribs also had fused/forked ribs and malaligned thoracic vertebral arches and contra. It was argued that the apparent reduction in the number of ribs was due to fused ribs being counted as one entity rather than two (see Annex 1). However, it is noted that fused/forked ribs was also observed in the control albeit at a lower incidence.

Table 14: Developmental skeletal anomalies in rabbits

Dose (mg/kg bw/day)	**0**	**15**	**30**	**60**
Number of foetuses examined	111	106	118	107
Number of litters examined	17	17	17	17
Number of foetuses with skeletal anomalies	0	0	2	5
Foetuses with less than twelve pairs of ribs				
- fetal incidence	0	0	1	4[1]
- litter incidence	0	0	1	2[1]
Foetuses missing/incomplete vertebrae				
- fetal incidence				
- lumbar	0	0	1	2[1]
- sacral (incomplete)	0	0	0	2[1]
- caudal	0	0	0	3[1]
- litter incidence				
- lumbar	0	0	1	1[1]
- sacral (incomplete)	0	0	0	1[1]
- caudal	0	0	0	1[1]

[1] Three out of four foetuses came from one litter (#27928). The observed foetuses with missing/incomplete vertebrae also come from this litter.

Table 15: Historical control information from literature for absent ribs (Ema et al. 2012)

Laboratory	**03**	**14**	**02**	**13**	**12**	**18**	**19**	**09**			
1994-2000	0.12 (0-1.39)					0.15 (0-0.8)		0.09 (0-0.65)			
Laboratory	**16**	**03**	**11**	**07**	**14**	**10**	**04**	**06**	**12**	**02**	**18**
2001-2010	0.09 (0-0.90)		0.22 (0-1.64)	0.12 (0-1.30)	0.10 (0-1.05)	0.06 (0-1.2)	0.04 (0-0.50)		0.22 (0-0.62)		0.23 (0-0.7)

10.10.6 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2, classification for effects on development is based on:

Category 1A:

Known human reproductive toxicant

Category 1B:

Presumed human reproductive toxicant largely based on data from animal studies

— clear evidence of an adverse effect on development in the absence of other toxic effects, or

— the adverse effect on development is considered not to be a secondary non-specific consequence of other toxic effects

Category 2:

Suspected human reproductive toxicant

— some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and

— the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).

— the adverse effect on development is considered not to be a secondary non-specific consequence of the other toxic effects

According to the CLP criteria classification as Repr. 1A is based on human data. No human data is available for pendimethalin and therefore, classification as Repr 1A is not justified.

In the 2-generation study reduced pup weight was observed from day 7, which only occurred at concentrations also inducing maternal toxicity. In the rat developmental toxicity study no effects occurred which would warrant classification for development.

In the rabbit developmental toxicity study an increase in the incidence of less than twelve pairs of ribs and an increase in the incidence of missing/incomplete vertebrae was observed. Although the skeletal finding in the top dose mainly occured in one litter, it was also observed in the mid-dose as well as in another litter in the top-dose. It was considered that since the effects was observed in multiple litters and considering the low reported historical control incidence that the finding should be considered as treatment related. The effects occurred in the absence of maternal toxicity.
There were some limitations to the study as it was not conducted fully in accordance with OECD guidelines. One of the limitations was that only Alizarin Red staining was performed and no staining for cartilage was included. It is therefore difficult to conclude if the less than

twelve pairs of ribs trully reflect fully missing ribs as was reported in the study report. However, there were no other indications of foetal skeletal ossification being affected.

Based on the observed developmental effects in the absence of clear maternal toxicity and taking into consideration the limitation of the developmental rabbit study it is proposed to classify pendimethalin with Category 2.

10.10.7 Adverse effects on or via lactation

No additional study carried out.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

No additional study carried out.

10.10.9 Comparison with the CLP criteria

According to Regulation EC No 1272/2008 (CLP), Table 3.7.2.2.2, classification for lactation effects is based on:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

In the 2-generation study in rats an effect on pup body weigth 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). Therefore, this effect on pup weight is not considered to be sufficient for classification and labelling.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Classification as reproductive toxicity category 2 is proposed for pendimethalin; H361d (Suspected of damaging the unborn child).

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	6 (2.6 %)	3 (1.2 %)	13 (5.6 %)	13 (5.1 %)
Litter incidence	3 (10.3 %)	3 (10.3 %)	7 (25 %)	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**.

10.11 Specific target organ toxicity-single exposure

This hazard class has not been evaluated.

10.12 Specific target organ toxicity-repeated exposure

This hazard class has not been evaluated.

10.13 Aspiration hazard

This hazard class has not been evaluated.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

The environmental studies of pendimethalin were assessed in the Renewal Assessment Report (February 2012) in the context of the renewal of the approval (Reg. (EU) No. 2017/1114), under Reg. (EC) 1107/2009. All studies were carried out under GLP unless indicated underwise. Generally studies were conducted in accordance with OECD test guideline. All studies were considered acceptable (Klimisch Score 1 or 2) unless indicated otherwise in the remarks.

11.1 Rapid degradability of organic substances

Table 16: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Ready biodegradability OECD 301 B, EPA 835.3110, (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to (EC) No 1907/2006 of European Parliament and of Council on the REACH - Part C.4, ISO 9439	Pendimethalin was not readily biodegradable Theoretical carbon dioxide ($ThCO_2$) values of <10 % $CO_2/ThCO_2$ at the end of the exposure	RI = 1	CA 7.2.2.1/1 Doc ID 2013/1125987
Hydrolysis	Hydrolytically stable at pH 5, 7 and 9 at room temperature	non-GLP RI = 2	IIA 2.9.1/01, Doc ID PD-M 11-73
Hydrolysis	Hydrolytically stable at pH 5, 7 and 9 at 37°C and 50°C	non-GLP RI = 2	IIA 2.9.1/02, Doc ID 1578
Hydrolysis	Hydrolytically stable at pH 4, 7 and 9 at 50°C	RI = 2	IIA 2.9.1/03 Doc ID CYA-004/7/20
Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test OECD 309 (April 2004)	DT50 193 days	Study not suited to investigate biodegradation. Too much uncertainty in degradation half-life. Endpoint not accepted.	CA 7.2.2.2./1 Doc ID 2013/1125943
Water sediment study Richtlinien fur die Prüfung von Pflanzenschutzmitteln im Zulassungsverfahren, Part IV, 5-1, BBA, Germany	Water: DT50 1.0-1.6 days. Whole system DT50 4.5-5.0 days	RI = 2	CA 7.2.2.3/1 Doc ID 2002/1026399 CA 7.2.2.3/5 Doc ID 2013/1132577
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems BBA IV 5-1, EPA 162-4, SETAC, OECD 308	Whole system DT50 26.4 days	RI = 2	CA 7.2.2.3/2 Doc ID 2004/1022517 CA 7.2.2.3/6 Doc ID 2007/1042029
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems OECD 308, EPA 835.430w	Water DT 50: 0.41-0.42 days Whole system DT50 101-103 days	RI = 1	CA 7.2.2.3/3 Doc ID 2012/1187651
Aerobic and Anaerobic Transformation in Soil	Soil DegT50: 146 days	RI = 2	CA 7.1.1.1/1 Doc ID PN-620-072 (study);

Method	Results	Remarks	Reference
SETAC Part 1 section 1.1			CA 7.1.2.1.1/6 DocID 2013/1110109 (kinetic evaluation)
Aerobic and Anaerobic Transformation in Soil OECD 307	Soil DegT50: 53.6-57.8 days	RI = 2	CA 7.1.2.1.1/5 Doc ID 2011/1257593 (study); CA 7.1.2.1.1/9 Doc ID 2013/1110110 (kinetic evaluation)
Aerobic and Anaerobic Transformation in Soil OECD 307	Soil DegT50: 97.0 days	RI = 1	CA 7.1.1.1/4 Doc ID 2012/1051587
Aerobic and Anaerobic Transformation in Soil OECD 307	Soil DegT50: 177.7 days (DFOP-slow fase)	RI = 1	CA 7.1.1.1/3 Doc ID 2001/1031363 (study); CA 7.1.2.1.1/7 Doc ID 2013/1110111 (kinetic evaluation)
Direct photochemical degradation EEC 94/37 2.9.2, EEC 94/37 2.9.3, SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides - Part 1 Fate and behaviour in the environment - 10 - Aqueous photolysis, Draft OECD Test Guideline: Phototransformation of Chemicals in Water - Direct and Indirect Photolysis (OECD Aug. 2000), Phototransformation of chemicals in water. Part A Direct phototransformation. Umweltbundesamt Berlin FRG (Sep. 1990)	DT50 35 hours	RI = 2	CA 7.2.1.2/2 Doc ID 2002/1026397
Direct photochemical degradation EEC 94/37 2.9.2, EEC 94/37 2.9.3, JMAF Guideline (No. 12-Nouan-8147, 2000)	DT50 5 days DT90 16.7 days	RI = 1	CA 7.2.1.2/3 Doc ID 2005/1026762
Direct photochemical degradation FAO Revised Guidelines, Rev. #, JMAF Guideline (No. 12-Nouan-8147, 2000), OECD Guideline Proposal, December 2007	DT50 4.1 days	non-GLP RI = 2	CA 7.2.1.2/4 Doc ID 2012/1282999
Indirect photochemical degradation	DT50 3.4 days	RI = 1	CA 7.2.1.3/1 Doc ID 2005/1026763

