CLH report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **BIFENTHRIN**[1]

EC Number: Not allocated

CAS Number: 82657-04-3

Submitted by: **France**

Date: **December 2009**

Version **2**

[1] According to the CAS entry Bifenthrin is defined as solely the cis-isomer (ratio of (1R,3R):(1S,3S) is 50:50); whereas the literature defines Bifenthrin as a combination of cis-isomers and trans-isomers (ratio 97:3) (BCPC & The Royal Society of Chemistry, 1994).

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Substance Name: bifenthrin

EC Number: not allocated

CAS number: 82657-04-3

Registration number (s): not applicable

Purity: >= 930 g/kg

Impurities: This information is confidential and then provided in the confidential part of the dossier provided in appendix 1.

Proposed classification based on Directive 67/548/EEC criteria:

Carc. Cat 3; R40
T; R23/25
Xn; R48/22
R43
N; R50/53

Proposed classification based on CLP criteria:

Carc.2 – H351
Acute Tox. 3 – H331
Acute Tox. 3 – H301
STOT Rep. 1 – H372
Skin Sens. 1 – H317
Aquatic. Acute 1– H400
Aquatic. Chronic 1 – H410

Proposed labelling:

Symbol(s): T, N

R-phrases: R23/25; R40; R43; R48/22; R50/53

S-phrases: S23, S36/37, S38, S45, S60, S61

Proposed specific concentration limits (if any):

A M-factor = 10 000 is proposed.

Proposed notes (if any):

None

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Bifenthrin
EC Name:	Not allocated
CAS Number:	82657-04-3
IUPAC Name:	Reaction mass of 2-methyl-3-phenylbenzyl (1R,3R)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1R,3R)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

1.2 Composition of the substance

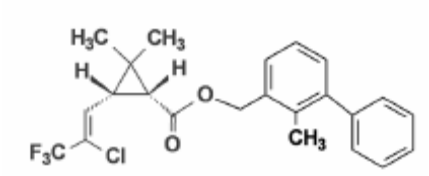
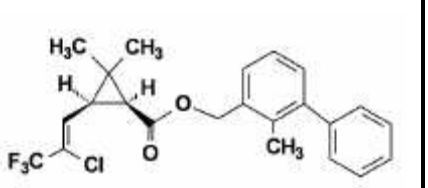
The substance bifenthrin includes 4 isomers. The cis-Z isomer pair is the predominant species comprising $\geq$ 98% total Bifenthrin (see structure below). The concentration of other isomers is presented in the confidential part (appendix 1).

Chemical Name:	Bifenthrin
EC Number:	Not allocated
CAS Number:	82657-04-3
IUPAC Name:	Reaction mass of 2-methyl-3-phenylbenzyl (1R,3R)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1R,3R)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate
CAS Name:	Cyclopropanecarboxylic acid, 3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethyl-, (2-methyl[1,1'-biphenyl]-3-yl)methyl ester, (1R,3R)-rel-
Related CAS information:	CAS#: 439680-76-9 ((1R-cis-Bifenthrin) CAS#: 439680-77-0 (1S-cis-Bifenthrin) CAS #: 552880-52-1 ((1R)-trans-Bifenthrin) CAS#: 83322-02-5

CAS#: 87648-90-6
CAS#: 87680-56-6
CAS#: 99267-18-2
CAS#: 107538-31-8
CAS#: 107538-33-0
CAS#: 107538-34-1
CAS#: 207347-00-0

Molecular Formula: $C_{23}H_{22}ClF_3O_2$

Structural Formula

Z-isomers, min. 98% (ratio 1:1)	
Z-(1R,3R)	Z –(1S,3S)
	

Molecular Weight: 422.88

Typical concentration (% w/w): ≥93%
with > 98% (Z isomeric pair)
<2 % (E isomeric pair)

Concentration range (% w/w): > 93%

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Purity/Specification	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	4.1	Purified bifenthrin (96.1%)	Waxy beige solid	Spruit W.E.T., et al. 2002
VII, 7.2	Melting/freezing point	4.2	Purified bifenthrin (96.1%)	66.6 - 69.0 °C	Spruit W.E.T., et al. 2002
VII, 7.3	Boiling point	4.3	Purified bifenthrin (96.1%)	Decomposition at 285°C before boiling.	Spruit W.E.T., et al. 2002
VII, 7.4	Relative density	4.4 density	Purified bifenthrin (96.1%)	1.316 g cm^3 at 24°C	Spruit W.E.T., et al. 2002
VII, 7.5	Vapour pressure	4.6	Purified bifenthrin (96.5%)	2.431 10^{-5} Pa at 25°C	Hu, H.C., 1983
VII, 7.7	Water solubility	4.8	Purified bifenthrin (97.8%)	< 1 µg/l (pH 4.05) at 20°C < 1 µg/l (pH 7.04) at 20°C 3.76 µg/l (pH 9.22) at 20°C	Françon B. & D. Zenide, 1999
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7 partition coefficient	Purified bifenthrin (96.5%)	log P > 6	Herbst R.M., 1983a
VII, 7.9	Flash point	4.11	Bifenthrin technical (94.93%)	Higher than 110°C	Spruit W.E.T., et al. 2002
VII, 7.10	Flammability	4.13	Bifenthrin technical (94.93%)	No pyrophoric properties	Spruit W.E.T., et al. 2002
VII, 7.11	Explosive properties	4.14	Bifenthrin technical (94.93%)	No explosive properties	Spruit W.E.T., et al. 2002
VII, 7.13	Oxidising properties	4.15	Bifenthrin technical (94.93%)	No oxidizing properties	Spruit W.E.T., et al. 2002
	Auto flammability	4.12	Bifenthrin technical (94.93%)	Not auto-flammable	Spruit W.E.T., et al. 2002
	Thermal stability	4.19	Bifenthrin technical (94.93%)	Not thermally stable in the sense of OECD 113	Spruit W.E.T., et al. 2002
	Solubility in organic solvents	4.9	Bifenthrin technical (94.93%)	Methanol = 48.0g/L Xylen= 556.3g/L Acetone = 735.7g/L N heptane = 144.5g/L Ethyl acetate = 579.8g/L 1,2 dichloroethane = 743.2g/L temperature: 20°C	Spruit W.E.T., et al. 2002

Table 4.1.1-1: Summary of physico- chemical properties

The purity indicated for the physico-chemical properties corresponds to the total bifenthrin. In order to obtain the purity of the substance (cis-Z isomers), a factor of 98% should be applied to the values indicated in the table.

2 MANUFACTURE AND USES

Not relevant for a classification and labeling report.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

The substance is not currently classified in annex I of Directive 67/548/EEC or in Annex VI of CLP regulation.

3.2 Self-classification(s)

A classification Xn; R20, T; R25, R43, N; R50/53 was first proposed by the industry in the scope of the Biocidal Product Directive (98/8/CE).

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Hydrolysis in water

A hydrolysis experiment (not under GLP) carried out in buffers with pH 5, pH 7 and pH 9 at 25°C and on test material with a purity of 96.5% showed that bifenthrin is **hydrolytically stable** in water. At initial test concentrations of 0.52 and 5.22 mg/L the DT_{50} value was >22 d at each pH tested (Herbst, 1983). This study suffers several deficiencies, mainly as regards the high concentrations tested, which are higher than the solubility of the substance. Repetition was not deemed necessary however since hydrolysis does not appear to be a major degradation pathway. This is confirmed by the relative stability of bifenthrin in simulation tests (soil, water/sediment).

Photolysis in water

Two photolysis studies are available. In the first photolysis experiment (not under GLP), bifenthrin (purity of test material: 96.6%) is degraded under artificial sunlight with half-life of 11.9 days (irradiation). The main degradation product is the TFP acid (max. 38.4%, 14d). Under natural late summer outdoor sunlight irradiation at 41° N (USA) photolysis of bifenthrin was slow with a half-life of about 255 days. No photoproduct accounted for more than 3% (Wu, 1986).

The second photolysis experiment (GLP; following the draft OECD guideline, 2000), performed under artificial lighting and on test material with a purity > 95%, shows that bifenthrin degrades in water under influence of light with irradiation half-life of ca 10 days (24.4 d under sunlight conditions comparable to natural sunlight of the first experiment) (Curry, 2006). In both studies, results obtained with artificial sunlight are comparable, however, the second study does not explain the differences observed between natural and artificial conditions in the first study.

