Committee for Risk Assessment

RAC

Annex 1

Background document

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

fenpyroximate (ISO); tert-butyl 4-[({(E)-[(1,3-dimethyl-5-phenoxy-1H -pyrazol-4-yl)methylene]amino}oxy)methyl] benzoate

EC Number: not allocated
CAS Number: 134098-61-6

CLH-O-0000002368-70-02/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to 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

5 December 2013

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Fenpyroximate

EC Number: **not allocated**

CAS Number: **134098-61-6**

Index Number: **not allocated**

Contact details for dossier submitter:

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Version number: 2 **Date: March 2013**

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Table 1: Substance identity

Substance name:	**Fenpyroxim**ate
EC number:	***Not allocated***
CAS number:	**134098-61-6**
Annex VI Index number:	***Not allocated***
Degree of purity:	***> 960g/kg***
Impurities:	There are a number of impurities claimed as confidential by the proposer

Proposed classification

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

	CLP Regulation (2^{nd} ATP to CLP)	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	None	None
Current proposal for consideration by RAC	Acute Tox 3; H301 Acute Tox 2; H330 Eye Irrit. 2; H319 Skin Sens. 1B; H317 Aquatic acute 1; H400 Aquatic chronic 1; H410 M_{acute} = 100 $M_{chronic}$ = 1000	Xn; R22 T+; R26 Xi; R36 R43 N; R50/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox 3; H301 Acute Tox 2; H330 Eye Irrit. 2; H319 Skin Sens. 1B; H317 Aquatic acute 1; H400 Aquatic chronic 1; H410 M_{acute} = 100 $M_{chronic}$ = 1000	Xn; R22 T+; R26 Xi; R36 R43 N; R50/53

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)]
2.1.	Explosives	none		none	conclusive but not sufficient for classification
2.2.	Flammable gases	none		none	data lacking
2.3.	Flammable aerosols	none		none	data lacking
2.4.	Oxidising gases	none		none	data lacking
2.5.	Gases under pressure	none		none	data lacking
2.6.	Flammable liquids	none		none	data lacking
2.7.	Flammable solids	none		none	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	none		none	data lacking
2.9.	Pyrophoric liquids	none		none	data lacking
2.10.	Pyrophoric solids	none		none	data lacking
2.11.	Self-heating substances and mixtures	none		none	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	none		none	data lacking
2.13.	Oxidising liquids	none		none	data lacking
2.14.	Oxidising solids	none		none	conclusive but not sufficient for classification
2.15.	Organic peroxides	none		none	data lacking
2.16.	Substance and mixtures corrosive to metals	none		none	data lacking
3.1.	Acute toxicity - oral	Acute Tox. 3 - H301		none	
	Acute toxicity - dermal	none		none	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Acute Tox. 2 - H330		none	
3.2.	Skin corrosion / irritation	none		none	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Eye Irrit 2 - H319		none	
3.4.	Respiratory sensitisation	none		none	data lacking

3.4.	Skin sensitisation	Skin Sens. 1B - H317		none	
3.5.	Germ cell mutagenicity	none		none	conclusive but not sufficient for classification
3.6.	Carcinogenicity	none		none	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	none		none	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	none		none	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	none		none	conclusive but not sufficient for classification
3.10.	Aspiration hazard	none		none	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic acute 1 - H400 Aquatic chronic 1 - H410	M_{acute}=100; $M_{chronic}$=1000	none	
5.1.	Hazardous to the ozone layer	none		none	data lacking

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

Labelling:

Signal word: Danger

Hazard statements: H301, H330, H317, H319, H410

Precautionary statements: (P102), P273, P280, P284, P301+P304+P310, P302+P352, P305+P351+P338, P333+P313, P337+P313, P391, P403+P233, P405, P501

Proposed notes assigned to an entry:

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	none		none	conclusive but not sufficient for classification
Oxidising properties	none		none	conclusive but not sufficient for classification
Flammability	none		none	conclusive but not sufficient for classification
Other physico-chemical properties	none		none	conclusive but not sufficient for classification
Thermal stability	none		none	data lacking
Acute toxicity	Xn; 22 T+; R26		none	
Acute toxicity – irreversible damage after single exposure	none		none	conclusive but not sufficient for classification
Repeated dose toxicity	none		none	conclusive but not sufficient for classification
Irritation / Corrosion	Xi; R36		none	
Sensitisation	R43		none	
Carcinogenicity	none		none	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	none		none	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	none		none	conclusive but not sufficient for classification
Toxicity to reproduction – development	none		none	conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	none		none	conclusive but not sufficient for classification
Environment	N; R50/53		none	

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Xi, Xn, T+, N
R-phrases: R: 22-26-36-43-50/53
S-phrases: S: (1/2-)26-28-36/37-38-45-60-61

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

No REACH registration dossiers were available for Fenpyroximate on 15 March 2013.

1.1 Name and other identifiers of the substance

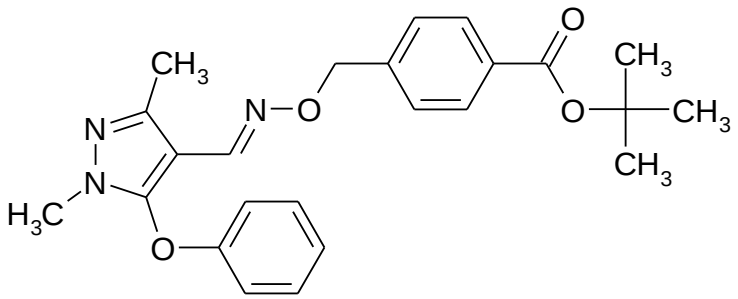
Table 5: Name and other identifiers of the substance

Chemical Name:	Benzoic acid, 4-[[[(E)-[1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino]oxy]methyl]-,1,1-dimethylethyl ester
EC Name:	not allocated
CAS Number:	134098-61-6
IUPAC Name:	tert-butyl 4-[({[(E)-(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate

1.2 Composition of the substance

There are a number of impurities stated as confidential by the producer.

Table 6: Composition of the substance

Chemical Name:	Benzoic acid, 4-[[[(E)-[1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino]oxy]methyl]-,1,1-dimethylethyl ester
EC Number:	not allocated
CAS Number:	134098-61-6
IUPAC Name:	tert-butyl 4-[({[(E)-(1,3-dimethyl-5-phenoxy-1H-pyrazol-4-yl)methylene]amino}oxy)methyl]benzoate
Molecular Formula:	$C_{24}H_{27}N_3O_4$
Structural Formula:	
Molecular Weight:	421.5 g/mol
Typical concentration (% w/w):	confidential information
Concentration range (% w/w):	confidential information

1.3 Physico-chemical properties

Table 7: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	white powder (purity 98.6 %)	Draft Assessment Report Monograph EFSA conclusions
VII, 7.2	Melting/freezing point	3.2	100 – 101 °C (purity 98.6 %)	
VII, 7.3	Boiling point	3.3	not detectable before decomposition	
VII, 7.4	Relative density	3.4 density	1.25 at 20 °C (purity 98.6 %)	
VII, 7.5	Vapour pressure	3.6	< $1x10^{-5}$ Pa at 25 °C (purity 98.6 %)	
VII, 7.6	Surface tension	3.10	72.2 mN/m (20 °C, 90% saturated) (purity 98.6 %)	
VII, 7.7	Water solubility	3.8	21.4 µg/L at pH 5 29.8 µg/L at pH 9 (25 °C, purity 99.8 %)	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	5.01	
VII, 7.9	Flash point	3.11	not relevant	
VII, 7.10	Flammability	3.13	not highly flammable (purity 98.6 %)	
VII, 7.11	Explosive properties	3.14	not explosive (purity > 96 %)	
VII, 7.12	Self-ignition temperature		no self-ignition (purity 98.6 %)	
VII, 7.13	Oxidising properties	3.15	no oxidising properties (based on structure)	
VII, 7.14	Granulometry	3.5	no data available, no data requirement	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not determined	
XI, 7.16	Dissociation constant	3.21	no dissociation	
XI, 7.17,	Viscosity	3.22	not determined	
	Auto flammability	3.12	no self-ignition	
	Reactivity towards container material	3.18	not determined	
	Thermal stability	3.19	215 - 219 °C (DSC) (purity 98.6 %)	