Method	Results	Remarks	Reference
FAO Revised Guidelines on Environmental Criteria for the Registration of Pesticides Revision 3 (28 August 1993), EEC 94/37, EEC 91/414, JMAFF No 12 Nosan No 8147			

11.1.1 Ready biodegradability

The ready aerobic biodegradability of BAS 455 H - pendimethalin was investigated in water containing mineral salts and a microbial inoculum (activated sludge from a municipal sewage plant) in accordance with OECD 301 (CA 7.2.2.1/1). Pendimethalin was added to the test medium and the inoculum to achieve a concentration of 20 mg TOC/L corresponding to approximately 36 mg pendimethalin /L. Duplicate control systems containing the microbial inoculum without test or reference substance were used to determine the endogenous microbial CO2 evolution. Duplicate test systems dosed with the test substance at a nominal concentration of 20 mg TOC/L were used to monitor biodegradation of the test substance. A reference substance system containing readily biodegradable aniline at a nominal concentration of 20 mg TOC/L was also tested to verify the viability of the microbial inoculum. All systems were sampled on days 0, 1, 4, 7, 11, 14, 18, 22, 25, 27, 28 and 29. The average CO2 evolved from the control systems was subtracted from the CO2 evolved in the test and reference substance systems. The test substance systems yielded mean theoretical carbon dioxide (ThCO2) values of <10 % CO2/ThCO2 at the end of exposure. Therefore, pendimethalin was not biodegradable under the conditions of the test. Biodegradation in the reference substance system reached 85 % CO2/ThCO2 at the end of the study, verifying that the microbial inoculum was viable and active. From the results obtained, it was concluded that pendimethalin is classified as not readily biodegradable.

This study is conducted according to the Guidelines and no limitations are reported. Therefore, the study is considered reliable (Ri = 1). Endpoints can be used for classification purposes.

11.1.2 BOD_5/COD

No data.

11.1.3 Hydrolysis

The hydrolys of pendimethalin was evaluated in three studies (CA 2.9.1/01; CA 2.9.1/02; CA 2.9.1/03) of which two were carried out with the formulations PROWL and STOMP. 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 to hydrolytic conditions at pH levels of 4, 5, 7 and 9 and temperatures of 20, 22, 37 and 50°C.

These studies are conducted according to the Guidelines, but two out of three studies are before the GLP framework was established. No limitations are reported, however the evaluation was very concises. Therefore, the overall conclusion based on three studies is considered reliable but with Ri = 2. Endpoints can be used for classification purposes.

11.1.4 Other convincing scientific evidence

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No data.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

The rate of biodegradation of pendimethalin was investigated in natural river surface water under aerobic conditions in accordance with OECD 309 (CA 7.2.2.2/1). The test systems were incubated in the dark for a period of 63 days at 20.7 + 0.2°C. Microbial activity of the test system was proven by the degradation of [^{14}C(U)]benzoic acid. Samples were taken for work-up after 0, 1, 3, 8, 14, 28 and 63 days of incubation. Despite the low test concentrations, pendimethalin adsorbed to a considerate amount to the test vessel walls. The remaining test item in the aqueous phase showed no significant degradation although some degradation products could be detected in trace amounts in the chromatograms which were not visible in the sterile vessels. A half-life of pendimethalin in water can therefore only be extrapolated far beyond duration of the study and was calculated to be 193 days for the high dose system.
This study is conducted according to the Guidelines. Several limitations are reported, most important of which concerns the effect of the low dose rate on the quantification of metabolites. Further, some minor limitations were reported regarding sampling and study setup. Overall, these limitations did not impact the integrity of the study. However, it can be concluded that the applied test conditions as required by the Guideline OECD 309 were not suitable to investigate the biodegradation of strong adsorbing substances in aqueous environments, because –for this substance- binding on the walls of the vessels used in the experiment had a very strong influence that the biodegradation half-life could only be estimated from comparision of the sterile and non-sterile systems and even then the results exceeded the study duration. It is considered that this causes too much uncertainty for a reliable half-live to be determined. It is noted that the the 'ECHA Guidance on the Application of the CLP Criteria' (Annex II, 2.3.1) states that results from aquatic simulation tests (e.g. OECD 309) may be used directly for classification purposes. However, in this case it is questionable whether "ultimate degradation is correctly determined" as also requested in the 'ECHA Guidance on the Application of the CLP Criteria' (Annex II, 2.3.1). The study can be used as supporting evidence for the conclusion on rapid degradability.

The degradation of BAS 455 H - pendimethalin was investigated in two aerobic water/sediment systems (CA 7.2.2.3/1). The systems were treated with [(benzene U)-14C]-labelled pendimethalin at about 147 µg test item per test vessel (0.67 mg/L). Samples were taken in duplicates at 0, 3, 7, 16, 30, 62, 93/94 and 121 days after treatment (DAT). The water samples, methanol extracts of the sediment, ^{14}C-carbon dioxide and other volatile ^{14}C-labelled metabolites and the bound residue were analysed by liquid scintillation counting (LSC) and HPLC. Due to the limited solubility of pendimethalin in water, the content of radioactivity shifted immediately from the water phase to the sediment, reflected by the values of the radioactivity in the water phase of 48% total applied radioactivity (TAR) at the start (day 0) in both systems decreasing to <8% TAR at the end of the study. Simultaneously, the radioactivity of the sediments increased from 45% to a maximum of 75% and 89% TAR at day 121 in the system "Rückhaltebecken" and "Schaephysen", respectively. The degradation kinetics of pendimethalin were calculated at the time of the study according to Timme et al. The DT50

values of pendimethalin in the water phases were calculated to be 2-4 days (DT90 7-14 days). The DT50 values of pendimethalin for the whole systems were between 2-2.5 days (DT90 27-57 days). Since the kinetic evaluation was outdated a new evaluation of the study was conducted in recommendation of the FOCUS Kinetics workgroup (CA 7.2.2.3/5). The experimental data on pendimethalin in the both test systems were evaluated at Level P-I. A kinetic evaluation at Level P-II was not pursued. The results at Level P-I showed that degradation of pendimethalin in the total system and dissipation from the water phase were best described by SFO kinetics. The best-fit $DegT_{50}$ was 4.5 and 5.0 days in the total system, and the best-fit $DisT_{50}$ was 1.0 and 1.6 days in the water phase of the two systems.
This study is conducted before the Guideline OECD 308 was established, but was generally in line with this guideline. The temporary anaerobic conditions during the study are not considered a problem. These mimic the possible conditions that natuarually also might occur and are therefore acceptable.
Overall, these limitations did not impact the integrity of the study. Therefore, the study is considered reliable (Ri = 2). Endpoints can be used for classification purposes.

The degradation of BAS 455 H – pendimethalin under aerobic aquatic conditions was investigated in accordance with OECD 308 over a period of up to 100 days at 20 °C in the dark (CA 7.2.2.3/2). Two different natural systems of water and sediment taken from a pond-like side-arm of a river (Berghäuser Altrhein) and a small stream surrounded by a forest (Ranschgraben) were treated with [phenyl-U-^{14}C]-labelled pendimethalin at about 200 µg test item per test vessel. Duplicates test vessels were sampled at 0 and 6 h, and 1, 3, 7, 14, 28, 58, 79 and 100 days after treatment (DAT). Since the system Ranschgraben showed a considerable and inexplicable drop of pH during the experiment, data obtained after 14 days with this system were not used to evaluate the behaviour of pendimethalin in aqueous environments. The distribution of radioactivity was very similar for both water/sediment systems during the first two weeks after treatment, therefore it is justified to assume that the results obtained with Berghäuser Altrhein are also representative for system Ranschgraben. Pendimethalin quickly dissipated from the water phase (1-3% TAR at 14 DAT) and was adsorbed to the sediment. Numerous polar degradation products were formed in the water (up to 30), however, none of them exceeding 3% of the total applied radioactivity (TAR) at any investigated sampling time in both systems. Pendimethalin disappeared rapidly from the water phase with - at that time - DT_{50} values of 1.1 and 0.6 days and DT_{90} values of 4.9 and 12.0 days in the water phase of the systems Berghäuser Altrhein and Ranschgraben, respectively. The DT_{50} and the DT_{90} values of pendimethalin in the complete system amounted to 27.1 / 24.2 days and 89.9 / 80.3 days in the systems Berghäuser Altrhein / Ranschgraben. Since the kinetic evaluation was outdated a new evaluation of the study was conducted in recommendation of the FOCUS Kinetics workgroup (CA 7.2.2.3/6). The average total degradation half-life in water-sediment systems was 26.4 days.
This study is conducted in accordance with the Guideline OECD 308. Because for one of the systems only datapoints for the first 14 days are available, the study is considered reliable, but with Ri = 2. Endpoints can be used for classification purposes.

