Committee for Risk Assessment

RAC

Annex 1

Background document

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

pyridaben (ISO)

EC number: 405-700-3
CAS number: 96489-71-3

CLH-O-0000002480-82-02/A2

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 public 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

23 August 2013

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: PYRIDABEN

EC Number: 405-700-3

CAS Number: 96489-71-3

Index Number: 613-149-00-7

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Version number: 2 **Date:** February 2012

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Pyridaben (ISO); 2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one
EC number:	405-700-3
CAS number:	96489-71-3
Annex VI Index number:	613-149-00-7
Degree of purity:	≥98%
Impurities:	No (Eco)toxicological relevant impurities are present.

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Acute Tox. 3* (H301) Acute Tox. 3* (H331) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	T; R23/25 N; R50/53
Current proposal for consideration by RAC	Removal of * from Acute Tox. 3 M-factor: Acute M-factor of 1000 Chronic M-factor of 1000	SCL: N; R50-53: C ≥ 0,025 % N; R51-53: 0,0025 % ≤ C < 0,025 % R52-53: 0,00025 % ≤ C < 0,0025 %
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 3 (H301) Acute Tox. 3 (H331) Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410) M-factor: Acute M-factor of 1000 Chronic M-factor of 1000	T; R23/25 N; R50/53 SCL: N; R50-53: C ≥ 0,025 % N; R51-53: 0,0025 % ≤ C < 0,025 % R52-53: 0,00025 % ≤ C < 0,0025 %

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

A review of the available toxicity data for pyridaben has revealed that the classification listed in Annex VI of Regulation EC no. 1272/2008 (including the 1st ATP) needs two minor adjustments: The * (star) indicting minimum classification can be removed, and harmonized M-factors and SCLs are to be included.

In accordance with the criteria of the CLP regulation, pyridaben should be classified as Acute Tox 3 (H301) and Acute Tox 3 (H331). The reference indicating minimum classification (*) is no longer necessary. It is therefore proposed that the acute toxicity classification listed in Annex VI, part 3, Table 3.1, for pyridaben be updated by removal of the minimum classification indicated by the reference *.

Pyridaben is classified as Aquatic Acute 1 and Aquatic Chronic 1. A harmonized M-factor according to Regulation EC no. 1272/2008 and SCLs according to Directive 1999/45/EC as amended by Directive 2006/8/EC are currently not listed in Annex VI of Regulation EC no. 1272/2008. In this dossier, a harmonized M-factor (both acute and chronic in accordance with the 2nd ATP criteria) and SCLs for pyridaben are proposed.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
					classification
2.1.	Explosives				conclusive but not sufficient for classification
2.2.	Flammable gases				conclusive but not sufficient for classification
2.3.	Flammable aerosols				conclusive but not sufficient for classification
2.4.	Oxidising gases				conclusive but not sufficient for classification
2.5.	Gases under pressure				conclusive but not sufficient for classification
2.6.	Flammable liquids				conclusive but not sufficient for classification
2.7.	Flammable solids				conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures				conclusive but not sufficient for classification
2.9.	Pyrophoric liquids				conclusive but not sufficient for classification
2.10.	Pyrophoric solids				conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures				conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases				conclusive but not sufficient for classification
2.13.	Oxidising liquids				conclusive but not sufficient for classification
2.14.	Oxidising solids				conclusive but not sufficient for classification
2.15.	Organic peroxides				conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals				conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox. 3 (H301)		Acute Tox. 3* (H301)	
	Acute toxicity -				conclusive but not

	dermal				sufficient for classification
	Acute toxicity - inhalation	Acute Tox. 3 (H331)		Acute Tox. 3* (H331)	
3.2.	Skin corrosion / irritation				conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				conclusive but not sufficient for classification
3.4.	Skin sensitisation				conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				conclusive but not sufficient for classification
3.6.	Carcinogenicity				conclusive but not sufficient for classification
3.7.	Reproductive toxicity				conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure				conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				conclusive but not sufficient for classification
3.10.	Aspiration hazard				conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	Acute M-factor 1000 Chronic M-factor 1000	Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	
5.1.	Hazardous to the ozone layer				conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Signal word:	Danger (Dgr)
Pictogram:	GHS06, GHS09
Hazard statements:	H301, Toxic if swallowed H331, Toxic if inhaled H410, Very toxic to aquatic life with long lasting effects
Precautionary statements:	No precautionary statements are proposed since precautionary statements are not included in Annex VI of Regulation EC no. 1272/2008.

Proposed notes assigned to an entry:

A note is not proposed.