2 MANUFACTURE AND USES

2.1 Manufacture

Nihon Nohyaku Co. Ltd., Japan

2.2 Identified uses

Acaricide in agriculture, horticulture and viticulture

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI (Tab. 3.2) of Regulation (EC) No 1272/2008

Fenpyroximate is not listed in Annex VI of .Regulation (EC) No 1272/2008

3.2 Classification in Annex VI (Tab. 3.1) of Regulation (EC) No 1272/2008

Fenpyroximate is not listed in Annex VI of Regulation (EC) No 1272/2008

4 ENVIRONMENTAL FATE PROPERTIES

The environmental fate properties assessment for fenpyroximate is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the possible inclusion of fenpyroximate in Annex I of Council Directive 91/414/EEC (DAR September 2005 + final addendum February 2008, RMS Germany) as well as the conclusion regarding the peer review of the pesticide risk assessment of the active substance fenpyroximate (EFSA Scientific Report (2008) 197, 1-104, Conclusion on the peer review of fenpyroximate).

4.1 Degradation

4.1.1 Stability

Hydrolysis

- Saxena A., McCann D. (1992), Report No. E-4013

Under sterile aqueous conditions at pH 5, 7 and 9 fenpyroximate was found to be hydrolytically stable at temperature of 25 °C. The study was performed according to US EPA Assessment Guidelines, Subdivision N, Section 161-1 (1982) with [pyrazole ^{14}C]-labelled fenpyroximate dissolved in sterile buffers at a nominal concentration of approximately 9.5 ng/L. Degradation of fenpyroximate was very slow at each pH studied.

The half-life for the hydrolytic degradation of [pyrazole-^{14}C]-fenpyroximate was calculated to be 180 days for pH 5 (correlation coefficient r^2 = 0.9671), 226 days for pH 7 (r^2 = 0.9344) and 221 days for pH 9 (r^2 = 0.6586).

Photolysis in water

- Swanson M.B. (1993), Report No. E-4015

Photodegradation of [pyrazole-^{14}C]-fenpyroximate (Batch No.: CP1275, radiochemical purity ≥ 98 %, specific activity 19.3 mCi/mmol) was studied in 0.01 M phosphate buffer at pH 7 under artificial light using xenon lamps that had a spectral energy distribution similar to that of natural sunlight.

The half-life for the decline of fenpyroximate was calculated of 1.5 hours according to first order kinetics.

The quantum yield (fraction of the absorbed photons that caused chemical change) was calculated to be 7.5 %, and the photon irradiance was 135 µmoles per hour per cm^2.

Environmentally relevant half-lives for Central Europe (55 degree of latitude) were assessed using the programme ABIWAS (Version 2.0) result in mean DT_{50} values of 1 hour (June, Minimum) to 24 hours (December, Maximum).

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

4.1.2.2 Screening tests

Readily biodegradability

- Desmares-Koopmans M.J.E. (2002), Report No.: E-4040

The ready biodegradability of fenpyroximate was determined according to the Modified Sturm test (OECD guideline 301B). Fenpyroximate of purity 98.6 % was incubated in the test medium, inoculated with activated sludge (from municipal sewage treatment plant), at a concentration of 17.5 mg/L. The released carbon dioxide was monitored for a period of 29 days and quantified by precipitation as $BaCO_3$ followed by back titration of $Ba(OH)_2$ with 0.05 M HCl. A parallel experiment was performed using inoculated sodium acetate as reference substance and inoculated fenpyroximate and sodium acetate as toxicity control to validate the test results.

The results, expressed as a percentage of the maximum theoretical CO2 production, for fenpyroximate, toxicity control (fenpyroximate + sodium acetate) and the reference substance (sodium acetate) are shown in Table 8.