The degradation of ^{14}C- pendimethalin was investigated in accordance with OECD 308 in two aerobic water/sediment systems under dark conditions (CA 7.2.2.3/3). The systems were treated with 4-methyl-^{13}C phenyl-^{14}C-labelled pendimethalin at about 60 µg test item per test vessel. Samples for the experiment were taken at 0, 0.25, 1, 3, 7, 14, 28, 55, 78, and 100 days after treatment (DAT). The amount of non-extractable residues and volatiles was determined by LSC. After 100 days, pendimethalin was found in the water at levels of 1.4% TAR in system Berghäuser Altrhein and 2.1% TAR in system Ranschgraben. Several metabolites were detected in both systems, however none of them ever exceeded 2% TAR. The sediment pendimethalin reached its highest amount after 7 days with 80%-83% TAR. At the end of study amounts of 48% TAR and 44% TAR were found in the systems Berghauser Altrhein and Ranschgraben, respectively. The non-extractable (bound) residues reached average amounts of 39% TAR in the

system Berghäuser Altrhein and 45% TAR in the system Ranschgraben. The bound residues were further characterised by NaOH extraction and humic substance fractionation. The highest amounts of radioactivity was always found in the insoluble humins and high molecular humic acids, indicating a tight incorporation into the organic matrix in the sediment. Overall, the degradation of pendimethalin was characterised by a very low mineralisation rate. The amount of $^{14}CO_2$ never exceeded 3.5% TAR in any of the samples over 100 days. Kinetic analysis and calculations of DT_{50} and DT_{90} values was performed following the recommendations of the FOCUS Kinetics workgroup. The DT50 for whole sediment was 101-103 days and the DT50 for water was 0.41-0.42 days.

This study is conducted in accordance with the Guideline OECD 308. Because no significant limitations are reported the study is considered reliable with Ri = 1. Endpoints can be used for classification purposes.

The aerobic soil degradation of pendimethalin was conducted using a 1:1 mixture of ^{13}C- and ^{14}C- labelled pendimethalin, with ^{14}C labelled uniformly on the benzene ring and ^{13}C labelled at the 3-methyl of the benzene ring (CA 7.1.1.1/1 and 7.1.2.1.1/6). The study was carried out in accordance with SETAC Part 1 section 1.1. Three soils were used for this study: a sandy loam soil (Norfolk) from North Carolina, a silt loam soil from Crowley (Louisiana) and a clay loam soil from Tensas (Mississippi). Only the soil in North Carolina was considered representative for European conditions. It was shown for the Louisiana and the Mississippi soil that they cannot be found in Europe because of the climatic weathering conditions that lead to these finally weathered soils. The material balance ranged from 94% to 105% total applied radioactivity (TAR) for the three soils. At the end of the experiment, up to 3.2, 4.9 and 7% TAR was trapped as organic volatiles in the Norfolk, Crowley and Tensas soils, respectively. Pendimethalin was degraded in all the three soils tested. Several minor degradation products were formed, each representing 0.1 to 4.8% of the applied radioactivity. Mineralisation was observed with levels of CO_2 reaching 1.7-2.4% after 120 days. However, the metabolic pattern was not properly identified, especially an unknown peak with the maximum amount of 4.8 % in the North Carolina soil at the end of the study. For this peak it was assumed that it may contain metabolite CL99900 (= M455H001) beside some others. The DT50 values based on current kinetic evaluation was 146 days.

This study predates Guideline OECD 307. Because this study lacks some clarity in metabolite identification the study is considered reliable, but with Ri = 2. Endpoints (for parent substance) can be used for classification purposes.

The rate of degradation of BAS 455 H - pendimethalin was investigated in three aerobic soils at a temperature of 20°C (CA 7.1.2.1.1/5 and 7.1.2.1.1/9). The study was carried out in accordance with OECD 307. The soils were agricultural soils from Germany that had been collected from the field and sieved before use. The soil was treated with the test item pendimethalin at a nominal rate of 5.3 mg per kg dry soil which corresponds to a field application rate of 2 kg pendimethalin per hectare, calculated on the basis of an equal distribution in the top 2.5 cm soil layer and a soil density of 1.5 g/cm^3. Soil aliquots of 100 g (dry weight basis) were weighed into test vessels and placed into an incubation cabinet. The incubation was carried out in the dark in the laboratory under aerobic conditions at a soil moisture of 40% to 50% of the maximum water holding capacity and a temperature of 20°C. A closed incubation system with continuous aeration was used with an attached trapping system for the determination of volatile compounds. Trigger DT_{50} were 76.5 and 64.0 d, while modelling DT_{50} values normalised to reference conditions (20°C, pF2) were 57.8 and 53.6 d in soil LUFA 5M and LUFA 2.3, respectively.

This study is conducted in accordance with the Guideline OECD 308. No significant limitations are reported for this study. However, during the EU review process some question arose with regard to the effect of volatility of the active substance in the study. It is concluded based on

these and other studies that the impact of volatility is limited. Therefore, the study conclusion is considered reliable with Ri = 2. Endpoints can be used for classification purposes.

The fate and behaviour of BAS 455H - pendimethalin was investigated in a German standard soil at 20 ºC and 50% of the maximum water holding capacity (approx. pF2) in the dark for 120 days (CA 7.1.1.1/4). The study was carried out in accordance with OECD 307. The nominal application rate was 5.3 mg/kg dry soil (corresponding to 2 kg test item/ha). A flow through system with humidified air was used. Absorption solutions for the determination of volatile compounds were set up to enable determination of a mass balance. Soil samples were taken 0, 1, 3, 7, 10, 14, 28, 63, 91 and 120 days after treatment (DAT), extracted, measured for radioactivity (LSC) and analysed by HPLC. Absorption solutions were removed at each sampling event and additionally 43, 77 and 105 DAT. Only one degradation product was detected above 5% of the total applied radioactivity (TAR), i.e. M455H001 occurred with a max of 6.9% of TAR at the end of incubation. With the HPLC system used, the detection limit for metabolites is 0.001 mg/kg. The degradation rate (SFO DT_{50}) of pendimethlin was calculated to be 97.0 days.

This study is conducted in accordance with the Guideline OECD 308. No significant limitations are reported for this study. Therefore, the study conclusion is considered reliable with Ri = 1. Endpoints can be used for classification purposes. Please note that this concerns only the endpoint (trigger value) for the parent substance.

The fate and behaviour of pendimethalin was investigated in a German standard soil adjusted to about 40% of the maximum water holding capacity (CA 7.1.1.1/3). The test item was applied at a concentration of 2 mg/kg dry soil, corresponding to a field concentration of 2 kg a.s./ha (considering the top 1 cm and a soil density of 1000 mg/kg). Duplicate samples were prepared for each timepoint and incubated at a temperature of 20 ± 2 ºC in the dark for 211 days. The metabolism was investigated by analysing the distribution of radioactivity by liquid scintillation counting (LSC) in the soil and gas phase (CO_2 and volatiles) of the test system. The mean recovery of radioactivity ranged from 94% to 95%. The content of pendimethalin and metabolites in the extracts was analysed by radio-HPLC. In total 7 metabolites (M1-M7) were observed in quantifiable amounts. None of them exceeded 2% of the initial dose. The DT50 values based on current kinetic evaluation was 58.5 days (SFO). A dramatic decline of the biomass by almost factor 3 was recorded at sampling day 120 and remained at low level until the end of the study. Therefore, the RMS conducted revised modelling where the datapoints from day 120 and later were left out, in accordance with the Guidance Document on Kinetics (FOCUS, 2014). The SFO model did not result in an acceptable fit, mainly because the residuals were not evenly spread around the x-axis. In line with the Guidance, the final endpoint for modelling 177.7 days (DFOP, slow phase) could also be used as trigger for further work (a slight improvement of the spreading of the residuals over the FOMC kinetics is seen in the DFOP kinetics).

This study is conducted in accordance with the Guideline OECD 308. No significant limitations are reported for this study, the kinetics is calculated separately. Therefore, the study conclusion is considered reliable with Ri = 1. Endpoints can be used for classification purposes.

11.1.4.4 Photochemical degradation

A moderate photolytical degradation in aqueous media was demonstrated for pendimethalin during the last Annex I inclusion procedure with a half-life of 21 days of continuous irradiation. All detected metabolites were below 10% AR. However, since most of the data were non-GLP and incomplete, new studies on the direct photochemical degradation of pendimethalin were conducted. The older non-GLP, incomplete studies which were not considered reliable are not further discussed in the CLH dossier.

Additionally also a study where indirect photolysis was studied was submitted for the renewal.

The aqueous photolysis study with ^{14}C-labeled pendimethalin was performed in purified, de-ionized water containing 10% acetonitrile (CA 7.2.1.2/2). The study was carried in accordance with EEC 97/37 2.9.2 and 2.9.3. The test solutions with initial concentrations of 0.2 mg/L, 0.5 mg/L and 0.8 mg/L pendimethalin were exposed to a Xenon arc lamp (wavelength > 290 nm) for up to 164 hours in 30 mL quartz glass reaction vessels. The temperature was kept constant at 20°C. Samples were taken after irradiation periods of 0, 1, 2, 4, 6, 10, 16, 72 and 164 hours. Dark control samples were incubated under the same conditions except for irradiation. A DT_{50} value of 35 hours considering continuous irradiation was calculated from a rate constant k_D of approximately 2.4 * 10^{-6} s^{-1}, assuming pseudo-first order kinetics for the photodecomposition process. The only degradation product amounting for more than 10% of the initial concentration was 2,6-dinitro-3,4-dimethylaniline. The results of this study indicate that direct photolysis is an important process for decomposition of pendimethalin in surface water.
This study is conducted in accordance with the SETAC Guidance. Because the recovery was low for both the dark and irradiated samples the study is considered reliable, but with Ri = 2. the rate of degradation was not corrected for the samples with the recovery. Endpoint can be used for classification purposes.