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness				conclusive but not sufficient for classification
Oxidising properties				conclusive but not sufficient for classification
Flammability				conclusive but not sufficient for classification
Other physico-chemical properties				conclusive but not sufficient for classification
Thermal stability				conclusive but not sufficient for classification
Acute toxicity	T; R23/25#		T; R23/25#	
Acute toxicity – irreversible damage after single exposure				conclusive but not sufficient for classification
Repeated dose toxicity				conclusive but not sufficient for classification
Irritation / Corrosion				conclusive but not sufficient for classification
Sensitisation				conclusive but not sufficient for classification
Carcinogenicity				conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity				conclusive but not sufficient for classification
Toxicity to reproduction – fertility				conclusive but not sufficient for classification
Toxicity to reproduction – development				conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation				conclusive but not sufficient for classification
Environment	N; R50/53	SCL: N; R50-53: C ≥ 0,025 % N; R51-53: 0,0025 % ≤ C < 0,025 % R52-53: 0,00025 % ≤ C < 0,0025 %	N; R50/53	

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
This dossier does not propose a change in the classification of this hazard property

Labelling:

Indication of danger: T; N : Toxic; Dangerous for the environment

R-phrases:
R23/25 : Toxic by inhalation and if swallowed
R50/53 : Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases:
(1/2) : Keep locked up and out of the reach of children
36/37 : Wear suitable protective clothing and gloves
45 : In case of accident or if you feel unwell seek medical

advice immediately (show the label where possible)

60 : This material and its container must be disposed of as hazardous waste

61 : Avoid release to the environment. Refer to special instructions/safety data sheet

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Pyridaben was added to Annex I of Directive 67/548/EEC in the 26th ATP (Commission Directive 2000/32/EC of 19 May 2000) with classification T; R23/25, N; R50/53.

2.2 Short summary of the scientific justification for the CLH proposal

A Draft Assessment Report (DAR) and Proposed Decision of the Netherlands has been prepared in the context of the possible inclusion of pyridaben in Annex I of Council Directive 91/414/EEC (Draft Assessment Report, March 2007 and subsequent addenda (2009 and 2010, RMS the Netherlands) concerning the placing of plant protection products on the market. The conclusions on the peer review of pesticide risk assessment of pyridaben was published in the EFSA journal (8(6):1632, 2010).

Review of these documents has revealed that the classification listed in Annex VI of Regulation EC no.1272/2008 (including the 1st ATP) needs two revisions.

In accordance with the criteria of the CLP regulation, pyridaben should be classified as Acute Tox. 3 (H301) and Acute Tox. 3 (H331). The reference indicating minimum classification (*) is no longer necessary. It is therefore proposed that the acute toxicity classification listed in Annex VI, part 3, Table 3.1, for pyridaben be updated by removal of the minimum classification indicated by the reference *.

Pyridaben is classified as Aquatic Acute 1 and Aquatic Chronic 1. However, a harmonized M-factor according to the CLP Regulation and SCLs according to Directive 1999/45/EC as amended by Directive 2006/8/EC are currently not listed in Annex VI of Regulation EC no. 1272/2008. In this dossier, a harmonized M-factor (both acute and chronic according to the criteria of the 2nd ATP) and SCLs for pyridaben are proposed.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Table 5: Current Annex VI table 3.1 classification and labelling

Classification		Labelling		
Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)
Acute Tox. 3* Acute Tox. 3* Aquatic Acute 1 Aquatic Chronic 1	H331 H301 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410	

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Table 6: Current Annex VI table 3.2 classification and labelling

Classification	Labelling
T; R23/25 N; R50/53	T; N R: 23/25-50/53

	S: (1/2-)36/37-45-60-61

2.4 Current self-classification and labelling

Not applicable

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Not applicable

2.4.2 Current self-classification and labelling based on DSD criteria

Not applicable

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Pyridaben is an active substance in the meaning of Directive 98/8/EEC and therefore subject to harmonised classification and labelling (CLP, article 36.2).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

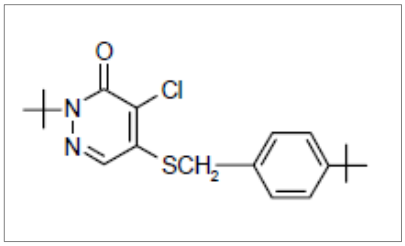
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 7: Substance identity

EC number:	405-700-3
EC name:	Pyridaben (ISO); 2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one
CAS number (EC inventory):	96489-71-3
CAS number:	96489-71-3
CAS name:	4-chloro-2-(1,1-dimethylethyl)-5-[[[4-(1,1-dimethylethyl)phenyl]methyl]thio]-3(2H)-pyridazinone
IUPAC name:	2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one
CLP Annex VI Index number:	613-149-00-7
Molecular formula:	$C_{19}H_{25}ClN_2OS$
Molecular weight range:	364.9

Structural formula:



1.2 Composition of the substance

Table 8 : Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Pyridaben	Minimum 980 g/kg	-	-

Current Annex VI entry:

Table 3.1: Acute Tox. 3* (H301), Acute Tox. 3* (H331), Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410)
Table 3.2: T; R23/25, N; R50/53

Table 9: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
			Based on the DAR there are no (eco)toxicological relevant impurities present.

Current Annex VI entry: Not applicable

Table 10: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
				Based on the DAR there are no (eco)toxicological relevant additives present.