However, since the photodegradation was not observed under natural sunlight or in presence of sensitizer, **photodegradation is expected to be limited** in natural water.

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

4.1.2.2 Screening tests

Ready biodegradation of bifenthrin was firstly investigated according to OECD 301b "Modified Sturm Test" (not under GLP; reliability = 1) and on test material with a purity of 94%. A 11% and 4% degradation was observed within 28 days at test substance concentrations of 10 and 20 $mg.L^{-1}$, respectively. Result from control substance (Sodium benzoate) attained 92% degradation after 28 days and thereby confirming the suitability of the *inoculum* and test conditions (Handley and Horton, 1991).

Therefore, bifenthrin is clearly **not readily biodegradable** in the strict terms of OECD 301b guideline.

4.1.2.3 Simulation tests

Biodegradation in water/sediments systems

A study under GLP was carried out to investigate the degradation of labelled bifenthrin in two types of sediment (test material purity: 94%). According to this experiment, bifenthrin was **slowly degraded** in the water/sediment systems, with a DT_{50} values of 95 d (180 d at 12°C) and 266 d (504 d at 12°C), function of the sediment type (El Naggar, 2003).

An other water/sediment study was performed using a pond system and a river system (test material purity: 94%). DT_{50} values were about 320 d for the pond system (608 d at 12°C), and about 180 d in the river system (370 d at 12°C) (Cresswell, 1986)

At least, a case study based on the two water/sediment study is available (Verhaar, 2003). In this study, DT_{50} and K_{om} were recalculated using the TOXSWA compartment model (water, sediment, glass vessel walls). This model indicate a rapid dissipation of bifenthrin from water, especially due to adsorption to sediment or into glass walls. Moreover, the overall dissipation of bifenthrin from the total system is due to degradation in the water phase. In other words, according to the model, almost no degradation takes place in the sediment.

Biodegradation in soils

Several reliable studies, all carried out under GLP, were performed on the rate and route of degradation of cyclopropyl- and phenyl-^{14}C labelled bifenthrin (purity 97.9%) in 4 soil types (Smith, 1991; Bixler, 1983 et 1984; Reynolds, 1986). Bifenthrin was slowly degraded in these soils. DT_{50} values normalized to 20 °C were generally > 90 days but < 180 days. The average DT_{50} was 161 d (4 soils, 2 labels). The normalisation at 12°C leads to an average value of 305 days.

4.1.3 Summary and discussion of persistence

According to the studies presented above, biodegradation of bifenthrin is expected to be limited in sediment, water and soil matrices.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

A screening adsorption test (according to OECD 106, test material purity of 97.3%) with 4 soils showed that **bifenthrin is very strongly adsorbed to soil**.

Bifenthrin has an average K_{oc} of 236610 $L.kg^{-1}$, range from 130526 to 301611 $L.kg^{-1}$ and therefore is likely to be essentially immobile in the soil. No leaching to groundwater is expected (Froelich, 1984).

4.2.2 Volatilisation

Bifenthrin is not volatile and its vapour pressure is low ($2.4 * 10^{-5}$ Pa at 25°C).

4.2.3 Distribution modelling

No relevant data available.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Based on its log K_{ow} > 6, bifenthrin is expected to have a high bioconcentration potential. However, BCFWIN v2.15 estimation does not predict a high bioaccumulation factor due to a significant correction related to the cyclopropyl-C(=O)-O- ester. For very hydrophobic products such as bifenthrin, linear equations however are not recommended. Using non-linear model such as Bintein et al. (1993) where Log BCF = 0.910 log P – 1.975 log (6.8.10-7 P + 1) – 0.786, BCF value of 12589 $L.kg^{-1}$ is estimated using a Log P = 6.6.

4.3.1.2 Measured bioaccumulation data

A BCF study was available with common carp (Shigeoka and Saito, 1993). The BCF value for uptake of bifenthrin (purity of test material: 97%) in fish from clean water based on the fitted steady state concentration at the high exposure level is 1082 $L.kg^{-1}$.

Two BCF studies were performed with the bluegill sunfish. The purity of the tested substances was not specified. The first one was performed by Surprenant (1985) and lead to BCF values of 6090 $L.kg^{-1}$ based on the ratio of concentration fish/water.

The results of the new study with bluegill sunfish (purity of test material > 95%) performed by Gries (2006) confirm the results of the carp study; indeed the whole steady state BCF was found to be 1414.

In addition, in a fish Full Life Cycle Test (US EPA-FIFRA 1458-145, guideline 72-5) conducted with radiolabelled bifenthrin. BCFs (based on the ratio of concentration fish/water) were calculated at several sampling points of the study.

In the parental generation, $BCF_{whole\ fish}$ (*Pimephales promelas*) was 21000 $L.kg^{-1}$ at day 127 and 28000 $L.kg^{-1}$ at day 254 (test material: 10.36% ^{14}C-bifenthrin in hexane with radiopurity of 33.52 mCi/mM). Results from this study however indicate that the steady state was not obtained after 127 days since BCF still increased after 254 days.

On the other hand, experiments carried out in the presence of soil sediment and on test material with a purity of 95% show that the bioconcentration is greatly diminished by the presence of sediment particles with BCF values ranging from 63 to 423, due to preferential adsorption to sediment.

4.3.2 Terrestrial bioaccumulation

Bioconcentration can be described as a hydrophobic partitioning between the pore water and the phases inside the organism and can be modeled according to the following equation as described by Jager (1998) (TGD, 2003):

$$BCF_{earthworm} = (0.84+0.012\ K_{ow}) / RHO_{earthworm}$$

where for $RHO_{earthworm}$ by default a value of 1 ($kg_{wwt}.L^{-1}$) can be assumed. Using a K_{ow} value of 6.6, the BCF for earthworm is estimated to 47774 $L.kg^{-1}$ and thus bioaccumulation is likely to be high.

4.3.3 Summary and discussion of bioaccumulation

According to the Guidance to Registration (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (part 4), a BCF in fish of ≥ 500 $L.kg^{-1}$ is indicative of the potential to bioconcentrate for classification purpose. Therefore, taken into account the studies presented above, it can be concluded that bifenthrin have a potential to bioaccumulate in fish.

4.4 Secondary poisoning

No data available.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Absorption

Bifenthrin is absorbed via oral route [oral absorption rate of 50% (corresponding to the summation of the urinary and biliary excretion and tissue residues) in rats] (Selim, 1987; El-Naggar and Tullman, 1991) and via dermal route (11.4% absorbed through human skin *in vitro*) (Gelis, 2007). There is no information about the potential of Bifenthrin to be absorbed following inhalation.

Elimination

In a metabolism study in rats, the majority of radioactivity was eliminated via faeces (66-83%) and at a lesser extent in urine (9-25%) within 48-72 hours (Selim, 1987). Biliary excretion was the second most significant excretion pathway (20-30%). No remarkable sex differences in elimination or distribution were observed.

Distribution

Blood bio-kinetics showed that blood level of radioactivity slowly increased with time and reached its peak at 4 and 6 hours after oral administration, following low and high dose administration, respectively, and then slowly declined thereafter (Selim, 1986). In a bioaccumulation study, the highest levels of residues were detected in fat and skin with parent chemical accounting for the majority of the residue (Hawkins *et al*., 1986). The estimated half-lives were 51 days (fat), 50 days (skin), 19 days (liver), 28 days (kidney), 40 days (ovaries and sciatic nerve). A steady state appeared in plasma concentrations of radioactivity at the 21st day (0.04 to 0.06 □g/ml) and then, decreased rapidly at 78 days and was below <0.01 □g/ml at the remaining sacrifice time. These long biological half-lives were anticipated based on the high log P_{ow} of bifenthrin (log P_{ow} 6.6).

In a range-finding developmental neurotoxicity study, exposure of the pups to the test article via the milk was determined based on measurements of the test material in milk on lactation days 5, 11 and 17 following dietary administration of the test article from gestation day 6 through lactation day 22 and comparing internal levels in the dams and pups via the blood (Nemec, 2006). The mean levels of bifenthrin in maternal plasma and in milk samples were clearly increased at the highest tested dose level showing that bifenthrin was excreted in breast milk. The pup plasma bifenthrin level was increased at PND4 when the dams were exposed to the highest dose. It could be then assumed that bifenthrin was able to cross the placenta barrier. However, the plasma bifenthrin level was not increased in pups from treated dams at PND22 compared to controls, showing that bifenthrin was not or slightly absorbed from the milk or rate of metabolism was faster in pup rats at PND22.