The aqueous photolysis of BAS 455 H – pendimethalin was studied by using a solution of [phenyl-U-^{14}C]-labelled pendimethalin (0.1 mg/L) in sterile phosphate-buffer at pH 7 (CA 7.2.1.2/3). The study was carried out in accordance with EEC 94/37 2.9.2 and 2.9.3 The test solutions of pendimethalin were continuously exposed to a Xenon arc lamp (wavelength > 290 nm), emitting a light spectrum similar to sunlight (>290 nm) at an intensity of about 3 mW/cm^2 for 15 days. Temperature was kept constant at 22°C. Samples were taken at 0, 1, 3, 7, 9, 11 and 15 days after treatment. Dark control samples were incubated under the same conditions except for irradiation. All samples were measured for total radioactivity (LSC) and analysed by HPLC. Characterization and identification of the photolytic degradation products in aqueous samples was performed by co-chromatography with reference compounds via radio-HPLC and by MS-analysis.
The results showed that photolysis of [phenyl-U-^{14}C]- pendimethalin in sterile water at pH 7 resulted in a fast decline of pendimethalin to 7.8 % TAR after 15 days. No degradation occurred in the dark control samples. The half-life of pendimethalin under continuous irradiation in buffer pH 7 was calculated to be 5 days according to single first-order kinetics.
This study is conducted in accordance with the EEC guidelines. No significant limitations are reported for this study. Therefore, the study conclusion is considered reliable with Ri = 1. Endpoints can be used for classification purposes.

The study of the aqueous photolysis of BAS 455 H – pendimethalin and the calculation of its quantum yield was performed by using a solution of [phenyl-ring-U-C^{14}, 4-methyl-C13]-pendimethalin in sterile phosphate-buffer at pH 7 (CA 7.2.1.2/4). The study was carried out in accordance with FAO Guidelines. The test solutions were continuously exposed to a Xenon arc lamp (wavelength > 290 nm) for 15 days in 20 mL glass reaction vessels with a quartz glass covering. The temperature was kept constant at 22°C. Samples were taken at 0, 1, 3, 7, 9, 11 and 15 days after treatment. Dark control samples were incubated under the same conditions except for irradiation. For determination of the quantum yield of pendimethalin, a mixture of p-nitroacetophenone (PNAP) and pyridine was used as chemical actinometer. The vessel with the actinometer solution (18 mL) was irradiated under similar conditions as the other test vessels.Samples were analysed by LSC and HPLC.
The results showed that photolysis of [phenyl-ring-U-C^{14}, 4-methyl-C13]-pendimethalin in sterile water at pH 7 resulted in a fast decline of pendimethalin with 4.8% TAR remained after 15 days. No significant degradation occurred in the dark control samples. Continuous photolytic

degradation of pendimethalin in aqueous solution at pH 7 was found in the course of the study. DT_{50} values for pendimethalin under irradiated and dark conditions were 4.1 and 154 days (non-GLP). The quantum yield calculation for pendimethalin was of 1.2 x 10^{-4}. The calculated half-life for the top layer of aqueous systems considering the quantum yield of pendimethalin varied between 2 and 5 days depending on the month of application.
This study is conducted in accordance with the (at that time) proposed OECD guideline. No significant limitations are reported for this study other than that the study was not carried out under GLP. Therefore, the study conclusion is considered reliable with Ri = 2. Endpoints can be used for classification purposes.

The indirect aqueous photolysis of BAS 455 H – pendimethalin in sterile natural water was studied in accordance with EEC 94/37 (CA 7.2.1.3/1). The test solutions containing [phenyl-U-^{14}C]-labelled pendimethalin (0.1 mg/L) were continuously exposed to a Xenon arc lamp (wavelength > 290 nm), emitting a light spectrum similar to sunlight (>290 nm) at an intensity of about 3 mW/cm^2 for 15 days. The temperature was kept constant at 22°C. Samples were taken at 0, 1, 3, 7, 9, 11 and 15 days after treatment. Dark control samples were incubated under the same conditions except for irradiation. All samples were measured for total radioactivity (LSC) and analysed by HPLC. Characterization and identification of the photolytic degradation products in aqueous samples was performed by co-chromatography with reference compounds via radio-HPLC and by MS-analysis. The results showed that photolysis of [phenyl-U-^{14}C]-pendimethalin in sterile natural water resulted in a fast decline of pendimethalin to 7.3 % TAR after 15 days. No degradation occurred in the dark control samples. Under continuous irradiation, pendimethalin was readily degraded in sterile natural water with half-life of 3 days according to a single first order kinetics.
This study is conducted in accordance with the FAO and EEC guidelines. No significant limitations are reported for this study. Therefore, the study conclusion is considered reliable with Ri = 1. Endpoints can be used for classification purposes.

Based on a 28-day biodegradability study pendimethalin was found to be not rapidly biodegradable. No information could be derived on BOD and COD data. Moreover, the water-sediment, soil degradation and hydrolysis studies did not provide in evidence of the degradation of the substance within a 28-day period. This is supported by the outcome of the 63 days OECD 309 water-sediment simulation study where the half-lives where so high that they could not be determined reliably.
Several direct and indirect photochemical degradation studies indicate a degradation of > 70% to carbon dioxide or NER within 16 days (DT50 is 5 days or lower) and metabolite 2,6-dinitro-3,4-dimethylaniline, which was formed > 10% of the active radiation was further degraded to unknown polar compounds and carbon dioxide.
However, in the ECHA GD on the application of the CLP criteria (2017) (Section II.2.3.9) it is stated that "Information on photochemical degradation e.g. OECD 1997 is difficult to use for classification purposes. The actual degree of photochemical degradation in the aquatic environment depends on local conditions e.g. water depth, suspended solids, turbidity as well as seasonal influences, and the hazard of the degradation products is usually not known." The information on photodegradation does therefore not alter the conclusion on the rapid biodegradability of the substance; **the substance is considered not rapidly biodegradable.**

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant for this dossier.

11.2.1 Summary of data/information on environmental transformation

Not relevant for this dossier.

11.3 Environmental fate and other relevant information

Volatility:

Pendimethalin has a vapour pressure of 1.39 x 10^{-3} Pa at 20°C (see Table 7) and therefore concluded to be semivolatile.

Adsorption/desorption from soil:

The adsorption and desorption behaviour of radiolabelled pendimethalin was investigated on four different soils (CA 7.1.3.1.1/1). The four soils covered a range of pH from 5.4 to 7.3, a range of organic carbon content from 1.26% to 4.10% and different textural classes. For the determination of the adsorption/desorption isotherm, five different concentrations (nominal 150, 100, 50, 20 and 10 µg/L of the test item in 0.01 M $CaCl_2$) were used. As determined in preliminary experiments, the appropriate ratio of soil versus test solution was 1/50, and the adsorption equilibrium time was 24 hours. Radioactivity in the aqueous supernatants and soil extracts was determined by liquid scintillation counting (LSC). To check if metabolites of pendimethalin were formed during the test, HPLC-analysis with UV- and radioactive detection was used. The amount of test substance adsorbed to soil was calculated as the difference between the amount of test substance initially present in solution and the amount remaining at the end of the experiment (indirect method). The following adsorption parameters were measured and evaluated for the test item pendimethalin in each soil: distribution coefficients K_d and K_{OC} at five concentration levels, the Freundlich adsorption coefficient K_F, the Freundlich exponent 1/n, and the corresponding K_{FOC} values. Freundlich adsorption coefficients K_F of 124 to 367 mL/g were determined corresponding to K_{FOC} values ranging from approximately 9000 to 12600 mL/g. Freundlich exponents 1/n ranged from 0.92 to 0.98. The determination of desorption isotherms was performed for each soil in one step. The desorption coefficient K_{Fdes} at five concentration levels ranged from 140 to 381 mL/g for the four soils corresponding to K_{FOCdes} values ranging from approximately 9000 mL/g to 18400 mL/g. The values show that pendimethalin was sorbed very strongly to the soils. Desorption kinetics and isotherms experiments showed that adsorption was not reversible.

This study is conducted in accordance with the OECD 106 guideline. The order of concentrations tested for the adsorption isotherm is small (one order of magnitude). Therefore, the study conclusion is considered reliable, but with Ri = 2. Endpoints can be used for classification purposes.

In a second study the aim was to determine the adsorption / desorption behavior of pendimethalin in five European soils in the laboratory (CA 7.1.3.1.1/2). The soils covered a range of pH ($CaCl_2$) from 5.6 to 7.4, a range of organic carbon content from 0.60% to 1.85%, and four different USDA textural classes: one sand, two sandy loams, one silt loam and one sandy clay loam. For the determination of the adsorption isotherm, five different nominal concentrations (1, 3, 10, 30 and 100 µg/L) of the test item in 0.01 M $CaCl_2$ solution were used. The ratio of soil versus test solution was 1/20, and the measurements were performed at the adsorption equilibrium time of 24 h. Desorption tests were performed in two steps on the samples used for the previous adsorption tests by adding 0.01 M $CaCl_2$ solution to the samples without the test item. HPLC-MS/MS was used to determine the amount of pendimethalin in $CaCl_2$ solution after extraction with pentane, and in the soil after extraction with methanol. Distribution coefficients K_d and K_{oc} at five concentration levels, the Freundlich adsorption coefficient $K_{f,}$ the Freundlich exponent 1/n, and the corresponding $K_{f,oc}$ values were determined. Resulting $K_{f,oc}$ values ranged from 10258 mL/g to 27578 mL/g, with Freundlich exponent 1/n values between 0.904 and 0.961.

This study is conducted in accordance with the OECD 106 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes.