Current Annex VI entry: Not applicable

1.2.1 Composition of test material

Not applicable

1.3 Physico-chemical properties

Table 11: Summary of physico-chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Pure: white crystalline solid with no detectable odour (23.6 °C) Technical: white odourless crystalline powder (25 °C)	DAR	
Melting/freezing point	109.4 to 110.6°C (100%) 107.9 to 109.6°C (98.3%)	DAR	measured
Boiling point	Thermal decomposition was observed before boiling occurred	DAR	measured
Relative density	1.201 g/cm^3 (100%) 1.204 g/cm^3 at 25°C (98.3%)	DAR	measured
Vapour pressure	<1x10^{-7} mbar at 52.7°C (98%) (equivalent to <1x10-5 Pa, calculated by RMS)	DAR	measured
Surface tension	Not applicable since the water solubility is below 1 mg/L (i.e. 0.022 mg/L)	DAR	
Water solubility	0.022 mg/L in distalled water at 20°C (99.9%)	DAR	measured
Partition coefficient n-octanol/water	Log Pow at 23°C: >6.37	DAR	measured
Flash point	Not applicable for solids	DAR	
Flammability	Not flammable	DAR	
Explosive properties	Not sensitive to shock. Thermally stable and not thermally explosive (98.3%)	DAR	
Self-ignition temperature	No auto-ignition up to 475°C	DAR	measured
Oxidising properties	No oxidizing properties	DAR	
Granulometry	No data	-	
Stability in organic solvents and identity of relevant degradation products	No data	-	
Dissociation constant	Not applicable, pyridaben does not dissociate.	DAR	
Viscosity	No data	-	

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this dossier

2.2 Identified uses

Pyridaben is an insecticide and acaricide.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

The physico-chemical properties of pyridaben were assessed in the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of pyridaben in Annex I of Council Directive 91/414/EEC (Draft Assessment Report, March 2007 and subsequent addenda (2009 and 2010, RMS the Netherlands) concerning the placing of plant protection products on the market.

No changes in the classification for the physico-chemical endpoints are proposed in this dossier. For this reason, it is considered not warranted to present the data relating on physical hazards in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

The human health hazards of pyridaben were assessed in the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of pyridaben in Annex I of Council Directive 91/414/EEC (Draft Assessment Report, March 2007 and subsequent addenda (2009 and 2010, RMS the Netherlands) concerning the placing of plant protection products on the market.

Based on a review of the available data on acute toxicity, an update in the classification is needed. The summaries included in this proposal are copied from the DAR (and its addenda and assessment reports when these contain updated information). Detailed information is only included for the key study used to derive the classification. For an overview of the hazard property being evaluated, all reliable information relating to that property has been summarized in a table. References to individual studies are not included. For more details the reader is referred to the DAR and its addenda.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this dossier.

4.2 Acute toxicity

The results of the acute toxicity studies relevant for the classification update are summarized in Table 12. Only reliable and validated acute toxicity tests accepted for risk assessment from Draft Assessment Reports are shown in this table.

Table 12: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Oral toxicity			
OECD 401	**LD_{50} male: 161 mg/kg bw** LD_{50} female: 181 mg/kg bw	Rat, CD strain	DAR
OECD 401	LD_{50} female: 205 mg/kg bw	Mouse, Crj:CD-1 (ICR), females	DAR
OECD 401	LD_{50} male: 253 mg/kg bw	Mouse, Crj:CD-1 (ICR), males	DAR
OECD 401	LD_{50} female: 383 mg/kg bw LD_{50} male: 424 mg/kg bw	Mouse, Crj:CD-1 (ICR)	DAR
OECD 401	LD_{50} female: 570 mg/kg bw LD_{50} male: 1100 mg/kg bw	Rat, Crj:CD (SD)	DAR
OECD 401	LD_{50} female: 820 mg/kg bw LD_{50} male: 1350 mg/kg bw	Rat, CD strain	DAR
Inhalation toxicity			
OECD 403	**LC_{50} female: 0.62 mg/L** LC_{50} male: 0.66 mg/L	Rat, Fischer (F344/Ducrj)	DAR

Remark: all above listed studies were performed with NC-129 (Pyridaben, 98.0% purity)).

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

The critical study for acute oral toxicity was performed in rats in accordance with OECD 401 (1987) and GLP and is considered acceptable. Animals (5 rats/sex/dose) received single gavage doses of 81, 128 and 202 mg/kg bw pyridaben in maize oil (doses based on a dose-range finding study).

Mortality: One female given 128 mg/kg bw was found dead on day 2. In the 202 mg/kg dose group, 3/5 females (1 was humanely killed) and 5/5 males died between day 2 and 5.

Symptoms of toxicity: In all dose groups, nearly all animals showed ungroomed appearance. Surviving animals in the 128 and 202 mg/kg dose groups, showed reduced activity, staggering gait, hair loss, piloerection, salivation, thin body conformation and hunched posture. These symptoms were also seen in rats before death. In surviving animals the symptoms disappeared before the end of the study in the low-dose group, in females of the mid-dose group, and in one female of the high-dose group.

Body weight: Rats given 128 and 202 mg/kg showed a decrease in body weight during the first 4 days and a regain thereafter. Body weight gain decreased too.

Pathology: No significant observations were seen at necropsy for animals surviving to study termination from any of the dosage levels. Three animals that died during the study showed yellow staining (external), and one showed hair loss. No internal macroscopic findings were observed.

Conclusions: The acute oral LD_{50} of NC-129 was found to be 161 mg/kg bw in male rats and 181 mg/kg bw in female rats.

4.2.1.2 Acute toxicity: inhalation

The critical study for acute inhalation toxicity was performed in accordance with OECD 403 (1981) and GLP and is considered acceptable. Animals (10 rats/sex/dose) were exposed (whole-body) to actual concentrations of 0, 0.41, 0.50, 0.57, 0.66, 0.73, 0.86, 1.02 and 5.48 mg/L pyridaben (MMAD: 3.7-4.8 μm; GSD 1.7-1.8 μm). White carbon was used as a vehicle. The findings are listed below.