Metabolism

Bifenthrin metabolism in the rat is similar to other pyrethroids that are also metabolised through typically hydrolysis with formation of the corresponding alcohol, oxidation of the resulting alcohol to the acid followed by a conjugation process (Cheng, 1988; Wu, 1988).

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Table 5.2.1-1 : Summary of the acute oral toxicity studies

Route	Method Guideline	Purity of test substance	Species Strain Sex no/group	dose levels duration of exposure	Value LD50/LC50	Clinical signs Gross abnormalities	Reference
Oral	EPA 81-1, OECD 401	93.7% (isomer cis-Z)	Rat, Sprague-Dawley, 5/sex/dose	Males: 100, 150, 200 and 300 mg/kg bw Females: 75, 100, 200 and 300 mg/kg bw (no vehicle used)	LD_{50} combined 186.1 mg/kg bw LD_{50} males: 168.4 mg/kg bw LD_{50} females: 210.4 mg/kg bw	Immediate lethality (day 1) observed at 150, 200 and 300 mg/kg bw. Clinical signs included tremors, vocalisation, clonic convulsions, twitching, abdominal gripping and hypersensitivity to touch. Other signs found were abdominal staining, oral discharge, chromorhinorrhea, chromodacryorrhea, diarrhea and broken tooth. In survivors signs were transient and ended by day 3. No gross internal lesions.	Watt, 1997
Oral	EPA 81-1	91.4% (90% cis/10% trans isomer)	Mice, Swiss Webster, 10/sex/dose	25, 35, 42 and 50 mg/kg bw in corn oil	LD_{50} males: 43.5 mg/kg bw LD_{50} females: 42.5 mg/kg bw	Immediate lethality (day 1) observed in all treated groups. Clinical signs included clonic convulsions, tremors and oral discharge. By day 1 all survivors had returned to normal. No gross internal lesions.	Rand, 1983a

5.2.2 Acute toxicity: inhalation

Table 5.2.2-1 : Summary of the acute inhalation toxicity study

Route	Method Guideline	Purity of the test substance	Species Strain Sex no/group	dose levels duration of exposure	Value LD50/LC50	Clinical signs Gross abnormalities	Reference
Inhalation	EPA, OPPTS 870-1300; OECD 403	94.8% (96.1% after exposure to the study heating regimen) (isomer cis-Z)	Rat, CrL CR^R (SD)IGS BR, 5/sex/dose	560, 990 and 2300 mg/m^3 (nominal) 4 hours Nose-only (liquid droplet aerosol)	LC_{50} combined 1010 mg/ m^3 LC_{50} males: 1100 mg/m^3 LC_{50} females: 800 mg/m^3	Immediate lethality (day 1) observed in all treated groups (†: 2/10 at 560 mg/m^3, 3/10 at 990 mg/m^3 and 10/10 at 2300 mg/m^3) Clinical signs included abnormal gait, tremors, convulsions, hypothermia, laboured respiration, rales, decreased defecation/urination, increased respiration rate, unkempt appearance and red/yellow staining on various body surfaces. Survivors in the 560 and 990 mg/m^3 groups were normal by day 4 and 10, respectively. Macroscopy revealed red discoloration and/or dark red areas of the lungs and distended gas-filled stomach and sections of the intestines for succumbed animals in all groups. No toxicologically significant effects for survivors in the 560 and 990 mg/m^3 group.	Kiplinger, 2003

5.2.3 Acute toxicity: dermal

Table 5.2.3-1 : Summary of the acute dermal toxicity study

Route	Method Guideline	Purity of the test substance	Species Strain Sex no/group	dose levels duration of exposure	Value LD50/LC50	Clinical signs Gross abnormalities	Reference
Dermal	EPA 81-2	88.35% (98% cis isomer)	Rat, Sprague-Dawley, 5/sex/dose	2000 mg/kg bw 24 hours (no vehicle used)	LD_{50} > 2000 mg/kg bw	There were no deaths. Male rats exhibited staggered gait on days 2 and 3. Female rats exhibited staggered gait, decreased locomotion and abdominogenital staining between days 2 and 4. All rats gained weight by termination of the study. No gross internal lesions. No irritation at the test sites.	Kedderis, 1985

5.2.4 Acute toxicity: other routes

No data available in the dossier.

5.2.5 Summary and discussion of acute toxicity

Based on the results of the acute oral toxicity study in rats, bifenthrin is classified as 'toxic' with the risk phrase **R25 - Toxic if swallowed** according to the Directive 67/548/EEC criteria. Besides, based on the CLP criteria, a classification Acute Tox.3-H301 is proposed.

Bifenthrin was found to be toxic to rat by inhalation. Based on the LC_{50} = 800 mg/m^3 in females, a classification with the risk phrase **R23 - Toxic by inhalation** is proposed, according to the Directive 67/548/EEC criteria. Besides, a classification Acute Tox.3-H331 is proposed, based on the CLP criteria.

No classification is proposed by dermal route.

5.3 Irritation

5.3.1 Skin

Table 5.3.1-1 : Summary of the skin irritation study

Species	Purity of the test substance	Method	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference
			Erythema	Edema			
New Zealand white Rabbit	88.35 % (98 % cis isomer)	EPA 81-5 (0.5 ml)	0	0	Not applicable	Not irritating	DeProspo, 1983

5.3.2 Eye

Table 5.3.2-1 : Summary of the skin irritation study

Species	Purity of the test substance	Method	Average Score (mean of 24, 48 and 72 hours)				Result	Reversibility yes/no	Reference
			Cornea	Iris	Redness Conjunctiva	Chemosis			
New Zealand white Rabbit	88.35% (98 % cis isomer)	EPA 81-4 (0.1 ml)	0	0	0.11	0	Not irritating	yes	DeProspo, 1983

5.3.3 Summary and discussion of irritation

Based on the results of the acute dermal and acute ocular toxicity studies, Bifenthrin was considered as not irritant to the rabbit’s skin and eyes.

5.4 Sensitisation

5.4.1 Skin

Table 5.4.1-1 : Summary of the sensitisation assay

Species	Method	Purity of the test substance	Number of animals sensitized/total number of animals	Result Concentration used	Reference
Guinea pig	OECD 406, maximization test	94.8% (98 % cis isomer)	15 animals tested (5 control and 10 test) Test group: 8/9* (discrete /patchy erythema) Negative control group: 0/5	Sensitizing Intradermal induction: 5% (in PEG 300). Epidermal induction: undiluted test material Challenge concentration: 3% (in PEG 300)	Arcelin, 2003

** One animal of the test group was found dead on day 18. At necropsy, no macroscopic findings were noted and death was considered to be unrelated to treatment.*

5.4.2 Respiratory system

There is no specific information regarding the ability of bifenthrin to cause irritation to the respiratory tract during the acute inhalation toxicity study. Few human case reports on bifenthrin was reported namely: chest pain, throat irritation, nasal irritation/stuffy nose, respiratory irritation and shortness of breath. The available information does not indicate that bifenthrin meets the EU criteria for classification for this end-point.

5.4.3 Summary and discussion of sensitisation

Bifenthrin was found to be a skin sensitiser to guinea-pigs in the maximisation test (89% of positive responses), and therefore a classification with **Xi; 'R43: may cause sensitisation by skin contact'** is proposed. The classification **Skin Sens. 1 – H317** is proposed according to CLP.