11.4 Bioaccumulation

Table 17: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
USEPA (1979) Fed Reg V44, no53, ASTM E-35.21 draft nos. 6 and 8 (1977 and 1978); Hamelink (1977) *Current bioconcentration test methods and theory*. Aquatic toxicology and hazard evaluation 634: 149-161.	No reliable endpoint	Study does not meet the validaty criteria in accordance with OECD 305. Study not acceptable for classification purposes.	CA 8.2.2.3/01 PN-519-002
OECD 305 (1996), OPPTTS 850.1730, Rainbrow trout (*Oncorhynchus mykiss)*	BCF_{KLG} (growth and lipid corrected): 931 L/kg BCFss: 903 L/kg	R= 1	CA 8.2.2.3/05 2013c/1224090
OECD 305 (1996), zebra fish (*Danio rerio*)	BCFk whole fish: 2900 L/kg, normalized to 5% fat content 1179 L/kg wwt BCFssl (steady stat, lipid corrected): 963-1180 L/kg wwt.	Fish were not fed during exposure. However, overall the endpoints of the study were considered acceptable as weight of evidence. RI = 2	CA 8.2.2.3/08 2003a/ 1033759
Bioaccumulation in fish in outdoor mesocosm enclosures (*Leuciscus idus melanotus*)	Maximum BCF 337, 207 and 97.3 L/kg, respectively, based on actual concentration, TWA concentration and initial nominal concentration in water; mean BCF based on actual concentration in water 199 L/kg	RI = 1	CA 8.2.2.3/07 2010a/ 1230332

11.4.1 Estimated bioaccumulation

No data available.

11.4.2 Measured partition coefficient and bioaccumulation test data

The bioaccumulation potential of 14C pendimethalin was determined for the bluegill sunfish, *Lepomis macrochirus* (CA 8.2.2.3/01). The validaty criteria for OECD 305 were not met due to the variation in the tested concentration (2.2 µg/L to 4.2 µg/L). No reliable endpoints could be drawn from the study and study was not considered acceptable for classification purposes.

Rainbow trout (*Oncorhynchus mykiss*, 4.9-6.9 cm and 1.6-2.4 g/fish at the start) were exposed to [phenyl-U-^{14}C] BAS 455 H (pendimethalin) in the water for 28 days in a flow-through system (~5 volume exchanges per day), followed by 16 days of depuration in clean water (CA 8.2.2.3/05). The study was carried out in accordance with OECD 305. All fish samples were separated into edible and inedible parts prior to analysis by combustion/LSC. The lipid content of 3 control fish was determined at the start and end of uptake and at the end of depuration. Water samples were removed for LSC measurement prior to feeding from treated and control aquaria on day -1, 0, 1, 2, 4, 7, 14, 21 and 28 of uptake and 1, 2, 3, 4 and 5 of depuration. Five fish were sampled from treated and control aquaria prior to feeding on day 1, 2, 4, 7, 14, 21, and 28 of uptake and 1, 2, 4, 8 and 16 of depuration. Length and weight of all sampled fish was measured. The actual measured concentration (LSC) of the saturated stock solution (0.147 mg/L) was below the water solubility (0.33 mg/L at 20°C; List of Endpoints review report pendimethalin (2003)), and radioactivity concentrations in centrifuged and uncentrifuged samples of the stock were essentially the same, indicating that the stock contained no undissolved test substance.
Fish growth rate in the control and the test group was 0.0086 and 0.0119/day, respectively. As these growth rates were statistically significantly different, the value of 0.0119/day was used as k_g value for growth-corrected calculations. The lipid content of 3 control fish was 2.4%, 4.8% and 7.0%, respectively, on day 1, 28 and 44, the value of 4.8% at the end of uptake was used for calculation of the lipid corrected BCF. All validity criteria specified in OECD 305 were satisfied. BCF_{KLG} (growth and lipid corrected) based on total radioactivity was found to be 931 L/kg.

This study is conducted in accordance with the OECD 305 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

Zebra fish (*Danio rerio*) were exposed to [phenyl-^{14}C]-pendimethalin for 14 days in a flow-through system (5 exchanges per day), followed by 21 days of depuration in clean water (CA 8.2.2.3/08). The study was carried out in accordance with OECD 305. Fish were not fed during exposure and fed at 1-2% of body weight daily during depuration.Mean fish weight of the sampled fish (n=4-6 per sampling day) was 347 mg during the uptake phase and 314 mg during the depuration phase. Radioactivity in water and in extracts was quantified by LSC and in extracted fish samples by combustion followed by LSC.
No adverse effects on fish or fish mortality were observed during the study. Fish lipid content in control fish was fairly stable during the study (lipid % per sampling day in range 7.4-18.4% during uptake (mean 12.3%, SD 3.1%) and in the range 11.9-26.2% during the first 8 hours of depuration (mean 17.7%, SD 6.1%). The modelled BCF values show a good agreement with the steady steady BCF values, confirming the reliability of the study results. The overall kinetic BCF was 2900 L/kg (rounded to 2 significant figures). When corrected for fat content (12.3% during uptake phase), the kinetic BCF normalised to 1% fat content is 236 L/kg, and the kinetic BCF normalised to 5% fat content (fat content recommended by OECD 305 (2012)) is 1179 L/kg. It was noted during review that the reported normalisation was not correct: based on BCF 2800 L/kg, a normalised BCF (1% fat content) of 22800 L/kg was reported, this should be 228 L/kg.
The fish were not fed during uptake, which is rather unusual. However, no adverse effects on fish and fish mortality were recorded, and there were no remarkable differences in fish weight and fat content between the uptake and depuration phase. That said, it is possible that the lack of feeding during the test resulted in changes in metabolism (generally, periods of starvation can result in slower metabolism). It is not known the effect these potential changes might have on the calculated BCF (though if, indeed, metabolism was slowed, it could be a worst-case.

BCF_K value for pendimethalin in whole fish 2900 L/kg wwt, BCF_K normalised to 5% fat 1179 L/kg wwt; CT_{50} for pendimethalin in whole fish 2.5-4.4 days. CT_{90} values 8.3-15 days, 96-97% clearance within 21 days of depuration.
BCF_{SSL} (steady state, lipid corrected) is estimated by RMS to be 963-1180 L/kg wwt. However, considering the lack of feeding and the lack of growth-correction, this endpoint does have some restrictions.

This study is conducted in accordance with the OECD 305 guideline with the exception that the fish were not fed during exposure. However, overall the endpoints of the study were considered acceptable as weight of evidence, with Ri = 2. Endpoints can be used for classification purposes

A study was conducted to investigate the bioaccumulation of pendimethalin in fish under realistic exposure conditions in outdoor mesocosm enclosures in Germany following a single application at 10 µg/L in June 2009 (CA 8.2.2.3/07). A 4 x 3 m pond (depth 120 cm, sublayer 10-15 cm clay) was established in April 2008 in Neu-Ulrichstein, 35315 Hombergh/Ohm, Germany.
The fish exhibited normal behaviour throughout the study. In each enclosure one fish died. Gross pathology of the two fish that died showed infection with common ecto-parasites and damage around the gill or the caudal fin. In addition, one fish was missing in each enclosure at the final sampling for unknown reasons. Fish weight increased by 2-3%, but fish length by about 4-5%, and as a result k-factors decreased during the study (from 1.60 at the start to 1.42-1.47 at the end). No effect of pendimethalin on fish growth could be observed. The abundance of macrozoobenthos decreased during the in-life phase by about 50%, with a slightly stronger decrease in the treated enclosure. This effect was mainly caused by the decreasing abundance of Asellus aquaticus and Gastropoda, which are both natural food items of golden orfe.
The maximum BCF in fish 337, 207 and 97.3 L/kg, respectively, based on actual concentration, TWA concentration and initial nominal concentration in water; mean BCF based on actual concentration in water 199 L/kg.
The study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes.

Based upon the three reliable BCF studies showing BCFs exceding 500 L/kg, it can be concluded that for classification purposes pendimethalin should be considered to have a potential to bioaccumulate.