Table 8: Ready biodegradability expressed as percentage of maximum theoretical CO_2 production

Time (days)	fenpyroximate (17.5 mg/L)	Toxicity control (fenpyroximate + sodium acetate)	Reference sodium acetate (20 mg/L)
7	0 %	17 %	54 %
14	1 %	24 %	68 %
23	1 %	30 %	70 %
29	1,5 %	33 %	74 %

Fenpyroximate was found to be not readily biodegradable within 29 days.

In the toxicity control less than 25 % degradation occurred in 14 days (based on theoretical CO_2 production). Due to an increase in the degradation after 14 days the degradation in the toxicity control was 33 % after completion of the study. Since the criterion for the toxicity control was not met the test substance was assumed to be inhibitory to micro-organisms in the study performed. Therefore this may affect the assessment of ready biodegradability determined in this test.

4.1.2.3 Simulation tests

Biodegradation in water/sediment systems

- Völkl, S. (2001), Report No.: E-4027

The distribution, degradation and metabolism of fenpyroximate (NNI-850) [pyrazole-^{14}C]-fenpyroximate (Batch No.: CP-1609, radiochemical purity 99 %, specific activity 21.8 mCi/mmol) in equilibrated water-sediment systems were investigated. The study was performed according to the guidelines BBA-Richtlinie Teil IV, 5-1 “Abbaubarkeit und Verbleib von Pflanzenschutzmitteln

im Wasser/Sediment System" (1990), Commission Directive 95/36/EC (1995) and SETAC Europe, Part 8.2 (1995). The water-sediment systems from a river (Rhine) and from a pond consisted of natural water filtered through a 0.2 mm sieve, and the uppermost 5 to 10 cm of sediment sieved through a 2 mm mesh (characterisation of the systems see Table 9)

Table 9: Water/sediment characteristics of river and pond systems

System	River		Pond	
	Sampling site	End of study	Sampling site	End of study
Water				
Temperature (°C) Surface 5 cm above sediment	 20.0 20.0	n.d.	 12.7 11.8	n.d.
PH Surface 5 cm above sediment	 8.31 7.74	8.42 [3)]	 7.67 7.55	8.08 [3)]
Redoxpotential (mV) Surface 5 cm above sediment	 211 193	207 [3)]	 102 38	213 [3)]
Oxygen content (mg/L) Surface 5 cm above sediment	 7.8 7.4	6.5 [3)]	 8.9 4.8	6.7 [3)]
NO_3-N /(mg/L) NO_2-N (mg/L) NH_4-N (mg/L) N-total[2)] (mg/L)	1.08 0.02 0.05 	0.14 0.03 0.01 1.20	0.29 0.02 0.07 	0.29 0.02 0.02 0.80
P as orthophosporous (mg/L) P-total[2)] (mg/L)	0.07	0.17 0.17	0.09	0.03 0.05
TOC[1)]	1.7	11.0	3.7	7.4
Hardness (°dH)	11	28	18.5	34
Sediment				
pH (KCl)	7.27	n.d.	6.89	n.d.
Redoxpotential (mV)	-154	-148	-78	-170
N-total (g/kg sediment)	1.0	n.d.	4.1	n.d.
P-total (g/kg sediment)	0.253	n.d.	0.482	n.d.
Total organic carbon (g C/100g dry soil)	0.74	n.d.	4.41	n.d.
Cation exchange capacity (mVal N/100g dry soil)	8.7	n.d.	8.9	n.d.
Particle size distribution: Soil characterisation Clay (%, < 2µm) Silt (%, < 2-50µm) Sand (%, < 50µm)	 Sandy loam 6.7 32.3 61.0		 Silt loam 2.7 59.6 37.7	
Dry mass (kg dry soil/kg fresh sediment)	0.6	0.6	0.3	0.3
Biomass (mg microbial C/100g dry soil)	51.6	61.0	256.0	214.5

[1)] Parameters determined at RCC
[2)] Determined after disintegration in the microwave oven
[3)] Mean of control samples
n.d. – Not determined

The results of the aerobic incubation of fenpyroximate are summarised in Table 10.