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Table 5.5.1-1 : Summary of the oral repeated dose and chronic toxicity studies

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral	28 day	91.4% (isomer cis-Z)	Rat (Sprague Dawley), 10/sex/ dose	0, 50, 100, 200, 300 and 400 ppm (equivalent approximately to 0, 4.4, 10.75, 21.9 and 34.5 mg/kg bw/day in males and to 0, 5.4, 11, 21.6 and 32.6 mg/kg bw/day in females)	**400 ppm:** Clonic convulsions and tremors, followed by death of all animals by day 15 of the study No significant treatment-related pathology No treatment related histopathology **300 ppm group:** Clonic convulsions and tremors Mortality: 6/10 males died by day 12 and 1/10 females died by day 20 of the study Significantly elevated adrenal weight and depressed testes weight (males), elevated relative adrenal, brain and kidney weights (males), elevated relative brain, kidney and liver weight (females) No significant treatment-related pathology No treatment related histopathology **200 ppm group:** Tremors in males and in females No significant treatment-related pathology No treatment related histopathology **100 ppm:**	200 ppm (22 mg/kg bw/d)	100 ppm (11mg/kg bw/d)	Rand, 1983b

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
					No significant treatment-related pathology No treatment related histopathology **50 ppm:** Significantly elevated brain weight (females) and significantly elevated brain and kidney weights (males) No significant treatment-related pathology No treatment related histopathology			
Oral	90 day	91.4% (90% cis/10% trans isomer)	Rat (Sprague Dawley), 15/sex/ dose (Recovery group of 10 animals at the highest dose level/control group).	0, 12, 50, 100 and 200 ppm (equivalent approximately to 0, 0.9, 3.4, 7.5 and 15 mg/kg bw/day in males and to 0, 1.05, 4.3, 8.5 and 17.15 mg/kg bw/day in females)	At 100 ppm: tremors in 2/15 males and in 3/10 females At 200 ppm : tremors observed in all the treated animals, subsiding within three days.	100 ppm (7.5 mg/kg bw/d in males and to 8.5 mg/kg bw/d in females)	50 ppm (3.4 mg/kg bw/d in males and to 4.3 mg/kg bw/d in females)	Rand, 1984

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral	90 day	88.35% (isomer cis-Z)	Dogs, Beagle, 4/sex / dose	2.5, 5.0, 10.0, 20.0 mg/kg bw daily by capsule	No mortality Tremors: - At 2.5 mg/kg/d: one ♂ (wk11) - At 5 mg/kg/d: 3/4 ♀ (wk10 to 13) and 3/4 ♂ (wk1, 3, 7, 9, 10, 11, 12, 13) - At 10 and 20 mg/kg/d: all animals displayed tremors throughout the 13-week study Ataxia and languid appearance at 5, 10 and 20 mg/kg bw/d. Pituitary cysts observed at gross necropsy at 20 mg/kg bw/d (4/8) vs 0/8 in the control group. At the histopathological examination, pituitary cysts were also observed in the control group 2/8 vs 3/8 at the highest tested dose.	5.0 mg/kg bw/d	2.5 mg/kg bw/d	Serota, 1984
Oral	52-week	88.35% (isomer cis-Z)	Dogs, Beagle, 4/sex / dose	0, 0.75, 1.5, 3.0, 5.0 mg/kg bw daily by capsule	No mortality Delayed tremors in all males and females at 5 mg/kg/day during weeks 15-29 and in one male and 2 females at 3 mg/kg/day during weeks 16-23 with the effect somewhat more pronounced in the males. This effect was first observed following 15 weeks of treatment and disappeared following 29 weeks of treatment. The lack of tremors after 29 weeks suggests that dogs may have developed a tolerance to treatment. In seven of the dogs (2 from the 3 mg/kg/day group and 5 from the 5 mg/kg/day group), tremors were noted prior to the daily dose, indicating a persistent effect from the previous day's dose Decreased body weight gain at 5 mg/kg bw/day. Tendency toward decreased mean erythrocyte count, hemoglobin and hematocrit values at 5 mg/kg bw/d from week 26.	3 mg/kg bw/d	1.5 mg/kg bw/d	Serota, 1985

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral	2-year (chronic and oncogenicity combined)	88.35% (isomer cis-Z)	Rat, Sprague Dawley 50 /sex/ dose	0, 12, 50, 100 or 200 ppm (equivalent approximately at week 104 to 0, 0.6, 2.3, 4.7 and 9.7 mg/kg bw/day in males and to 0, 0.7, 3, 6.1 and 12.7 mg/kg bw/day in females).	Tremors at 200 ppm and in one female at 100 ppm. Treatment-related decreased body-weight (gain) at 200 ppm in females. Decreased Red Blood Cell levels in males at 200 ppm. No treatment-related effects neither on organ weight, nor at necropsy or at the histopathological examination (including the sciatic nerve examination) .	100 ppm (4.7 mg/kg bw/day for males and 6.1 mg/kg bw/day for females	50 ppm (2.3 mg/kg bw/d for males and 3 mg/kg bw/d for females)	McCarty, 1986

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral (food)	2-year	88.35% (isomer cis-Z)	Mice, Swiss Webster, 50/sex/ dose	0, 50, 200, 500, 600 ppm ad libitum in diet (equivalent approximately at termination to 0, 7.6, 29, 74 and 92 mg/kg bw/day in males and to 0, 10, 37, 93 and 110 mg/kg bw/day in females.	Lethality at 500 ppm (1♀/50) and at 600 ppm (2♂/50 and 2♀/50). Minimal clinical signs of toxicity observed in males at 200 ppm (tremors). From 500 ppm (♂ and ♀) mainly, clinical signs of toxicity such as tremors, jerks, twitching and convulsions, occurring during the first three months of the study. Although in-life clinical observations identify the nervous system as the target system, there was no evidence of damage to these tissues at the microscopic level From 500 ppm (♂ and ♀), decrease of food consumption and body weight gain. Statistically significant increase in retinal atrophy at 600 ppm (♂♀). Statistically significant increase in bilateral germinal epithelial degeneration in testes from 50 ppm, without any dose-response relationship. The etiology of this change is obscure even though the incidence figures indicate an association with treatment.. No evidence of damage of the nervous system at microscopic examination	200 ppm (29 mg/kg bw/d for males) and 500 ppm (93 mg/kg bw/d for females), based on tremors..	50 ppm (7.6 mg/kg bw/d for males) and 200 ppm (37 mg/kg bw/d in females).	Geiger, 1986

5.5.2 Repeated dose toxicity: inhalation

No data available.

5.5.3 Repeated dose toxicity: dermal

Table 5.5.3-1 : Summary of dermal repeated dose study.

Route	duration of study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Dermal	21 day	93.2% (isomer cis-Z)	Rat (Sprague Dawley), 10/sex/ dose	0, 25, 50, 100, 1000 mg/kg bw/day (exposure duration: 6 hours)	Tremors observed in 9 females at 1000 mg/kg bw/day. Staggered gait observed in 1 male and in 1 female at 100 mg/kg bw/day and in 1 female at 1000 mg/kg bw/day, exaggerated hindlimb flexion observed in 1 female at 100 mg/kg bw/day and in 4 females at 1000 mg/kg bw/day. Local irritation observed from day 7 of observation and from 25 mg/kg/d. Paraesthetic reaction (vocalization, thrashing in cage and lying on back) observed during the first half-period of treatment (until day 11 at the maximum) at - 25 mg/kg/day and 50 mg/kg bw/day: one female - 100 mg/kgbw/day: one male and one female - 1000 mg/kgbw/day: one male and six females Hyperplasia with increased severity at 1000 mg/kg bw/day marked in males, moderate to marked in females), sometimes associated with ulceration and secondary dermal inflammation.	25 mg/kg bw/d (local)	50 mg/kg bw/d (systemic)	Watt *et al*., 2000

5.5.4 Summary and discussion of repeated dose toxicity:

In a 21-day rat dermal repeated dose study, clinical signs considered indicative of systemic toxicity were observed at the high dose (staggered gait and exaggerated hindlimb flexion) and very high dose (tremors). No other signs of systemic toxicity were noted, indeed, the clinical signs *vocalization, trashing in cage,* and *lying on back* were not considered indications of systemic toxicity or neurotoxicity, but were considered indications of a pyrethroid (paraesthetic) reaction.

Bifenthrin has been evaluated via the oral route for chronic toxicity in dogs, rats and mice. In these studies, the most sensitive treatment-related toxic effect observed was the occurrence of tremors. Signs of neurotoxicity (tremors and convulsions) were observed either at the beginning of the study (in

mid and high-dose groups) or as delayed effects throughout the exposure period (in low-dose groups). No histological damage of the nervous system was observed but pyrethroids could exert neurotoxic effects by disturbing nerve impulse (in particular, via their action onto the voltage-dependant sodium channel of excitatory nerves, to alter permeability of the sodium ion (Miyamoto *et al.*, 1995). Overall, tremors are considered as a major functional change.