11.5 Acute aquatic hazard

Table 18: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
Acute, 96 hr (static, with and without sediment) None-guideline	*Oncorhynchus mykiss* (Rainbow trout)	pendimethalin (batch AC12053-136A, purity 94.6%)	LC50 without sediment: **0.196 mg a.s./L** (mean measured)	RI = 2	CA 8.2.1/03/ PN-511-006
Acute, 96 hr (flow through) OECD	*Pimephales promelas* (Fathead minnow)	Pendimethalin (batch COD-001337, purity 93.3%)	LC50 > 0.240 mg a.s./L (mean measured)	RI =1	CA 8.2.1/04/ 2010/1155847

203					
Acute, 48 hr (static) OECD 202	*Daphnia magna*	Pendimethalin (batch 20703, purity 98.4%)	EC50**: 0.147 mg a.s./L** (mean measured)	RI = 1	CA 8.2.4.1-02/ PN-521-012
Acute, 48 hr (static) EEC method C.2.	*Daphnia magna*	Pendimethalin (Batch AC12053-136A, purity 94.6%)	EC50: Without sediment: > 1.0 (nominal) / 0.701 mg as/L (mean measured) With sediment: >1.0 (nominal) / 0.606 mg as/L (mean measured)	RI = 1	CA 8.2.4.1-05/ PN-521-017
Acute, 72 hr OECD 201 (2006)	*Selenastrum capricornutum* [a]	Pendimethalin (Batrch 0261, purity 94.5%)	72 h E_rC_{50}: **9.3 µg/L** Mean measured	RI = 1	CA 8.2.6-02/ PN-521-005 CA 8.2.6/07/ 2013a/1160822 (amendment)
120 hr EPA, 1971	*Selenastrum capricornutum*	Pendimethalin (Batch AC-6539-77A, purity 92.98%)	72-h ErC50 >55 µg/L Mean measured	RI = 1	CA 8.2.6-03/ PN-521-006 CA 8.2.6/08 2013b/1160823 (amendment)
Acute, 72 hr OECD 201	*Selenastrum capricornutum*	Pendimethalin (Batch AC12053-136A, purity 94.6%)	72 h ErC50: 24.3 µg/L (mean measured)	RI = 1	CA, 8.2.6/11 PN-521-016
120 hr EPA 1971	*Anabaena flos-aquae*	Pendimethalin (batch AC-6539-77A, purity 92.98%)	EyC50: >0.174 mg/L (mean measured)	RI = 1	CA 8.2.6-04 PN-521-010
14-d study OECD 221 (2006)	*Lemna gibba*	Pendimethalin (batch AC12053-136A, purity 94.6%)	ErC50: 22 µg/L	RI = 1	CA 8.2.7/01/ PN-521-007 8.2.7/02/ 2013a/1160824 (amendment)
7-d study OECD 221 (draft 2002)	*Lemna gibba*	Pendimethalin (batch 115, purity 97.5%)	7-day ErC50 = 15.6 µg a.s./L (initially measured)	RI = 1	CA 8.2.8/01/ TLA91811
Public literature	*Lemna minor*	Pendimetalin, purity 98.0%	EC50 (4d exp.) 85 µg/L EC50 (7d exp.): 177 µg/L	Non-GLP, public literature study RI = 2	CA 8.2.7/03

[a] The current name of this species is *Raphidocelis subcapitata* and formerly also known as *Pseudokirchneriella subcapitata*.

11.5.1 Acute (short-term) toxicity to fish

The 96-hour LC50 of pendimethalin (94.6% purity, batch AC12053-136A) was determined in rainbow trout (*Oncorhynchus mykiss*) in both the presence and absence of natural sediment under static conditions (CA 8.2.1/03). No guideline was reported. The NOEC was also determined. Mortality was the toxic endpoint. Evidence of abnormal behaviours was also recorded. The nominal test concentrations were 1000, 500, 250, 125, 63 and 32 µg/l of pendimethalin. The fish were observed after 1, 3, 6, 24, 48, 72 and 96 hour for mortality and sub-lethal effects. The analytical results for aquaria with sediment showed that measured water concentrations were between 105 and 134% of nominal concentrations at the start of the test, between 52 and 65% after 6 hours and between 0.6 to 5.6% at the end of the exposure.For aquaria without sediment, the measured concentrations were between 90 to 110% of nominal concentrations at the start of the test, between 39 and 57% after 6 hours and between 0.9 to 3.4% of nominal concentrations at the end of exposure. The toxicity of pendimethalin to rainbow trout was based on nominal initial concentration. The results of the test showed that the LC50 96 hours with sediment was 932 µg/l and the NOEC was 125 µg/l (nominal). The results for no sediment vessels showed a LC50 96 hour of 890 µg/l and a NOEC of 125 µg/l. No significant difference in toxicity of pendimethalin to rainbow trout with sediment or without sediment was recorded. However, from the study report it can be read that concentrations in the test media without sediment fell <80% during the study. Based on the measured concentrations on LC50 96 hours without sediment of 195.7 µg/L was derived. For the endpoint in the presence of sediment no measured concentration was available and hence the endpoint in the presence of sediment cannot be used for classification purposes. The study conclusion is considered reliable, with Ri = 2.

In a flow-through acute toxicity study in Fathead minnow (*Pimephales promelas*) the 96-hour LC50 of pendimethalin (93.3% purity, batch COD-001337) was determined in accordance with OECD 203 (CA 8.2.1/04). The test concentrations were Control, 6.25%, 12.5%, 25%, 50% and 100% of a saturated stock solution, corresponding to mean measured concentrations of 0, 0.015, 0.036, 0.055, 0.119 and 0.240 mg pendimethalin/L. Assessment of mortality and symptoms of toxicity were assessed within 1 hour after start of exposure and 6, 24, 48, 72 and 96 hours after start of exposure. After 96 hours of exposure no mortality was observed in the control and at concentrations of up to 0.055 mg pendimethalin/L, whereas 5% and 10% mortality was observed at 0.119 mg a.s./L and 0.240 mg a.s./L. Even though the mortalities in the 0.240 mg a.s./L treatment were marginal, they were preceeded by observeable toxic signs (after 24 and 48 h) and thus considered test substance related. However, the mortality at 0.119 mg/L is not considered to be a toxicologically relevant effect. After 96 hours of exposure no symptoms of toxicity were observed for surviving fish at any of the test item concentration. The LC_{50} (96 h) for pendimethalin was determined to be > 0.240 mg a.s./L based on mean measured concentrations.

This study is conducted in accordance with the OECD 203 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

In a static acute toxicity study, *Daphnia magna* were exposed to seven measured concentrations of the test substance pendimethalin in a static system over 48 hours (CA 8.2.4.1-02). The study was carried out in accordance with. Acetone was used as a slolvent. The test parameter was the cumulative immobilization of the daphnids after 24 and 48 hours. The EC50 value was based on measured concentrations of pendimethalin. The mean analytical concentrations were 0, 0.029, 0.06, 0.12, 0.21, 0.39, 0.8 and 1.68 mg as./L. Because there was no renewal, test concentrations

were calculated as the average of the 0 and 48 hour analyses. The pendimethalin concentration measured after 48 h of static exposure ranged between 75 and 92% of those reported for time 0, with an average value of 82%. The EC 50 value (48 hours) was 0.147 mg a.s./L.

This study is conducted in accordance with the OECD 202 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

In a second study in *Daphnia magna* the 48-hour EC50 of pendimethalin (batch AC 12053-136A, purity 94.6%) was determined in both the presence and absence of natural sediment under static test conditions (CA 8.2.4.1-05). The study was carried out in accordance with EEC method C.2. Immobilisation was used as toxic endpoint, but abnormal behaviour was also recorded. The nominal test concentrations were 1000, 500, 250, 125 and 63 µg/l of pendimethalin. Based on the mean measured water concentrations the EC50s were 606.3 µg/L (including sediment) and 700.86 µg/L (without sediment).

This study is conducted in accordance with the EEC method C.2. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

11.5.3 Acute (short-term) and chronic toxicity to algae or other aquatic plants

An algal growth inhibition test was conducted to determine the 24-, 48- and 72-hour EC50 values of pendimethalin for the freshwater alga *Selenastrum capricornutum* (current name *Raphidocelis subcapitata*) (CA 8.2.6-02). The study was carried out in accordance with OECD 201. The tested concentration range of pendimethalin (Batch No. 0.261, purity 94.5%) was 1 to 128 µg/L. Mean measured concentration ranged from 0.51 to 54.18 µg/L. Biomass was determined by cell counts at 24, 48 and 72 hours. The calculated endpoints based on mean measured concentrations were ErC50 9.3 µg/L and EyC50 3.8 µg/L. The NOEC was determined to be 7.59 µg/L. The EyC10 was 0.74 µg/L and ErC10 was 2.8 µg/L.

This study is conducted in accordance with the OECD 201 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

In a second alga growth inhibition test in *Selenastrum capricornutum* pendimethalin (batch AC 6539-77A, purity 92.98%) was tested at . 2.00, 6.25, 12.5, 25.0, 50.0 and 100 µg/L (CA 8.2.6-03). The study was conducted in accordance with EPA, 1971 guideline. The test was conducted for 5 days under static, non-renewal conditions. Standing crop values were determined by electronic particle counting on test days 3, 4 and 5. Three replicates were tested for each concentration. The measured concentrations (average of day 0 and day 5 analysis) were 0.795, 3.02, 4.85, 13.4, 26.2 and 51.7 µg/L. The EC50 values were ErC50 > 55 µg/L and EyC50 4.3 µg/L. The NOEC was determined to be 3.0 µg/L.

This study is conducted in accordance with the EPA, 1971 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

In an acute toxicity study in *Selenastrum capricornutum* pendimethalin (batch AC12053-136A() was tested at nominal concentraitons of 50, 25, 12.5, 6.3, 3.2 and 1.6 µg/l (CA 8.2.6/11). The study was conducted in accordance with OECD 201 Pendimethalin concentration analysis was performed at the start and at the end of the 72 h exposure period. The effect of the test substance

on survival and growth was evaluated. The results of the test showed that the EC50 72 hours for growth rate was 33.7 µg/l (24.3 µg/l based on measured concentrations) and the EC50 72 hours for yield was 18 µg/l (12.7 µg/l based on measured concentrations). The NOEC for both effects was 6.3 µg/l (4.1 µg/l based on measured concentrations).