Mortality: During exposure or within 1 hour after exposure, 5/10, 6/10, 10/10, 8/10 and 10/10 males were found dead at 0.66, 0.73, 0.86, 1.02 and 5.48 mg/l pyridaben, respectively. 1/10 female given 0.41 mg/l was found dead on day 1. Within 1 day after exposure, 4/10 females given 0.50 and 0.57 mg/l and 6/10 females given 0.66 and 0.73 mg/l were found dead. All females died within 5 hours after exposure to 0.86, 1.02 and 5.48 mg/l.

Symptoms of toxicity: All animals (including controls) showed eyelid closure and slow and deep respiration during exposure. Several exposed females in all dose groups showed lacrimation. At 0.66 mg/l and above, some animals gasped during exposure. After exposure several animals in all dose groups showed slow and deep respiration, a blotted fur of the perianal region and/or loose faeces around the anus, and reddening of the auricles. Nearly all animals (including controls) showed reddish brown staining around the nose after exposure. In surviving animals all symptoms disappeared before the end of the study.

Body weight: Mean body weights of male rats given 1.02 and 0.73 mg/l decreased after exposure, and increased after day 5. Male rats exposed to 0.66 mg/l or less showed decreased mean body weights after exposure, and increases after day 3. Mean body weights of female rats given 0.73 mg/l or less decreased after exposure, and increased after day 3. Control animals showed a decrease after exposure that recovered after day 1.

Pathology: Several animals that survived to the end of the study (including controls) showed dark redcoloured lungs and/or dark red spots in the lungs. Symptoms seen in dead animals were among others distended stomach, lung oedema, dark red (spots in the) lungs, white powder in tracheal lumen, hydrothorax, and dark-coloured liver. No histopathological changes were observed.

Conclusions: The acute inhalation LC_{50} of pyridaben in rats was found to be 0.66 mg/l for male rats, and 0.62 mg/l for female rats.

4.2.1.3 Acute toxicity: dermal

No change is needed for this hazard property and therefore, no data are included in the dossier.

4.2.1.4 Acute toxicity: other

No data available.

4.2.2 Human information

No data available.

4.2.3 Summary and discussion of acute toxicity

The lowest LD_{50}/LC_{50} values of pyridaben were 161 mg/kg bw (male rat) for the oral route and 0.62 mg/L (female rat) via the inhalation route.

4.2.4 Comparison with criteria

CLP

According to the CLP pyridaben should be classified as Acute Tox. category 3 for the oral route because the lowest LD_{50} is within the limits, 50 < ATE ≤ 300 (oral, mg/kg bw) and Acute Tox. category 3 for the inhalation route because the LC_{50} is within the limits, 0.5 < ATE ≤ 1.0 (dusts and mists (mg/L)). Pyridaben is classified as such already in Annex VI, table 3.1. Therefore, the minimum classification Acute Tox Cat 3* is considered no longer necessary and consequentially the * can be removed.

67/548/EEC

The current classification according to 67/548/EEC remains unchanged.

4.2.5 Conclusions on classification and labelling

Table 13: Conclusion on classification for acute toxicity

	CLP Regulation	**Directive 67/548/EEC (DSD)**
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 3 (H301) Acute Tox 3 (H331)	T; R23/25

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Pyridaben has currently the harmonized classification of acute oral and inhalation toxicity in the Annex VI to CLP Regulation: Acute Tox. 3* (H301) and Acute Tox. 3* (H331); and T; R23/25

The Dossier Submitter provided the following data on oral and inhalation toxicity of pyribaden indicating that the "*" could be removed:

Method	**Results**	**Remarks**	**Reference**
Oral toxicity			
OECD 401	**LD_{50} male: 161 mg/kg bw** LD_{50} female: 181 mg/kg bw	Rat, CD strain	DAR 2007, Vol 3 B 6
OECD 401	LD_{50} female: 205 mg/kg bw	Mouse, Crj:CD-1 (ICR), females	DAR 2007, Vol 3 B 6
OECD 401	LD_{50} male: 253 mg/kg bw	Mouse, Crj:CD-1 (ICR), males	DAR 2007, Vol 3 B 6
OECD 401	LD_{50} female: 383 mg/kg bw LD_{50} male: 424 mg/kg bw	Mouse, Crj:CD-1 (ICR)	DAR 2007, Vol 3 B 6
OECD 401	LD_{50} female: 570 mg/kg bw LD_{50} male: 1100 mg/kg bw	Rat, Crj:CD (SD)	DAR 2007, Vol 3 B 6
OECD 401	LD_{50} female: 820 mg/kg bw LD_{50} male: 1350 mg/kg bw	Rat, CD strain	DAR 2007, Vol 3 B 6
Inhalation toxicity			
OECD 403	**LC_{50} female: 0.62 mg/L**	Rat, Fischer (F344/Ducrj)	DAR 2007, Vol 3 B 6

	LC_{50} male: 0.66 mg/L		

Based on these data the Dossier Submitter concluded that according to the CLP pyridaben should be classified as Acute Tox. category 3 for the oral route because the lowest LD50 is within the limits, 50 < ATE ≤ 300 (oral, mg/kg bw) and Acute Tox. category 3 for the inhalation route because the LC50 is within the limits, 0.5 < ATE ≤ 1.0 (dusts and mists (mg/L)). Pyridaben is classified as such already in Annex VI, table 3.1. Therefore, the minimum classification Acute Tox Cat 3* is considered no longer necessary and consequentially the * can be removed. [Font]The current classification according to 67/548/EEC should remain unchanged.