According to the findings of the 90-day rat study, tremors are observed from 100 ppm (approx. 8 mg/kg bw/d). Based on the Directive 67/548/EEC criteria, a classification with Xn; R48/22 is justified when serious damages are observed between 5 and 50 mg/kg/d by oral route in 90-day studies and **Xn; R48/22 is therefore proposed for bifenthrine.** Besides, a classification with STOT Rep.1 – H372 is also considered, according to the CLP criteria (threshold for classification in cat. 1 ≤10 mg/kg/d).

5.6 Mutagenicity

5.6.1 In vitro data

Table 5.6.1-1: Summary of the *in vitro* mutagenicity studies

Test system Method Guideline	organism/ strain(s)	Purity of the test substance	concentra-tions tested	Result		Remark	Reference
				+ S9	- S9		
Ames test (comparable to EEC B.14)	*Salmonella typhimurium:* strains TA1535, TA1537, TA98, TA100, TA1538	91.4% (isomer cis-Z)	0, 75, 375, 1875, 3750, 7500 µg/plate	-	-	No cytotoxicity. Test compounds precipitated at 333 µg/plate and upwards. Positive-control compounds yielded expected responses. No replication of the experiment	Haworth, 1983

Test system Method Guideline	organism/ strain(s)	Purity of the test substance	concentra-tions tested	Result		Remark	Reference
				+ S9	- S9		
Mammalian chromosome aberration test - 92/69/EEC Method B10	Chinese hamster Ovary (CHO) cells	35 % (isomer cis-Z)	1, 2.5, 5, 10 mg/mL	-	-	Test concentrations were based on preliminary cytotoxicity testing. Positive-control compounds yielded expected responses. No replication of the experiment or confirmation of the result with different time of exposure, very short time of exposure with metabolic activation (2 hours), 50 cells analysed per culture instead of 100 as recommended by technical guideline.	Thilagar, 1984a
HGPRT assay - 87/302/EEC Method B17	CHO cells	88.3% (isomer cis-Z)	20 - 100 µg/ml	?	?	Equivocal It is not known if the equivocal results are observed with or without S9. Cytotoxic doses not reported	Thilagar, 1984b
Unscheduled DNA synthesis - 87/302/EEC Method B18	Primary rat hepatocytes	Data not available in the study report	0.01 - 2.0 µg/ml	-	No data	Equivocal in a first assay Negative in the replicate Cytotoxic doses not reported	Thilagar, 1983a Thilagar, 1983b

Test system Method Guideline	organism/ strain(s)	Purity of the test substance	concentra-tions tested	Result		Remark	Reference
				+ S9	- S9		
Sister chromatid exchange assay in mammalian cells - OECD 479	Chinese hamster Ovary (CHO) cells	88.35% (isomer cis-Z)	1, 5, 10, 30, 60, 100 µL	-	-	Test concentrations were based on preliminary cytotoxicity testing. Positive-control compounds yielded expected responses.	Heidemann, 1989
Mammalian cell gene mutation test - 87/302/EEC Method B17	Mouse lymphoma L5178Y cells (TK +/-)	88.3% (isomer cis-Z)	Without S9 mix: 0.013-1 µL/mL With S9 mix: 0.0013-0.1 µL/mL	+	+	The test was carried out with 1/8 log dilutions of the concentrations giving rise to 100% toxicity This gene mutation test (TK) with tissue culture cells showed a positive response. The dossier contains, , another type of gene mutation test (HGPRT), with CHO cells and one with mouse lymphoma cells. One of these was inconclusive due to a positive effect in at a lower concentration, while the two other yielded negative results. Positive-control compounds yielded expected responses.	Putman, 1983a

5.6.2 In vivo data

Table 5.6.2-1 : Summary of the *in vivo* mutagenicity studies

Type of test Method/ Guideline	Species Strain Sex no/group	Purity of the test substance	frequency of application	sampling times	dose levels	Results	Remarks	Reference
Cytogenetics assay -	Rat, Sprague	91.1% (isomer cis-	1 per day for 5	4-8 h after the fifth	3, 10 and 30	No apparent change in ploidy.	Negative and positive control	Putman,

Type of test Method/ Guideline	Species Strain Sex no/group	Purity of the test substance	frequency of application	sampling times	dose levels	Results	Remarks	Reference
92/69/EEC Method B11	Dawley , 5 males/ group	Z)	consecutive days	daily treatment.	mg/kg bw/ day	No effect on mitotic index. Incidence of aberrations and number of aberrations per cell not statistically significantly increased in treated groups.	compounds yielded expected responses for determination of valid test. 50 metaphases analysed per animals instead of 100 as recommended by technical guideline.	1983b
Micronucleus test-OECD 474	Mice, ICR, 5 animals/sex/group	94.7%	Single oral administration (gavage)	24 and 48 hours	8.75, 17.5, 35 mg/kg	No significant increase in the incidence of micronucleated PCEs in mouse bone marrow was observed at dose up to 35 mg/kg (at 24 hours) or at 35 mg/kg (48 hours post-dosing). Clinical signs of toxicity were observed from 8.75 mg/kg but no modification of the ratio P/N was observed.	The maximum dose was determined in a range-finding study where lethality was observed from the lowest tested dose, namely 50 mg/kg. Therefore, 35 mg/kg was chosen as the maximum dose level.	Krsmanovic and Hudson, 2005
Unscheduled DNA Synthesis test – OECD 486	Rat-Sprague Dawley	94.7%	Single oral administration (gavage)	2- 4 hours and 12-16 hours	0, 7.5, 15 and 30 mg/kg	No significant increase in the mean number of net nuclear grain counts in hepatocytes isolated either 2 to 4 hours or 12 to 16 hours after dose	The maximum dose was determined in a range finding study where tremors were observed from 40	Kamala Pant and Sly, 2005

Type of test Method/ Guideline	Species Strain Sex no/group	Purity of the test substance	frequency of application	sampling times	dose levels	Results	Remarks	Reference
						administration up to the highest tested dose (30 mg/kg).	mg/kg and lethality from 75 mg/kg. No individual data reported, only mean reported. Poor response of the positive control group at 2-4 hours with value lower than the historical values.	

5.6.3 Human data

No data available

5.6.4 Other relevant information

No data available

5.6.5 Summary and discussion of mutagenicity

Bifenthrine yielded negative results *in vitro* in the Ames test (Haworth, 1983), in the chromosome aberration assay in CHO cells (Thilagar, 1984a), and in a SCE in CHO cells (Heidemann, 1989). Positive results were observed in a gene mutation assay on mouse lymphoma L5178 Y cells with detection of trifluorothymidine resistance (Putman, 1983a). Bifenthrine showed equivocal results in another gene mutation assay (HPRT) in CHO cells (Thilagar, 1984b) and in an *in vitro* unscheduled DNA synthesis (UDS) assay (Thilagar, 1983a), but the replicate yielded negative responses (Thilagar, 1983b). However, the three available *in vivo* genotoxicity assays were negative: an *in vivo* chromosome aberration assay in rats (Putman, 1983b), a mouse micronucleus assay (Krsmanovic and Hudson, 2005) and a rat UDS assay (Kamala Pant and Sly, 2005).