Table 10: Dissipation times of [^{14}C-pyrazol] labelled fenpyroximate in aquatic systems

Substance	Test system	Total system (days)		Water (days)		Sediment (days)	
		DT_{50}	DT_{90}	DT_{50}	DT_{90}	DT_{50}	DT_{90}
[^{14}C]-labelled fenpyroximate	River	27.6	248.0	2.8	9.2	52.5	n.d.
	Pond	24.3	126.7	3.1	24.3	40.8	n.d.

n.d. – Not determined

Fenpyroximate was rapidly eliminated from the water phase with a half-life of 2.8 days and 3.1 days in the river and pond water, respectively. The corresponding DT_{90} values were 9.2 days and 10.3 days. Elimination proceeded mainly by cleavage of the oxime-ether bond and by adsorption to the sediment. Thus it will not persist in the aqueous phase. The degradation of the parent molecule in the sediment was slower leading to DT_{50} values of 27.6 days and 24.3 days for the river and pond system, respectively. The metabolism of [^{14}C]-fenpyroximate proceeded mainly via cleavage of the substituted oxime ether bonding.

Fenpyroximate adsorbs to sediment very fast. Therefore, around 40 % of the applied radioactivity is found in the sediment immediately after application, and disappearance from the water phase is rapid.

However, the active substance is very slowly mineralised in the water/sediment system (1.9 % CO_2 after 105 days), and bound residues were increasingly formed during the study period up to 28 % after 105 days.

4.1.3 Summary and discussion of persistence

Fenpyroximate was found to be not readily biodegradable in the available study.

In water/sediment systems fenpyroximate was metabolised at a moderate rate with DT_{50} values of 27.6 days and 24.3 days.

4.2 Environmental distribution

Not relevant for this dossier.

4.2.1 Adsorption/desorption

4.2.2 Volatilisation

4.2.3 Distribution modelling

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Fenpyroximate has a log Kow of 5.01.

4.3.1.2 Measured bioaccumulation data

The bioconcentration of [^{14}C]-fenpyroximate in bluegill sunfish (*Lepomis macrochirus*) was determined in a 36-day study, which included a 14-day uptake period and a 22-day depuration period. The lipid content of test fish was determined with an average of 9.2 % total lipids at test initiation (day 0) and an average of 9.4 % total lipids at study termination (day 36).

Fenpyroximate rapidly accumulated, principally in the non-edible tissues. Whole fish residue on days 7, 10 and 14 were within ± 20 % of each other and BIOFAC modelling determined that residues in whole fish achieved 90 % of steady state by day 14. The maximum bioconcentration factor for whole fish of 1601 L/kg ww was reached after 14 days. Based on the fitted uptake and depuration rate constants, the kinetic BCF is 1842 L/kg ww. These BCF-values should be corrected for the high lipid content of test fish (9.2 %) to maximum BCF of 870 L/kg ww and BCF kinetic of 1001 L/kg ww (lipid normalized to 5 % lipid content).

Accumulated fenpyroximate was over 90 % depurated (97 % by BIOFAC data) after 22 days.

Table 11: Results of aquatic bioconcentration measurements

guideline/ test method	exposure	log Kow	Initial conc. [µg/L]	Steady state BCF [L/kg ww]	Kinetic BCF	Depuration time CT50(d)	Depuration time CT90(d)	Remarks	reference
OECD 305 & 305 E	14 d, flow - trough	5.1	0.115 (real) 0.1 (nom)	1601	1842	4.2	21	Whole fish based on TRR [1)]	Smith, S.M. and Young, B.M. (1997), Document No.: W-4045

[1)] Majority of the total radioactive residues (TRR) in water and fish are chromatographic analysed as parent substance (fenpyroximate)

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

Fenpyroximate has a log Kow of 5.01. The experimentally derived steady state BCF of 1601 and kinetic BCF of 1842 (lipid normalized to 5 % lipid content to maximum BCF of 870 L/kg ww and BCF kinetic of 1001 L/kg ww) are above the trigger of 500 for not readily biodegradable substances. Based on the results of the bioconcentration study, fenpyroximate does significantly bioaccumulate.