Comments received during public consultation

Three MSCAs expressed support for the classification of pyridaben as acute tox. 3 (H301 and H331) based on the data provided.

Assessment and comparison with the classification criteria

The lowest acute oral LD_{50} of Pyridaben was found in rats to be 161 mg/kg bw in male and 181 mg/kg bw in female rats and 205mg/kg bw for female and 253 for male mice. Since the acute oral median lethal dose (LD_{50}) of Pyribaden to rats and mice is within the range of 50 < ATE ≤ 300 (oral, mg/kg bw), this substance meets CLP classification criteria for category Acute Tox 3 with hazard statement H301.

The acute (4 hours exposure) median lethal concentration LC_{50} for inhalation of Pyridaben (as an aerosol) was found in rats to be 0.62 mg/L in males and 0.66 mg/L in females. Since the acute median lethal concentration (LC_{50}) for inhalation of Pyribaden for rats is within the range 0.5 < ATE ≤ 1.0 (dusts and Mists, mg/L), this substance meets CLP classification criteria for category Acute Tox 3 with hazard statement H331.

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental fate and ecotoxicological properties of pyridaben were assessed in the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of pyridaben in Annex I of Council Directive 91/414/EEC (Draft Assessment Report, March 2007 and subsequent addenda (2009 and 2010, RMS the Netherlands) concerning the placing of plant protection products on the market.

Based on a review of the available data on aquatic toxicity, an update of the environmental classification is needed. The summaries included in this proposal are copied from the DAR (and its addenda and assessment reports when these contain updated information). Detailed information is only included for the key study used to derive the classification. For an overview of the hazard property being evaluated, all reliable information relating to that property has been summarized in a table. References to individual studies are not included. For more details the reader is referred to the DAR and its addenda.

5.1 Degradation

Table 14: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Hydrolysis: guideline EPA N:161.1	No hydrolytic degradation after 30 days incubation at pH 5.0, pH 7.0 and pH 9.0 at 25°C.	Test substance: Pyridaben-^{14}C, 99.18% pure	DAR
Ready biodegradability: guideline EEC C.4-C, OECD 301B	not readily biodegradable	Test substance: Pyridaben technical, 99.2% pure	DAR
Water-sediment simulation test: guidelines SETAC 1995, BBA IV, 5-1	Not rapidly degradable	Test substance: Pyridaben, chemical purity not reported, radiochemical purity 99.5 - 99.8%	DAR

5.1.1 Stability

Pyridaben is hydrolytically stable in water at pH 5.0, pH 7.0 and pH 9.0 and 25°C.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

Not relevant

5.1.2.2 Biodegradation screening tests

The ready biodegradability of pyridaben was studied in a modified Sturm test in accordance with OECD 301B and GLP. Test solutions (3000 mL, duplicate) containing pyridaben (10 mg C/L) and activated sludge inoculum (30 mg solids/L) were incubated in siliconised flasks (to reduce

adsorption to glass) in the dark for 28 days at a measured temperature of 20.8-22.9°C under continuous magnetic stirring with a supply of CO_2 free air. Outgoing air was passed through three adsorption bottles containing 0.025 N $Ba(OH)_2$ solution. Duplicate flasks for inoculum blank controls (inoculum, no test substance) and single flasks for the reference substance (sodium benzoate, 10 mg C/L) and the inhibition control (pyridaben and sodium benzoate, both 10 mg C/L) were included. On day 28, concentrated HCl (1 mL) added to each flask to drive off dissolved CO_2 and the contents of the vessels were aerated overnight. CO_2 evolution from each flask was determined by titration of residual $Ba(OH)_2$ on day 2, 3, 5, 7, 9, 13, 20, 28 and 29.

Results: CO_2 evolution in the controls (83-84 mg after 29 days) satisfied the validity criterion of OECD 301B (≤120 mg). The pass level for the reference substance (60% degradation) was reached within 7 days. Pyridaben did not show inhibitory effects on the inoculum. Pyridaben was not readily biodegradable in this test (≤3% biodegradation after 29 days).

5.1.2.3 Biodegradation simulation tests

The behaviour of [benzene-U-^{14}C]-pyridaben and [pyridazinone-3,6-^{14}C]-pyridaben was studied in two water/sediment systems (silty clay and sandy silt loam) according to guidelines SETAC, 1995 and BBA IV, 5-1. The water/sediment systems were treated with a test substance concentration of 12 µg/L and incubated at 20°C in the dark for 120 days. The levels of parent pyridaben reached a maximum in sediment of 41-55% AR on day 2-14, and pyridaben dissipated from the sediment with persistence half-lives of 49-207 days, and from the water phase with persistence half-lives of 0.4-7.7 days. The non-extractable fraction in sediment increased to a maximum of 34-47% AR on day 59-120. Mineralisation of the radiolabels accounted for between 0.1 and 6.2 % AR on day 120 (presumably CO_2).
The RMS re-calculated the persistence endpoints by taking the mean of the two radiolabels for each system and then taking the geomean over the two systems. This resulted in DT_{50} values of 1.9 days for the water phase, 20.5 days for the total water/sediment system and 90.6 days for sediment.
The main metabolite was PB-7, which reached maximum levels in water and sediment of 5.8-17% AR and 11-14% AR respectively. No DT_{50} values could be determined for PB-7. No other metabolites were found at >10% AR in water or sediment.