Overall, based on the *in vitro* and *in vivo* mutagenicity tests and it is considered that bifenthrin has no genotoxic potential. Therefore, no classification for mutagenicity is proposed.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

Table 5.7.1-1 : Summary of carcinogenicity data

Route	Duration of treatment/ study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Tumours	Reference
Oral (food)	104 weeks	88.35% (isomer cis-Z)	Rat, male Sprague Dawley, female Tac (SD) fBR, 50/sex/dose	0, 12, 50, 100, 200 ppm *ad libitum* in diet	No treatment-related tumour induction up to 200 ppm NOAEL (systemic) = 50 ppm (tremors) NOAEL (tumours) ≤ 12 ppm	McCarty, 1986

Route	Duration of treatment/ study	Purity of the test substance	Species Strain Sex no/group	dose levels frequency of application	Tumours	Reference
Oral (food)	104 weeks	88.35% (isomer cis-Z)	Mice, Swiss Webster, 50/sex/dose	0, 50, 200, 500, 600 ppm *ad libitum* in diet (corresponding in males to 0, 7.6, 29, 74 and 92 mg/kg bw/d and in females to 0, 10, 37, 93 and 110 mg/kg bw/d respectively).	No statistically significant compound-related effects on survival. Increased incidence of pericytoma (initially qualified as leiomyosarcoma) in the urinary bladder in males from 50 ppm (corresponding to 7.6 mg/kg bw/d) statistically significant at 600 ppm (92 mg/kg bw/d). The incidence was as follows: 2/48 (4%), 6/50 (12%), 8/50 (16%), 7/50 (14%) and 14/49** (29%) in males at 0, 50, 200, 500, 600 ppm respectively. Statistically significant increased incidence of lymphoblastic lymphosarcoma and leukaemia at 600 ppm in females. The incidence for lymphoblastic leukaemia was as follows: 12/50 (24%), 14/50 (28%), 17/50 (34%), 10/50 (20%) and 22/49* (44%) in females at 0, 50, 200, 500, 600 ppm respectively. Slight dose-related increased incidence of liver adenocarcinoma and adenoma in males from 200 ppm but not statistically significant. The incidence for combined tumours was as follows: 2/49 (4%), 2/50 (4%), 4/50 (8%), 4/50 (8%), 7/49 (14%) in males at 0, 50, 200, 500, 600 ppm respectively. Slight increased incidence of bronchiolar-alveolar adenocarcinoma and adenoma, statistically significant at 50, 200 and 600 ppm, without dose-related relationship. The incidence was as follows: 14/50 (28%), 26/50* (52%), 23/50* (46%), 19/50 (38%), 23/48* (48%) at 0, 50, 200, 500, 600 ppm respectively in females. NOAEL (systemic) = 50 ppm (♂)-200 ppm (♀) ppm (tremors) NOAEL (tumours) ≤ 500 ppm	Geiger, 1986

5.7.2 Carcinogenicity: inhalation

No data available.

5.7.3 Carcinogenicity: dermal

No data available.

5.7.4 Carcinogenicity: human data

No data available.

5.7.5 Other relevant information

No data available.

5.7.6 Summary and discussion of carcinogenicity

The oncogenicity study in Sprague Dawley rats (McCarty, 1986) indicated that bifenthrin is not oncogenic. In this study, tremors were observed at 100 and 200 ppm in females and at 200 ppm in males. The NOAEL for systemic toxicity was set at 50 ppm, based on tremors.

In the oncogenicity study in Swiss Webster mice (Geiger, 1986) increased incidence of leiomyosarcoma in the urinary bladder were observed in males at 50, 200, 500 and 600 ppm (statistically significant at 600 ppm). These tumours were slowly growing and did not metastasize. After re-evaluation of this study by a panel of pathologists, it was concluded that the mouse bladder tumour was not a leyomyosarcoma but rather a tumour arising in the submucosa. This latter tumour has an unknown pathogenesis, may arise from the vascular mesenchyme and may be qualified as a pericytoma (predominantly benign). Other tumours such as lymphoblastic lymphosarcoma and leukaemia were observed in females and are statistically significant at the very high dose (600 ppm). Besides, statistically significant bronchiolar-alveolar adenocarcinoma and adenoma were observed in females at low, medium ad very high dose. Based on the available information, it cannot be considered that these effects are not relevant to human as long as mechanistic explanations or further information are not provided showing that these tumours are specific to the mice and cannot be extrapolated to human.

Overall, bifenthrine presents:

- No carcinogenic effect in rats
- A carcinogenic effect in mice
- An absence of genotoxic effect or other supporting evidence for carcinogenicity

Based on induction of tumours in one species without supporting evidence, a classification **Carc. Cat. 3; R40** is proposed.

Because evidence of carcinogenicity in mice is obtained from a single study, it is considered that there is a “limited evidence of carcinogenicity effects” which deserves a **classification Category 2 – H350** according to CLP criteria.

5.8 Toxicity for reproduction

5.8.1 Teratogenicity

Table 5.8.1-1 : Summary of developmental toxicity data

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Purity of the test substance	Exposure Period	Doses	Critical effects dams fetuses	NOAEL maternal toxicity	NOAEL Teratogenicity Embryotoxicity	Reference
Oral (gavage)	EPA 83-3	Rabbit, New Zealand White, 20/sex/ dose	88.35% (isomer cis-Z)	Day 7-19 post mating	2.67, 4.0, 8.0 mg/kg/day (corn oil)	Tremors and twitching in dams. No major malformations in foetuses were noted. Foetotoxicity was suspected based on abortions and early delivery observed at mid and high doses. The most of the animals showed clinical signs attributed to an infection to *Pasteurella multocida* so results of abortion and early delivery were not considered as relevant.	2.7 mg/kg bw/day	= 2.7 mg/kg bw/day	DeProspo, 1984
Oral (gavage)	EPA 83-3	Rat , Sprague Dawley, 25 females/ dose	88.35% (isomer cis-Z)	Day 6-15 post mating	0, 0.5, 1, 2 mg/kg bw/day (corn oil)	Intermittent tremors (between day 10 & 19) in dams. There were no major malformations noted in any of the fetuses from groups 1 through 4. Minor malformations were observed sporadically and were not considered to be related to test material administration.	1 mg/kg bwday	≥2 mg/kg bw/day	DeProspo, 1984b
Oral (food)	EPA OPPTS 870.3700	Rat, Sprague Dawley, 25 females/ dose	95.3% (isomer cis-Z)	Day 6-20 post mating	30, 60, 90, 200 ppm in diet (2.5, 5, 7.4, 16.3	Clinical signs of neurotoxicity at 200 ppm, decrease of food consumption at 200 ppm, body weight gain and adjusted (for gravide uterine weight) body weight gains in dams at 200 ppm. No treatment- related changes were	90 ppm (equivalent to 7.4 mg/kg b.w./ day)	≥200 ppm (equivalent to 16.3 mg/kg b.w./day)	Watt *et al*., 2001

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Purity of the test substance	Exposure Period	Doses	Critical effects dams fetuses	NOAEL maternal toxicity	NOAEL Teratogenicity Embryotoxicity	Reference
					mg/kg bw/day), respectively)	observed in number of live and dead fetuses, fetal weights, or sex ratios.			

5.8.2 Fertility

Table 5.8.2-1 : Summary of fertility toxicity data

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Purity of the test substance	Exposure Period	Doses	critical effect	NOAEL Parental		NOAEL F1		NOAEL F2		Reference
							male	female	male	female	male	female	
Oral (food)	EPA 83-4	Rat, Tac (SD) fBR, 25 animals/sex/ dose	88.35% (isomer cis-Z)	From start of study until sacrifice of parent, F1, F2-generation	30, 60, 100 ppm ad libitum equivalent to 1.5, 3 and 5 mg/kg b.w./day)	Tremors in females of parent and F1 generation There were no treatment-related effects on reproductive parameters (mating, male fertility, female fertility and gestation indices)	S&R ≥ 100 ppm (5 mg/kg b.w./day)	S = 60 ppm (3 mg/kg b.w.) R≥100 ppm (5 mg/kg b.w.)	S&R ≥ 100 ppm (5 mg/kg b.w.)	S= 60 ppm (3 mg/kg b.w.) R≥100 ppm (5 mg/kg b.w.)	S&R >≥ 100 ppm (5 mg/kg b.w.)	S= 100 ppm R≥100 ppm (5 mg/kg b.w.)	DeProspo, 1986

5.8.3 Summary and discussion of reproductive toxicity

Bifenthrin was evaluated for the embryo/foetotoxicity and teratogenicity potentials by oral route in rabbits and rats.

No evidence of teratogenicity or embryotoxicity up to maternal toxicity doses was observed after diet or gavage administration of bifenthrin. However, foetotoxicity was suspected in rabbits based on abortions and early delivery observed at mid and high doses. Nevertheless, as most of the animals showed clinical signs attributed to an infection to *Pasteurella multocida*, results of abortion and early delivery were not considered as relevant, possibly due to *Pasteurella multocida*.