4.4 Secondary poisoning

Not relevant for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

More details on the available toxicological studies are summarised in chapter B.6 of the Draft Assessment Report (DAR, 30 September 2005) prepared by Germany in the context of the evaluation of the fenpyroximate for possible inclusion into Annex I under Directive 91/414/EEC, which is attached to the IUCLID Dossier. A redacted version of the DAR is publically available from EFSA's homepage under http://dar.efsa.europa.eu/dar-web/provision/request/subid/112.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

After oral administration of [pyrazole-^{14}C]-labelled fenpyroximate to rats the blood bio-kinetics showed no relevant sex differences which is in contrast to those of the [benzyl-^{14}C] - labelled compound. The benzyl moiety was eliminated more rapidly in females when a high dose (400 mg/kg bw) was applied while elimination was more rapidly in males after using a low dose (2 mg/kg bw). Both absorption and elimination of the pyrazole and the benzyl labelled fenpyroximate were greatly delayed and half-lives were much longer for the high dose in relation to the low dose.

In the low dose group radioactivity in blood increased slowly with T_{max} values of 11.0 hours for males and 11.4 hours for females after applying the pyrazole labelled and 7.8 hours for males and 7.2 hours for females after applying the benzyl labelled compound. Radioactivity declined with half-lives between 6.1 and 8.9 hours for both labelled compounds. The mean concentration of radioactivity had decreased to or below the limit of detection after 72 hours and 48 hours for the pyrazole labelled and for the benzyl labelled fenpyroximate, respectively.

In the high dose group radioactivity increased slowly with T_{max} values of 100.8 hours for males and 90.0 hours for females after administration of the pyrazole labelled or 28.8 hours for males and 86.4 hours for females after administration of the benzyl labelled compound. Radioactivity declined with half-lives between 35.4 and 48.7 hours for both labels. The mean concentration of radioactivity had decreased to or below the limit of detection after 216 hours and 168 hours for the pyrazole labelled and for the benzyl labelled fenpyroximate, respectively.

A great number of metabolites was identified indicating that fenpyroximate was extensively metabolised by e.g. hydrolytic cleavage of the oxime bond, hydrolysis of the tert-butyl ester moiety, oxidation of the tert-butyl group, hydroxylation of the phenoxy ring and 3-methyl group, by isomerisation, N-demethylation and conjugation.

There were no changes in the metabolism of [pyrazole-^{14}C]- or [benzyl-^{14}C]-fenpyroximate upon repeated dosing or after applying the low or the high dose. The relative increase of the parent compound in the faeces after administration of the high dose was due to a lowered absorption rate.

Biliary excretion in rats after oral administration of either [pyrazole-^{14}C]- or [benzyl-^{14}C]-fenpyroximate showed no significant differences between sexes and between the two labels. Radioactive material was excreted in bile at about 55 and 47 %, in urine at about 5 and 10 %, and in faeces at about 28 and 17 % for males and females, respectively, when the pyrazole labelled compound was used, and in bile at about 51 and 47 %, in urine at about 6 and 8 %, and in faeces at about 40 and 28 % for males and females, respectively, after administration of the benzyl labelled compound. In consequence excretion in bile, urine and faeces within 48 hours after dosing of the pyrazole labelled test substance resulted in 88 % and 73 % for males and females, respectively, and 97 % and 83 % for males and females, respectively, after administration of the benzyl labelled

substance. The systemically available fenpyroximate (i.e.: absorbed in the gastrointestinal tract and excreted via bile and urine) amounted for both labels roughly between half and two thirds of the applied dose.

Oral administration of a single low dose of either [pyrazole-^{14}C]- or [benzyl-^{14}C]-fenpyroximate resulted in approximately 70 - 85 % of the applied dose being excreted via faeces and approximately 10 - 20 % via urine. 6 to 12 hours after dosing most radioactivity was found in the gastrointestinal tract with liver and some sections of the gastrointestinal tract being the tissues containing the highest concentration of radioactivity. 24 hours after dosing only little radioactivity remained in the gastrointestinal tract. Tissue residues were low 168 hours after administration.