5.1.2 Summary and discussion of degradation

Pyridaben is hydrolytically stable and does not readily biodegrade. In a water-sediment simulation study the substance had a half-live in the total system and in sediment of 20.5 and 90.6 days, respectively. Mineralisation of pyridaben was slow with radioactivity in traps at levels of 0.1 - 8.2% AR at 90 to 120 days. Based on these findings pyridaben is qualified as not rapidly degradable.

Pyridaben is susceptible to primary degradation under formation of a range of metabolites of which only PB-7 exceeds levels of 10% AR.

5.2 Environmental distribution

Not applicable for this dossier.

5.3 Aquatic Bioaccumulation

The log Kow of pyridaben is > 4 and has therefore a potential for bioaccumulation. This end point is not further evaluated as it does not influence the determination of an M-factor or the specific concentration limits.

5.4 Aquatic toxicity

The results of the aquatic toxicity data relevant for the classification update are summarized in Table 15. Only reliable and validated ecotoxicity tests accepted for risk assessment from Draft Assessment Reports are shown in this table.

Table 15: Summary of relevant information on aquatic toxicity (the lowest toxicity values are in bold)-

Test Guideline	Purity	Species	Condition	Endpoint	Toxicity values in µg/L* a.s
Short and Long-Term Toxicity to Fish					
Short-Term					
EPA 72-1	100 %	Rainbow trout (*Oncorhynchus mykiss*)	Flow-through	96h-LC_{50}	0.73
EPA 72-1	100%	Bluegill sunfish (*Lepomis macrochirus*)	Flow-through	96h-LC_{50}	3.5
EPA 72-3	100%	Sheepshead minnow (*Cyprinodon variegatus*)	Flow-through	96h-LC_{50}	17
Long-Term EPA 72-5	labelled: 93.2%; unlabelled: 99.5-99.8%	Fathead minnow (*Pimephales promelas*)	Flow-through	NOEC (301d)	0.28
Short and Long-Term Toxicity to Aquatic Invertebrates					
Short-Term					
EPA 72-2 (a)	99.7%	*Daphnia magna*	Flow-through	48h-LC_{50}	1.0
EPA 72-3	99.7%	Marine shrimp (*Mysidopsis bahia*)	Flow-through	**96h-LC_{50}**	**0.67**
Long-Term					
EPA 72-4	labelled: 100%; unlabelled > 99%	*Daphnia magna*	Flow-through	NOEC (21d)	0.086
EPA 72-4 (c)	labelled: 99.6%; unlabelled: > 99%	*Mysidopsis bahia*	Flow-through	**NOEC (35d)**	**0.047**
Algae					
EPA 122-2	99.7%		Static	EbC_{50} and Erc_{50}	
		S. capricornutum		72-h	>17
		A. flos-aquae		120-h	>13
		N. pelliculosa		120-h	>14
		S. costatum		120-h	>16

* mean measured concentration

5.4.1 Aquatic invertebrates

5.4.1.1 Short-term toxicity to aquatic invertebrates

The critical study for acute aquatic toxicity was performed with *Mysidopsis bahia* in accordance with EPA 72-3 and GLP and is considered acceptable. In this study the salt-water shrimp *Mysidopsis bahia* (4 replicates of 5 shrimps each per concentration) was exposed to pyridaben (99.7% purity) at nominal test concentrations of 0, 0.14, 0.24, 0.40, 0.66 and 1.1 µg/L and vehicle control for 96 hours under flow-through conditions.

Results: The measured concentrations were 0.14, 0.21, 0.47, 0.65 and 0.87 µg/L at test initiation (representing 79-116% of nominal), and 0.16, 0.15, 0.36, 0.69 and 0.76 µg/L at the end of exposure (representing 63-113% of nominal). Endpoints were based on mean measured concentrations, which is acceptable. Water quality parameters (pH, oxygen concentration and temperature) were in accordance with the EPA 72-3 guideline. The 96-hour LC50 value was 0.67 µg/L based on mean measured concentrations.

5.4.1.2 Long-term toxicity to aquatic invertebrates

The critical study for chronic aquatic toxicity was performed with *Mysidopsis bahia* in accordance with EPA 72-4 (c) and GLP and is considered acceptable. In this study the chronic toxicity of [^{14}C]Pyridaben Technical (radiochemical purity >99%, chemical purity >99%) to *Mysidopsis bahia* was assessed in a 35-day flow-through study. Mysids (≤24 hours old, 60 per treatment, 30 mysids per replicate vessel) were used to initiate the study. The nominal concentrations were 0.0094, 0.019, 0.038, 0.075 and 0.15 µg/L plus a blank- and solvent-control (acetone). Mean measured radioactivity concentrations, determined by LSC, were 0.0086, 0.017, 0.033, 0.070 and 0.13 µg eq./L, representing 86 to 93% of nominal. HPLC analysis confirmed that the stock solution contained the nominal pyridaben concentration at the start and the end of the test, but the mean measured concentration of the test solutions of the highest test concentration during the test period was 0.10 µg a.s./L, representing only 67% of nominal. Radioactivity in test solutions of lower concentrations was not analysed by HPLC. Water quality parameters were in accordance with the EPA 72-4 guideline. On day 15, males and females were paired and redistributed into glass pairing jars (1 pair from each exposure aquarium per jar). The remaining mysids were pooled and placed in one of the initial retention chambers until study end. Survival and sub-lethal effects were assessed during the first 15 days of the study, reproduction and mortality of males and females were assessed after pairing (day 15) and body length and dry weight were assessed at the end of the test.