The multi-generation reproduction study in rats showed no evidence of fertility toxicity. A slightly but significant decrease of ovary weights was observed in the F_1 generation but not in the F_2 generations. Moreover, a statistically lower live birth index and a statistically higher incidence of stillborn pups were observed solely in the F_{2a} litter and were not dose-related.

Overall, based on the reproductive toxicity tests, it is considered that bifenthrin has no effects on reproductive performance and fertility. Therefore, no classification for reproductive toxicity is proposed.

5.9 Neurotoxicity

5.9.1 Neurotoxicity

Table 5.9.1-1 : Summary of neurotoxicity data

Route	Duration of study	Purity of the test substance	Species Strain Sex no/group	Dose levels frequency of application	Results	LOAEL	NOAEL	Reference
Oral (gavage)	43 days	88.3% (isomer cis-Z)	Domestic laying hen, hybrid brown laying strain, 10 females/ dose	5000 mg/kg bw, single doses at day 0 and 21.	Clinical signs of neurotoxicity at 5000 mg/kg but no delayed neurotoxicity effects observed.	5000 mg/kg bw (neurotoxicity)	5000 mg/kg bw (delayed neurotoxicity)	Roberts *et al*., 1984
Oral (diet)	91 days	93.7% (isomer cis-Z)	Rat Sprague Dawley	0, 50, 100 and 200 ppm	Clinical signs of neurotoxicity (tremors, twitching, FOB) from 100 ppm No microscopic lesions of the nervous system tissues at the highest tested dose level.	100 ppm (6 and 7.2 mg/kg bw/d in males and females respectively)	50 ppm (2.9 and 3.7 mg/kg bw/d in males and females respectively)	Freeman, 1988

5.9.2 Developmental neurotoxicity

Table 5.9.2-1 : Summary of neurotoxicity data

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Purity of the test substance	Exposure Period	Doses	Critical effect	NOAEL				Reference
							Maternal neurotoxicity	Maternal systemic and reproductive toxicity	Developmental toxicity (body weights, clinical findings, mortality)	Developmental neurotoxicity	
Oral (diet)	Range-finding study	Rat	94.8%	From gestation day 6 through lactation day 22	0, 50, 65, 80, 100 and 125 ppm (3.6, 4.6, 6.0, 7.4 and 9.3 mg/kg bw/day during gestation and 9.2, 11.7, 14.3, 17.2 and 22.5 mg/kg bw/day during lactation	Tremors and clonic convulsion at 125 ppm	100 ppm (in females)	-	-	-	Nemec, 2006
Oral (diet)	OECD 426	Rat	94.8%	From gestation day 6 through lactation day 21	50, 100 and 125 ppm (3.6, 7.2 and 9 mg/kg bw/d during gestation and 8.3, 16.2 and 20.7 mg/kg bw/day during	Clinical signs of neurotoxicity from 100 ppm in dams (mainly during lactational period) and at 125 ppm in offspring.	50 ppm	≥ 125 ppm	≥ 125 ppm	50 ppm	Nemec, 2006

					lactation)	Changes in auditory startle and motor activity from 100 ppm in offspring.					

5.9.3 Summary and discussion of neurotoxicity study

In an acute oral delayed neurotoxicity study in adult hens, bifenthrin did produce signs of neurotoxicity (unsteadiness, jerking movements of the head, trembling, violent movements of the head and legs and inability to stand), but did not show signs of delayed neurotoxicity or histopathological lesions of the nerve tissue.

In a range finding developmental neurotoxicity study, bifenthrin was administered in the diet during gestation and lactation. The only significant effect observed in parental animals was whole-body tremors. No effects were observed on neonatal survival.

In the developmental neurotoxicity study, exposure-related overt signs of maternal neurotoxicity (tremors, clonic convulsions) were observed during gestation and lactation. In offspring, no significant effects were observed on survival, post natal growth body weight. No test article-related macroscopic findings were noted, there were no adverse neurobehavioural findings observed.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

In a standard study (Spruit W.E.T et al., 2002), bifenthrin was found not to exhibit any explosive properties.

No classification for explosivity is proposed.

6.2 Flammability

In standard studies (Spruit W.E.T et al., 2002) bifenthrin was found to be none highly flammable, it did not exhibit any pyrophoric properties and it has no self-ignition temperature.

No classification for flammability is proposed.

6.3 Oxidising properties

Examination of the chemical structure of bifenthrin establishes that it does not contain any chemical groups typical for oxidizing agents. Thus the active substance can be regarded as incapable of reacting exothermically with a combustible material such as powdered cellulose.

No classification for oxidising properties is proposed.

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Several acceptable studies are available and all performed under GLP. Four studies were conducted with *Onchorynchus mykiss* or *Lepomis macrochirus*, following relevant standard test (EPA, 1975) using a flow through test design. 96-h LC_{50} values were ranged from 0.1 $\mu g.L^{-1}$ to 0.35 $\mu g.L^{-1}$.

Two additional higher tests with sediment are available. Both tests are conducted with *Onchorynchus mykiss*. The toxicity of bifenthrin was tested in static water/sediment system under repeated spray conditions (two applications, interval 4 days). The results were expressed as initial concentrations deduced from the measured stock solution concentrations. Recovery of the test substance range from 30.0 to 58.8% at the test initiation and it was not possible to determine the concentrations for some test conditions after 4 days (before the second application) or 8 days, due to de dissipation of the substance from the water column. In this case the 96-h LC_{50} was 0.00626 $mg.L^{-1}$.

Table 7.1-01: Summary of the acute toxicity to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results			Relia-bility	Reference
			design	duration	LC_0 (µg/L)	LC_{50} (µg/L)	LC_{100} (µg/L)		
EPA, 1975	*Oncorynchus mykiss* *(purity of test material not known)*	Mortality	Flow through	96 h	<0.094[1]	0.15[1]	0.38[1]	2	LeBlanc (1983c)
EPA, 1975	*Lepomis macrochirus* *(purity of test material not known)*	Mortality	Flow through	96 h	<0.180[1]	0.35[1]	0.42[1]	2	LeBlanc (1983b)
EPA, 1975	*Lepomis macrochirus* *(purity of test material not known)*	Mortality	Flow through	96 h	0.1[2]	0.26[2]	0.4[2]	1	Surprenant (1985a)
EPA, 1975	***Oncorynchus mykiss*** (test material: 10.36% 14C-Bifenthrin in hexane with radiopurity of 33.52 mCi/mM)	**Mortality**	**Flow through**	**96 h**	**0.03**[2]	**0.1**[2]	**0.3**[2]	**1**	**Surprenant (1985c)**
Higher tier test with sediment	*Oncorynchus mykiss* *(purity of test material not known)*	Mortality	Static	96 h	1.3[3]	6.26[3]	>9.7[3]	2	Aufderheide (1999a)

Higher tier test with sediment	*Oncorynchus mykiss* *(purity of test material not known)*	Mortality	Static	96 h	9[3]	>9[3]	-	2	Aufderheide (1999b)

[1] Based on nominal concentrations (no measures of test concentrations were carried out)
[2] Based on mean-measured concentrations
[3] Based on the concentrations measured in the stock solutions (measured nominal concentrations)

Conclusion: It is proposed to retain as key study for the classification, the work of Surprenant (1985c): **LC_{50} = 0.1 µg a.s.L^{-1}**. Therefore, due to the EC_{50} value lower than 1 mg/l, it is consistent with classification as R50 or H400.

Long-term toxicity to fish

Two studies are available for chronic toxicity to fish. The first study is a flow-through ELS test (larval survival) using the freshwater fish *Oncorhynchus mykiss*. This study was performed following OECD 210 guideline on 10.36% ^{14}C-bifenthrin in hexane with radiopurity of 33.52 mCi/mM. The 76-d NOEC was 0.012 µg.L^{-1}.

In a second study, *Pimephales promelas* was exposed to bifenthrin in a flow through full life cycle test design during 120d. This study was performed following EPA 72.5 guideline. The purity of the test material was not specified. The 120-d NOEC was 0.04 µg.L^{-1}.

Conclusion: The chronic toxicity of bifenthrin to fish is very high.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Several acceptable study, all performed under GLP were performed with *Daphnia magna*, *Cerodaphnia dubia*, *Thamnocephales platyurus*, *Caddisfly* sp. and *Gammarus pulex*, following relevant standard test (ECC C.2, EPA OPP 72-2) and using flow through or static test design. 96-h LC_{50} values were ranged from 0.11 µg.L^{-1} to 5.7 µg.L^{-1}.