When preceded by 14 daily doses of non radioactive fenpyroximate residues in tissues were also low 168 hours after administration of low doses of either [pyrazole-^{14}C]- or [benzyl-^{14}C]-fenpyroximate. Again the greatest part of the applied dose was excreted via faeces (more than 75 %). No alterations in tissue distribution were found after multiple dosing of fenpyroximate.

Oral administration of a single high dose of either [pyrazole-^{14}C]- or [benzyl-^{14}C]-fenpyroximate resulted in approximately 75 - 80 % of the applied dose being excreted via faeces and approximately 10 - 15 % via urine. Tissues with higher concentrations of radioactivity were fat, liver and portions of the gastrointestinal tract. 6 to 12 hours after dosing the majority of the applied radioactivity was still found in the contents of the gastrointestinal tract. Although excretion was delayed, most of the radioactivity was eliminated in urine and faeces at the 168 hours collection period and no evidence for accumulation of radioactivity in specific tissues could be found. In general residues in most tissues were low at this time. Tissues that contained still the highest amounts of radioactivity were liver, fat and kidney and some sections of the gastrointestinal tract.

5.1.1 Dermal absorption

The extent of the applied dose absorbed into the systemic circulation (systemic bioavailability = sum of [^{14}C] - fenpyroximate equivalents recovered in the urine, faeces, non-application site skin and carcass) ranged from 0 to 5.3 % (1 mg/mL treatment group), 0.4 to 2.5 % (10 mg/mL treatment group), and 0.1 to 1.5 % (52 mg/mL treatment group). In general, systemic bioavailability increased with time and decreased with respect to dose. When application site skin values were included the percent of dose values ranged from 11 to 24 % (1 mg/mL treatment group), 4 to 7 % (10 mg/mL treatment group), and 3 to 8 % (52 mg/mL treatment group). Based on these results, for the further calculation a dermal absorption of 7% is used for the concentrate formulation and 24% is used for the spray dilution.

RAC evaluation of [physical hazards]

Summary of the Dossier submitter's proposal

No classification for physical hazards is proposed by the Dossier Submitter.

Comments received during public consultation

None

Assessment and comparison with the classification criteria

The submitted studies include information for the following physical hazard classes: Explosives, flammable solids, self-heating substances and mixtures and oxidising liquids. None of the enclosed studies indicates a need for the classification of physical hazards.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Oral LD_{50} of fenpyroximate was between 350 mg/kg bw in rats (245 mg/kg bw in females and 480 mg/kg bw in males) and 500 mg/kg bw in mouse.

In the rat study clinical signs seen on the day of dosing in most groups included urinary and faecal staining, soft stool, eyes partially closed and hypoactivity. Additional signs seen in single animals included evidence of oral discharge in the 200 mg/kg dose group and hypopnea, prostration, abdominal griping and/or dry rales in the 600 and 800 mg/kg dose groups. Decreased food consumption was noted in a few surviving animals on the day after dosing and in most surviving animals on the second day after dosing; this continued in a few animals through day 6.

Table 12: Dose levels and corresponding mortality in the oral rat study

Dose level (mg/kg)	Range-finding study	LD_{50} determination study		
	Total mortality	Mortality		
		Male	Female	Total
200	0/2	0/5	1/5	1/10
280	1/2	2/5	4/5	6/10
400	1/2	2/5	4/5	6/10
600	1/2	2/5	5/5	7/10
800	2/2	4/5	5/5	9/10
LD_{50} (mg/kg)	--	480	245	350

In the mouse study clinical signs seen on the day of dosing in most groups included ataxia, hypopnea, hypoactivity and prostration. Decreased food consumption was observed in most surviving animals on the day after dosing, this continued in some animals through day 5. Additional signs seen in two or more groups included urinary staining and abdominal griping. Hyperpnea, dyspnea, hypothermia or hyperactivity was observed in single animals in the 800 mg/kg dose group. Coarse tremors were seen in animals in the 1200 and 1700 mg/kg dose group.