Results: Survival and growth of mysids were not affected at any concentration when compared to the pooled controls. At termination of the standard 28 day exposure, reproduction among solvent control organisms did reach the minimum requirement of the OPPTS 850.1350 guideline (≥75% of females should be producing young), but that of the dilution water control organisms did not (55% of females were producing young). For this reason, the study was extended from 28 to 35 days, but there was no improvement in the dilution water control. The other validity criterion of the OPPTS 850.1350 guideline however (at least 3 young per female) was satisfied by both controls. Therefore, the test is accepted. Reproduction was reduced by 47% and 46% at 0.13 µg eq./L, when compared to the pooled control group, after 28 and 35 days, respectively. This difference was not statistically significant due to large variation in the control and treated groups (the number of offspring per female per reproductive day in the two replicates of the blank-control, solvent-control and 0.13 µg eq./L, respectively, was 0.15-0.17, 0.12-0.26 and 0.05-0.13 at day 28, and 0.10-0.11, 0.08-0.19 and 0.03-0.10 at day 35). The reported NOEC value was 0.13 µg eq./L, based on the lack of statistically significant effects. However, the effect at 0.13 µg eq./L on reproduction was almost 50%, and the results at the lower test concentration do not provide a justification to discount this large reduction as a random finding. The DAR states that the rapporteur (RMS) set the NOEC at 0.070 µg eq./L, which is equivalent to 0.047 µg a.s./L when taking into consideration the percentage of pyridaben in the test solution of the highest test concentration (67%, as measured by HPLC; no HPLC measurements were performed at lower concentrations). The overall NOEC for mysid mortality, reproduction and growth was 0.070 µg eq./L, equivalent to 0.047 µg a.s./L.

5.5 Comparison with criteria for environmental hazards

CLP- Acute aquatic hazards

Acute toxicity data are available for all three trophic levels. The lowest L(E)C_{50} value of 0.67 µg/L is obtained for aquatic invertebrates. Based on this information pyridaben fulfils criteria for classification as Aquatic Acute Cat. 1. with an M-factor of 1000 (toxicity band: 0.0001 < L(E)50 ≤ 0.001 mg/L).

M-factor for chronic aquatic hazard (CLP)

Chronic toxicity data are available for all three trophic levels. The lowest NOEC value of 0.047 µg/l is obtained for aquatic invertebrates . Pyridaben is qualified as not rapid degradability. Based on this

information pyridaben fulfils criteria for classification as Aquatic Chronic Cat. 1. with an M-factor of 1000 (toxicity band: 0.00001 < NOEC ≤ 0.0001 mg/L).

SCL (Directive 67/548/EEC)

The lowest $L(E)C_{50}$ obtained for pyridaben is 0.67 µg/L in invertebrates. Therefore, the specific concentration limits (SCL) of N; R50-53: C≥ 0,025 %, N; R51-53: 0,0025 % ≤C< 0,025 %, R52-53: 0,00025 % ≤ C< 0,0025 % are proposed, where C is the concentration of pyridaben in a mixture.

5.6 Conclusions on classification and labelling for environmental hazards

Table 16 : Conclusion on environmental classification

	CLP Regulation	**Directive 67/548/EEC (DSD)**
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410) M-factor Acute M-factor 1000 Chronic M-factor 1000	N; R50-53 SCL: N; R50-53: C ≥ 0,025 % N; R51-53: 0,0025 % ≤ C < 0,025 % R52-53: 0,00025 % ≤ C < 0,0025 %

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Pyridaben is already classified in Annex VI of the CLP Regulation as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410), but without harmonized M-factors. The Dossier Submitter proposed to set an M-factor of 1,000 for both acute and chronic hazard in accordance with CLP (with equivalent specific concentration limits under the DSD). This proposal was based on short- and long-term marine invertebrate toxicity results (96-h LC_{50} of 0.67 µg/L and 35-d NOEC of 0.047 µg/L, respectively), together with the fact that the substance is not rapidly degradable (or readily biodegradable).

Comments received during public consultation

Five EU Member States indicated support for the proposal, and no further information was submitted.

Assessment and comparison with the classification criteria

Degradability: Pyridaben is hydrolytically stable in water at pH 5, 7 and 9 at 25°C. It failed a test for ready biodegradation (achieving at most 3% mineralization in 29 days). Simulation tests in two aerobic water-sediment systems using radio-labeled substance indicated primary degradation, with a half-life of approximately 20.5 days for the total water/sediment system (results were averaged for the two test systems as well as differently radio-labelled test substance; this is not considered important for classification purposes in this case). A maximum of 6.2% mineralization occurred over 120 days.