An additional higher test with sediment are available. An EC_{50} value of 2.3 µg.L^{-1} is observed with *Daphnia magna*.

Table 7.1-01: Summary of the acute toxicity to invertebrates

Guideline / Test method	Species/ Endpoint	Exposure		Results			Relia-bility	Reference
		design	duration	EC_0 [µg/L]	EC_{50} [µg/L]	EC_{100} [µg/L]		
OECD 202 EEC C.2.	*Daphnia magna*/ Mortality *(purity of test material not known)*	Flow-through	48 h	<0.60[1]	1.6[1]	>10[1]	2	LeBlanc (1983a)
EPA OPP 72-2	***Daphnia magna*/ Mortality** (test material: 95% ^{14}C-Bifenthrin with radiopurity of 33.52 mCi/mM)	**Flow-through**	**48 h**	**<0.025**[2]	**0.11**[2]	**>0.48**[2]	**1**	**Surprenant (1985b)**
Higher tier test with sediment	*Daphnia magna*/ Mortality *(purity of test material not known)*	Static	48 h	0.49[3]	2.3[3]	10.3[3]	2	Aufderheide (1999)

OECD 202 EEC C.2.	*Daphnia magna*/ Mobility (Test material 93.8 % Bifenthrin technical)	Static	48 h	0.056[1]	0.37[1]	-	1	Hooftman (2002)
OECD 202 EEC C.2.	*Cerodaphnia dubia*/ Mobility (Test material 93.8 % Bifenthrin technical)	Static	24 h	0.043[1]	0.31[1]	-	1	Hooftman (2002)
OECD 202 EEC C.2.	*Thamnocephales platyurus*/ Mobility (Test material 93.8 % Bifenthrin technical)	Static	24 h	0.032[1]	5.7[1]	-	1	Hooftman (2002)
OECD 202 EEC C.2.	*Hexagenia sp.*/ Mobility (Test material 93.8 % Bifenthrin technical)	Static	48 h	0.039[1]	0.39[1]	-	1	Hooftman (2002)
OECD 202 EEC C.2.	*Caddisfly sp.*/ Mobility (Test material 93.8 % Bifenthrin technical)	Static	48 h	0.031[1]	0.12[1]	-	1	Hooftman (2002)
OECD 202 EEC C.2.	***Gammarus pulex*/ Mobility** (Test material 93.8 % Bifenthrin technical)	**Static**	**48 h**	**0.032**[1]	**0.11**[1]	-	**1**	**Hooftman (2002)**

[1] Based on nominal concentrations (no measures of test concentrations were carried out)
[2] Based on mean-measured concentrations
[3] Based on the concentrations measured in the stock solutions (measured nominal concentrations)

Conclusion: Its proposed to retained as key study for the classification, the work of Surprenant (1985b) and Hooftman (2002): **EC_{50} = 0.11 µg.L^{-1}**, obtained with *Daphnia magna* or *Gammarus pulex.* Therefore, due to the EC_{50} value lower than 1 mg/l, it is consistent with classification as R50 or H400.

Long-term toxicity to aquatic invertebrates

Three studies are available for chronic toxicity to invertebrates. Two reproduction studies was performed under GLP following OECD 202, with *Daphnia magna* in a flow-through test design. The 21-d NOEC values are 0.0013 µg.L^{-1} (purity of test substance not specified) and 0.00095 µg.L^{-1} (test material: 10.36% ^{14}C-bifenthrin in hexane with radiopurity of 33.52 mCi/mM). The thirds study was performed with *Mysidopsis bahia* in a flow through test design, following OECD 202 test guideline. The purity of the test material was not specified. The 21-d NOEC was 0.0012 µg.L^{-1}.

Conclusion: The chronic toxicity of bifenthrin to invertebrates is very high.

7.1.1.3 Algae and aquatic plants

A study was performed on *Chlorella pyrenoidosa* and *Scenedesmus acutus*, following the OECD guideline 201 (purity not specified). This test was however invalidated. Indeed, the use of 0.1% acetone as solvent was deleterious to the growth rate of algae, but there was no effect of bifenthrin on growth rate above that observed in the solvent control.

Conclusion: No acceptable data are available.

7.1.1.4 Sediment organisms

A study under GLP revealed that bifenthrin has a high toxicity to *Chironomus riparius* larvae in a spiked water phase test (purity not specified). The 28-d LC_{50} was 3.96 µg.L^{-1} and the 28-d NOEC was 0.32 µg.L^{-1}. In a spiked sediment test the 10-d EC_{50} was > 2500 µg.kg^{-1}, the EC_{50} for growth was 780 µg.kg^{-1} sediment and the 10 day NOEC for growth was 83 µg.kg^{-1} (Kelly, 2002 ; Putt 2005).

7.1.1.5 Other aquatic organisms

No data available

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

Two studies are available for soil macro organisms toxicity assessment. The first study (under GLP) has been performed on the acute toxicity of bifenthrin to the earthworm *Eisenia fetida*. Earthworms were exposed to contaminated soils with bifenthrin technical (purity: 88.35%) during a period of 14 days, following OECD 207 guideline. The results of these studies showed that bifenthrin has an acute 14-d LC_{50} higher than 18.9 $mg.kg^{-1}$ soil and the corrected 14-d LC_{50} in standard European soil is higher than 6.426 $mg.kg^{-1}$ (Roberts and Hakin, 1985).

The second study is a 56 days reproduction study, performed with *Eisenia fetida*, according to ISO 11268-2 guideline (purity of tested substance not specified). The 56-d NOEC for reproduction equal to 2.13 $mg.kg^{-1}$ in test conditions and the corrected 56-d NOEC for reproduction in standard European soil equal to 0.7242 $mg.kg^{-1}$ (Stäbler, 2002).

7.2.1.2 Toxicity to terrestrial plants

Bifenthrin tested as formulated product (purity not specified) has no effect on the emergence of seedlings of 4 dicotyledons and 2 monocotyledons, at a soil addition rate of 0.08 mg/kg dry soil weight. Since only one dose was tested it is noted that no true DT_{50} or NOEC can be defined.

7.2.1.3 Toxicity to soil micro-organisms

No data available

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

No data available

Toxicity to other above ground organisms

No data available

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Not relevant for this type of dossier.

7.3 Atmospheric compartment

No data available

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

A study under GLP showed little to no effect of bifenthrin (purity: 97.8%) on the respiration of activated sludge micro-organisms. However concentrations applied were higher than the solubility limit (214, 619, 1929 $mg.L^{-1}$) and were not measured during the test. The NOEC determined was > 1929 $mg.L^{-1}$.

Conclusion: no effect was detected at the solubility limit.

7.4.2 PNEC for sewage treatment plant

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

Summary of relevant ecotoxicological endpoints for classification

Acute toxicity to fish	96h-LC_{50} = 0.1 µg.L^{-1}
Acute toxicity to invertebrates	48h-EC_{50} > 0.11 µg.L^{-1}
Chronic toxicity to fish	76d-NOEC = 0.012 µg.L^{-1}
Chronic toxicity to invertebrate	21d-NOEC = 0.00095 µg.L^{-1}

The LC_{50} and EC_{50} values for fish and invertebrates, are lower than 1 mg.L^{-1}, respectively. In addition to this ecotoxicological endpoints, bifenthrin is not readily biodegradable, expected to be stable in water and the bioaccumulation potential of this substance in fish is expected to be high.

Therefore, **N; R50/53 is proposed**.

Based on CLP criteria, the proposed classification is **Aquatic Acute 1– H400** and **Aquatic Chronic 1 – H410**.

In addition, as the 96h-EC_{50} value for fish is 0.00001 mg.L^{-1} < EC_{50} ≤ 0.0001 mg.L^{-1}, a M-factor of 10 000 is thus proposed to determine the specific concentration limit.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Bifenthrin was evaluated in the context of the Biocidal Product Directive (98/8/EC) and it is therefore a requirement to harmonise classification for all endpoints.

OTHER INFORMATION

The information available was submitted in the scope of the Biocidal Product Directive for inclusion of the active substance bifenthrin in annex I of directive 98/8/CE.

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