This study is conducted in accordance with the OECD 201 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

A test was conducted to evaluate the effect of pendimethalin (batch AC-6539-77A, purity 92.98%) on blue-green alga (*Anabaena flos-aquae*) (CA 8.2.6-04). The study was carried out in accordance with EPA 1971 test guideline. The criterion for effect was inhibition of growth in comparision to controls after 5 days of exposure. The nominal test concentrations were 17.5, 35.0, 70.0, 140 and 280 µg/L. Tree replicates were tested for each test substance concentration and control. The highest concentration was slightly above the maximum water solubility limit of the test substance (275 µg/L). The test was conducted for 5 days under static non-renewal conditions. The measured concentrations were 11.7, 24.2, 47.0, 98.0 and 174 µg/L. The effect of pendimethalin on standing crop ranged from 4.1% inhibition at 47.0 µg/L to 19.6% inhibition at 174 µg/L. Therefore the EyC50 was determined to be >0.174 mg/L. The NOEC was determined to be 174 µg/l.
This study is conducted in accordance with the EPA, 1971 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

The acute toxicity of pendimethalin (batch 6539-77A, purity: 92.98%) has been determined for duckweed, *Lemna. gibba* G3 in accordance with OECD 221 (CA 8.2.7/01). Nominal test concentrations were 0, 2.5, 5, 10, 20 and 40 µg/L. The actual concentrations of pendimethalin were measured on test days 0 and 14 in all treatments and the controls. The measured concentrations represented 102-114% of nominal at the start and 5-25% of nominal at the end of exposure. The ErC50 value was 22 µg/L and the EyC50 value was 8.4 µg/L. The NOEC was not reported, but an EC_{10} for growth rate of 4.15 µg/l and and EC_{10} for yield of 2.27 µg/l were calculated.
This study is conducted in accordance with the OECD 221 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

In a second study in *Lemna gibba* pendimethalin (batch 115, purity 97.5%) was tested at concentrations of 1.00, 3.00, 7.54, 28.9 and 65.0 µg/L in accordance with OECD 221 (CA 8.2.8/01). Static exposure over 7 days was carried out. Three replicates were investigated for the the test concentrations and six replicates for the control. Frond numbers were assessed on days 0, 2, 5 and 7. Inhibition of log biomass growth, specific growth rate and log biomass dry weight were determined.
The NOEC for yield and growth rate was 3.7 µg a.s./L. Based on biomass, the NOEC was 10 µg a.s./L for both yield and growth rate. The 7-day ErC50 was 15.6 µg a.s./L (Initially measured concentration) and the 7-day EyC50 was 6.4 µg a.s./L (initially measured concentration).

This study is conducted in accordance with the OECD 221 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

In a public literature study six herbicides, including pendimethalin, were evaluated for their effect on *Lemna minor* (CA 8.2.7/03). Frond measures were taken every day for 7 days. For each herbicide six or eight concentrations increasing in steps of a factor two plus a control were used. The EC50 values for *Lemna minor* after a short-term exposure pulse of pendimethalin over 3 hours followed by a 4 day and 7 day recovery period were determined to be 0.551 mg a.s./L and 0.549 mg a.s./L, respectively. Longer term exposure over 4 days and 7 days resulted in ErC50 values of 0.085 mg a.s./L and 0.177 mg a.s./L, respectively. The study conclusion is considered reliable, with Ri = 2. Endpoints can be used for classification purposes

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No other relevant studies.

11.6 Long-term aquatic hazard

Table 19: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
Full life cycle toxicity test (up to 288 days) US EPA 1971, US EPA 1975	Fathead minnow *(Pimephales promelas*)	Pendimethalin (batch AC-2603-47, purity 98.3%)	NOEC: 6.3 µg/L (measured) EC_{10}: **7.2 µg/L** (measured) BCF: 1810 L/kg	RI = 1	CA 8.2.2.2/01 PN-513-001
Full life cycle toxicity test (up to 172 days) OECD 210	Zebrafish *(Danio rerio)*	Pendimethalin (batch D-1346, purity 95.03%)	NOEC: 20 µg/L (nominal) EC_{10}: 53 µg/L	RI = 1	CA 8.2.2.2/02 2012/1364165
Full life cycle toxicity test (up to 184 days) OECD 210	Zebrafish *(Danio rerio)*	Pendimethalin (batch AC 12053-136A, purity 94.6%)	NOEC: 50 µg/L (nominal) EC_{10}: not possible to calculate	RI = 1	CA 8.2.2.2/03 2011/1020765
Flow-through test (21 days)	*Daphnia magna*	Pendimethalin (batch no. not reported)	NOEC: **14.5 µg/L** (mean measured) EC_{10}: not possible to calculate	RI = 2	CA 8.2.5.1-01 PN-523-001

in house protocol					
Semi-static test (21 days) OECD 211 (1998)	*Daphnia magna*	Pendimethalin (batch 115, purity 97.5%)	Reproduction NOEC: 17.3 µg/L EC_{10}: not calculated	RI = 1	CA 8.2.5/01 DRE91811
30 days Draft BBA guideline	*Chironomus riparius*	Pendimethalin, Lot AC 5213-72A, purity 92.4%	NOEC: 0.138 mg/L (initial measured) 0.082 mg/L (mean measured) NOEC (219 mg a.s./kg sed dw; mean measured) EC_{10}: not possible to calculate	spiked water RI = 2	CA 8.2.5.4-01/ PN-549-002
static test (28 days) BBA guideline proposal (Streloke & Köpp, 1995)	*Chironomus riparius*	Pendimethalin technical, batch no.: 115, purity: 97.5 %;	NOEC: ≥0.261 mg a.s./L (initial measured) NOEC: ≥0.0011 mg a.s./L (mean measured) EC_{10}: not possible to calculate	spiked water RI = 1	CA 8.2.7/1 IZA91811
static test (28 days) OECD 218 (draft): Sediment-water chironomid toxicity test using spiked sediment (Feb. 2004)	*Chironomus riparius*	Pendimethalin (BAS 455 H, Reg. no. 900 072), batch no. FH2933, purity 94.9%	NOEC: 227.3 mg a.s./kg sed dw; initial measured NOEC: (0.1099 mg a.s./L; initial measured, 0.080 mg a.s./L; mean measured) EC_{10}: not possible to calculate	spiked sediment RI = 1	CA 8.2.5.4-02 2008/1010543
Acute, 72 hr OECD 201 (2006)	*Selenastrum capricornutum* [a]	Pendimethalin (Batrch 0261, purity 94.5%)	NOErC 7.59 µg/L ErC_{10}: 2.8 µg/L EyC_{10}: 0.74 µg/L	RI = 1	CA 8.2.6-02/ PN-521-005 CA 8.2.6/07/ 2013a/1160822 (amendment)
120 hr EPA, 1971	*Selenastrum capricornutum*	Pendimethalin (Batch AC-6539-77A, purity 92.98%)	NOEC 3.0 µg/L ErC_{10}: **1.8 µg/L** EyC_{10}: 0.47 µg/L	RI = 1	CA 8.2.6-03/ PN-521-006 CA 8.2.6/08 2013b/1160823 (amendment)
Acute, 72 hr	*Selenastrum capricornutum*	Pendimethalin (Batch AC12053-136A, purity	NOEC: 4.1 µg/L (mean measured)	RI = 1	CA, 8.2.6/11 PN-521-016

OECD 201		94.6%)	EC_{10}: not calculated		
120 hr EPA 1971	*Anabaena flos-aquae*	Pendimethalin (batch AC-6539-77A, purity 92.98%)	NOEC: 174 µg/L EC_{10}: not possible to calculate	RI = 1	CA 8.2.6-04 PN-521-010
14-d study OECD 221 (2006)	*Lemna gibba*	Pendimethalin (batch AC12053-136A, purity 94.6%)	ErC_{10} = 4.15 µg/l EyC_{10} = 2.27 µg/l	RI = 1	CA 8.2.7/01/ PN-521-007 8.2.7/02/ 2013a/1160824 (amendment)
7-d study OECD 221 (draft 2002)	*Lemna gibba*	Pendimethalin (batch 115, purity 97.5%)	NOEC = 3.7 µg a.s./L (initially measured) ErC_{10}: 2.9 µg a.s./L EyC_{10}: 4.2 µg a.s./L	RI = 1	CA 8.2.8/01/ TLA91811

[1] Indicate if the results are based on the measured or on the nominal concentration

11.6.1 Chronic toxicity to fish

The chronic toxicity of ^{14}C pendimethalin has been determined for the fathead minnow, *Pimephales promelas*, in a full life cycle test carried out in accordance with US EPA 1971, US EPA 1975 (CA 8.2.2.2/01). Effects on hatchability of eggs, survival, growth, and reproduction of first generation fish, and on egg hatchability, survival, and growth of their offspring were evaluated. The bioaccumulation and depuration of pendimethalin were also studied. During the first 14 days of the test measured concentrations ranged between 33% - 40% of nominal concentrations, which were 6.3, 13, 25, 50 and 100 µg/L nominal. After the change to DMSO, the nominal concentrations were lowered by 50% and set at half the initial values (i.e. 3.1, 6.3, 13, 25 and 50 µg/L), and the mean measured concentrations accounted for 64% - 90% of these nominal concentrations. Measured concentrations corresponding to 33% - 40% of nominal concentrations 6.3, 13, 25, 50 and 100 µg/L are roughly equivalent to measured concentrations corresponding to 64% - 90% of nominal concentrations 3.1, 6.3, 13, 25 and 50 µg/L. Statistically significant reductions of survival of F1 fry were noted at the two highest treatment levels (mean measured concentrations 22 and 36 µg/L), and these effects are considered to be biologically relevant since there was also a reduction (not statistically significant) of F2 fry spawned from solvent control eggs at the highest concentration of 40 µg/L. compared to the pooled controls. Hatchability was reduced by 9% and 15% at 22 and 43 µg/L, respectively. These reductions of 9% and 15% are considered to be biologically relevant, although they were not statistically significant at the 95% level when compared to the controls, probably due to the relatively large variation of hatchability at these two treatment levels compared to all lower treatment levels and the controls. In addition, a statistically significant reduction of the number of eggs per female of 56% compared to the pooled control was determined at 9.8 µg/L. As a consequence, the NOEC is 6.3 µg/L.