On this basis, pyridaben does not meet the criteria for being rapidly degradable (or readily biodegradable) in the environment.

Bioaccumulation: The log n-octanol-water partition coefficient (K_{ow}) of pyridaben is >6.37 at 23°C. It therefore has a potential for bioaccumulation. However, in view of the degradability conclusion this end point does not influence the determination of an M-factor or the specific concentration limits, so was not considered further.

Ecotoxicity: The lowest reliable ecotoxicity results were as follows (the key studies are highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	*Oncorhynchus mykiss*	96-h LC_{50} = 0.73 µg/L	-
	Pimephales promelas	-	301-d NOEC = 0.28 µg/L
Aquatic invertebrates	*Daphnia magna*	48-h LC_{50} = 1.0 µg/L	21-d NOEC = 0.086 µg/L
	*Americamysis bahia**	**96-h LC_{50} = 0.67 µg/L**	**35-d NOEC = 0.047 µg/L**
Aquatic algae and plants	*Four species*	Acute E_rC_{50} > 13 µg/L	-

* The CLH report uses the former name *Mysidopsis bahia*

All toxicity values are based on mean measured concentrations, with the exception of the aquatic algal toxicity studies. The DAR (2007; but not the CLH report) indicates that test

substance concentrations in the algal tests dropped below the analytical detection limit after 5 days (due to light instability), so initial measured concentrations were used (the same nominal concentration was used for each species). Only one of the tested species (*Skeletonema costatum*) experienced a significant level of growth inhibition (20% after 120 hours), so failure to maintain test concentration and lack of information on algal EC_{10}/NOECs is not considered to be relevant to the classification.

A long-term result is not available for the most acutely sensitive fish species, and there appear to be no acute data for the only species for which long-term data are available. The acute sensitivity for three species presented in the CLH report varies over an order of magnitude. The reported long-term NOEC was very similar to the reported acute LC_{50}. It is therefore relevant to consider the surrogate approach for fish.

The *Americamysis* studies were considered to provide the key data. The long-term result was obtained from a slightly longer duration than the usual 28-day test. Reproduction among dilution water control organisms did not reach the minimum requirement of the test guideline after 28 days. The study was therefore extended to 35 days, but there was no improvement in the dilution water control. All other validity criteria were satisfied, so overall the test was considered to be acceptable.

The substance is an insecticide and acaricide but no aquatic insects were included in the data set presented by the dossier submitter. RAC noted that the DAR included a long-term toxicity study with one insect species (*Chironomus riparius*), but this involved sediment as well as aqueous exposure. The NOEC in this study (based on the concentration in the aqueous phase) was two orders of magnitude higher than the NOEC obtained for* Americamysis bahia*, so it was not considered further for the classification of pyridaben.

Classification according to CLP

Acute aquatic hazard:
Acute toxicity data were available for all three trophic levels. The lowest reliable short-term aquatic toxicity result was a 96-h LC_{50} of 0.67 µg/L for the marine invertebrate *Americamysis bahia*. This result was very similar to acute toxicity values for both fish and other invertebrates. Pyridaben was therefore classified as Aquatic Acute 1 (H400), with an M-factor of 1,000 ($0.0001 < L(E)C_{50} < 0.001$ mg/L).

Chronic aquatic hazard:
Pyridaben was not considered to be rapidly degradable. Although the CLH report indicated that long-term toxicity data were available for all three trophic levels, no information was provided for algae, and it is not clear whether the result for fish was from the most acutely sensitive species. Algae appear to be significantly less sensitive than fish and invertebrates. The lowest reported value was a 35-d NOEC of 0.047 µg/L for the marine invertebrate *Americamysis bahia*. This is supported by a similar value for *Daphnia*. These concentrations are below the threshold value of 0.1 mg/L for non-rapidly degradable substances, leading to classification as Aquatic Chronic 1 (H410) with an M-factor of 1,000 ($0.00001 < NOEC < 0.0001$ mg/L).

The surrogate approach was considered for fish since it was not clear what the chronic toxicity would be for the most acutely sensitive species. However, based on the lowest acute LC_{50} of 0.73 µg/L combined with the substance's lack of rapid degradability, a more stringent M-factor was not necessary.

In summary, pyridaben classification as Aquatic Chronic 1 (H410), with an M-factor of 1,000 is justified.

Classification according to DSD

The lack of ready biodegradation and a 96-h LC_{50} of 0.67 µg/L for invertebrates (with a

similar value for fish) mean that pyridaben fulfils the criteria for classification with N; R50-53. The following specific concentration limits are therefore applicable:

Concentration of pyridaben in the mixture, C (w/w)	Classification of the mixture
C ≥ 0.025%	N; R50-53
0.0025% ≤ C < 0.025%	N; R51-53
0.00025% ≤ C < 0.0025%	R52-53

In summary, the RAC agreed with the original proposal of the Dossier Submitter.

5 OTHER INFORMATION

6 REFERENCES

1. European Commission (2007). Pyridaben, Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of pyridaben in Annex I of Council Directive 91/414/EEC, March 2007. Rapporteur Member State: The Netherlands.

2. European Food Safety Authority (2010). Conclusion on the peer review of the pesticide risk assessment of the active substance pyridaben. EFSA Journal 2010; 8(6):1632