This study is conducted in accordance with the US EPA, 1971 and US EPA 1975 guidelines. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

11.6.2 Chronic toxicity to aquatic invertebrates

The chronic (21 days reproduction inhibition) toxicity of pendimethalin (batch number not reported) has been determined for the water flea, *Daphnia magna* (CA 8.2.5.1-01). The study was carried out following an in-house protocol. Groups of daphnids were exposed in a flow-

through system to technical pendimethalin, dissolved in acetone, in a flow-through test system. Mortality, number of young produced and mean brood sizes produced were recorded. Concentrations of pendimethalin in each dose level were determined on test days 0, 1, 3, 7, 10, 14, 17, and 21. The calculated 21 day reproduction no observed effect concentration (NOEC) was 14.5 µg/L, while 100% mortality was reported for all higher concentrations. The test differed slightly from the current daphnid chronic toxicity test in that fewer daphnids were used per dose than typical for a flow-through exposure system. However, the study conclusion is considered reliable, with Ri = 2. Endpoints can be used for classification purposes

The chronic (21 days) toxicity of pendimethalin (batch 115, purity 97.5%) was determined for *Daphnia magna* (CA 8.2.5/01*)*. The study was carried out in accordance with OECD 211. The mean measured test concentrations were of 125, 54.3, 17.3, 7.12 and 2.28 µg a.i./L. Observations included immobilisation, size and general condition of the parental generation, number and first appearance of juveniles. The results were expressed in terms of mean measured concentrations. One and five parent animals appeared pale at mean measured concentrations of 7.12 and 54.3 µg a.i./L, respectively. The mean length was significantly reduced at 54.3 µg/L. An immobilisation rate of 100 % was observed at 125 µg a.i./L after 5 days of exposure, whereas no immobilisation occurred at any other test level. The reduction in reproduction was significantly different at 54.3 and 125 µg a.i./L when compared to the control ($p < 0.05$). No biologically significant numbers of aborted eggs were observed at any tested concentration. In contrast, biological significant numbers of stillborn juveniles were reached at 54.3 µg a.i./L. The NOEC was 17.3 µg/L.

This study is conducted in accordance with the OECD 211 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

A 30-day toxicity study has been performed for the effect of pendimethalin (purity 92.4%) on larvae of the chironomid midge, *C. riparius* (CA 8.2.5.4-01). The study was carried out following the BBA Guideline proposal. The water solubility of the substance was exceeded, producing low and non-linear recoveries. In the highest nominal treatment groups, the test substance was observed to form an insoluble crystalline surface film at the time of dosing. The crystalline film then precipitated, remaining as crystals on the surface of the sediment. Therefore, at the higher nominal concentrations, lower amounts of the material actually went into solution, resulting in the lower actual water concentrations at the higher treatments. The measured water concentrations decreased in all treatments at the day-10 and day-30 observation periods. A NOEC of 0.138 mg/L was derived (initial measured). Based on the mean measured concentration a NOEC of 0.082 mg/L is derived. The study conclusion is considered reliable, with Ri = 2. Endpoints can be used for classification purposes

A 28-day static test study has been performed for the effect of pendimethalin (purity 97.5%) on the development of *C. riparius* (CA 8.2.7/1). The test concentration of 0.3 mg/L (nominal initial concentration) was based on a preliminary range-finding study and represents the maximum water solubility of pendimethalin. At the limit test concentration, no statistical significant difference was noted for the emergence rate, transformed emergence rate, mortality and the development rate when compared to the pooled control. Thus, the overall No-Effect-Level (NOEC) was 0.3 mg/L (initial measured). The mean measured concentration declined over the study duration. The geomean of the concentration in the water column over 28 days is calculated as 1.1 µg a.s/L. Therefore the endpoint, based on the geomean concentration is NOEC ≥ 1.1 µg a.s/L. The study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

Another 28-day static test evaluated the effect of pendimethalin (purity 94.9%) on the development of *C. riparius* (CA 8.2.5.4-02). The study was carried out in accordance with OECD 218 (draft, Feb. 2004). The test concentrations were 15, 30, 60, 120 and 240 mg a.s./kg dry sediment. Recoveries in the sediment were in a range between 92.0% - 106.8% of the nominal concentrations at test initiation. The following initial concentrations were measured: 14.3, 31.4, 64.1, 110.4 and 227.3 mg pendimethalin/kg dry sediment. At test termination the detected concentrations ranged from 74.4% - 94.6% of the nominal values (12.5, 25.4, 56.7, 96.4 and 178.5 mg a.s./kg dry sediment). First emerged midges were observed on DAI 16 (= day after insertion of larvae). In the control and all test item treatments 13 to 20 midges emerged. No statistically significant differences were found for the emergence rates (ANOVA with $Chi^2$2x2 Table Test with Bonferroni correction, $\alpha = 0.05$) and development rates (ANOVA followed by Williams Multiple Sequential t-test procedure, $\alpha = 0.05$) at any test item concentration when compared to the solvent control. Therfore, the NOEC was 227.3 mg a.s./kg dry sediment (initially measured). The overlying water concentration was 0.1099 mg a.s./L (initially measured).

This study is conducted in accordance with the OECD 218 guideline. No limitations are reported. Therefore, the study conclusion is considered reliable, with Ri = 1. Endpoints can be used for classification purposes

11.6.3 Chronic toxicity to algae or other aquatic plants

See short-term toxicity for summaries.

11.6.4 Chronic toxicity to other aquatic organisms

No further data relevant for classification.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

The criteria for Category Acute 1 in line with Table 4.1.0 from the Guidance on the Application of the CLP Criteria are:

96 hr LC50 (for fish)	≤ 1 mg/l and/or
48 hr EC50 (for crustacea)	≤ 1 mg/l and/or
72 or 96 hr ErC50 (for algae or other aquatic plants)	≤ 1 mg/l.

Acute toxicity data is available for all three taxa. For fish, invertebrates, algae and aquatic plants, the lowest LC/EC50 values are 0.196 mg/L in Rainbow trout, 0.147 mg/L in *Daphnia magna*, 0.0093 mg/L in *Selenastrium carpricornutum* and 0.0156 mg/L in *Lemna gibba*, respectively. Based on the ErC50 of 0.0093 mg/L in *Selenastrium carpricornutum* pendimethalin should be classified as Category Acute 1 (H400). The corresponding M-factor is 100.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Based on a 28-day biodegradability study pendimethalin was found to be not rapidly biodegradable. No information could be derived on BOD and COD data. Moreover, the water-sediment, soil degradation and hydrolysis studies did not provide in evidence of the degradation of the substance within a 28-day period. This is supported by the outcome of the 63 days OECD

309 water-sediment simulation study where the half-lives where so high that they could not be determined reliably.
Several direct and indirect photochemical degradation studies indicate a rapid degradation Howewer, because the actual degree of photochemical degradation in the aquatic environment depends on local conditions and cannot be used for classification purposes, the information on photodegradation does therefore not alter the conclusion on the rapid degradability of the substance; **the substance is considered not rapidly degradable.**
The BCF ranged between 97.3-1179 L/kg for different species. Overall, it is concluded that pendimethalin, for which adequate chronic toxicity data is available, is not rapidly degradable and has a potential to bioaccumulate therefore the following criteria apply:

Category Chronic 1:

Chronic NOEC or ECx (for fish)	≤0.1 mg/l and/or
Chronic NOEC or ECx (for crustacea)	≤0.1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤0.1 mg/l.

Category Chronic 2:

Chronic NOEC or ECx (for fish)	> 0.1 to ≤1 mg/l and/or
Chronic NOEC or ECx (for crustacea)	> 0.1 to ≤1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	> 0.1 to ≤1 mg/l.

Chronic toxicity data is available for all three taxa. For fish, invertebrates, algae and aquatic plants, the lowest NOEC/EC10 values are 0.0072 mg/L in Fathead minnow, 0.0145 mg/L in *Daphnia magna* and 0.0018 mg/L in *Selenastrum capriconutum*, respectively. Based on the ErC10 of 0.0018 mg/L for *Selenastrum capriconutum* exposed to pendimethalin via spiked water, Category 1 (H410) should be assigned. The corresponding M-factor for chronic ecotoxicity is 10.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Acute (short-term) aquatic hazard: category Acute 1, M-factor: 100.

Long-term aquatic hazard: category Chronic 1, M-factor: 10.

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 1810 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).

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

No data.

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

No data.

12.1.2 Comparison with the CLP criteria

Not relevant.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

No classification proposed. Data lacking.

13 ADDITIONAL LABELLING

None.

14 REFERENCES

A full reference list of the studies from the DAR is included in Annex 1. In addition, to these studies the following references were used:

1. EFSA (2016). Peer review of the pesticide risk assessment of the active substance pendimethalin. EFSA Journal 14(3):4420.

2. ECHA (2017). Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017.

3.FOCUS (2014). Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration. Version 1.1, January 2014. annexes

The study summaries from the DAR of pendimethalin have been included in Annex I.

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