Table 13: Dose levels and corresponding mortality in the oral mouse study

Dose level (mg/kg bw)	Range-finding study	LD50 determination study		
	Total mortality	Mortality		
		Male	Female	Total
200	0/2	1/5	1/5	2/10
280	2/2	0/5	2/5	2/10
400	0/2	1/5	4/5	5/10
600	½	3/5	2/5	5/10
800	2/2	4/5	2/5	6/10
1200	--	--	5/5	5/5
1700	--	--	5/5	5/5
LD_{50} (mg/kg bw)	--	520	440	500

Table 14: Summary of acute oral toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 401	Oral	Rat, SD 5M + 5F	200-280-400-600-800	Male: 480 Female: 245 Combined: 350	Vehicle: Tween 80	Blaszcak, D.L. (1989), report no. T-4001
OECD 401	Oral	Mouse, CD-1(ICR)BR 5M + 5F	200-280-400-600-800-1200-1700	Male: 440 Female: 520 Combined: 500	Vehicle: Tween 80	Blaszcak, D.L. (1989), report no. T-4002

5.2.2 Acute toxicity: inhalation

In a first study Sprague-Dawley CD rats were exposed (whole body) to fenpyroximate as a dust at analytical concentrations of 0.067, 0.14, 0.36, 0.78 and 0.74 mg/L resulting in mortalities of 10 %, 0 %, 20 %, 100 % and 90 %, respectively. The LC_{50} of fenpyroximate as active ingredient was 0.33 mg/L in males and 0.36 mg/L in females (0.36 mg/L for combined sexes). During exposure the most commonly signs of toxicity were laboured breathing or gasping. Other observations included lacrimation or nasal discharge. Most animals which died during exposure were observed to have died by the third hour. Upon removal from the chamber one male from group I and III, two males from group IV and nine animals (4 males, 5 females) from group V were found dead. Among survivors signs similar to those seen during exposure were exhibited. One additional group III female died on test day 6 and eight additional group IV animals (3 males, 5 females) died between test day 4 and 12. Signs associated with poor conditions preceded these death. Among surviving animals signs similar to those seen following exposure continued during the first week of the recovery period, after which they decreased in incidence.

Table 15: Mean analytical, gravimetric and nominal concentrations of fenpyroximate and the resultant mortalities of rats exposed to fenpyroximate via inhalation in the first study (Hoffman, 1989)

Group	Fenpyroximate concentration (mg/L)			Mortality		
	Analytical	Gravimetric	Nominal*	Male	Female	Total
I	0.067	0.072	0.63	1/5	0/5	1/10
II	0.14	0.17	0.52	0/5	0/5	0/10
III	0.36	0.41	1.4	1/5	1/5	2/10
IV	0.78	0.90	28	5/5	5/5	10/10
V	0.74	0.81	1.8	4/5	5/5	9/10
* - the high nomonal level in group IV was the result of the fluidised bed generator being used instead of the Sibata dust feeder						

In a second study Sprague-Dawley CD® rats were exposed via nose-only inhalation to fenpyroximate as a dust at analytical concentrations (active ingredient) of 0.51, 0.20 and 0.096 mg/L resulting in mortalities of 67 %, 40 % and 0 %, respectively. The LC_{50} was calculated to be 0.31 mg/L for the combined sexes, 0.21 mg/L for the males and 0.33 mg/L for the females. During exposure the most commonly signs of toxicity were laboured breathing, however, it should be noted that observations are limited during exposure while the animals are restrained in the nose-only tubes. Upon removal from the chamber six animals (2 males, 4 females) were found dead following group I exposure (including one accidental death) and two males were found dead following group II exposure. One additional group I male died within an hour following exposure. The surviving

animals from all three exposures showed various responses including laboured breathing, rales, gasping, nasal discharge and ano-genital staining. An additional group II male and female rat were found dead on test day two. Among surviving animals signs similar to those seen immediately following exposure were noted during the first few days of the recovery period, after which they generally abated.

Table 16: Mean analytical, gravimetric and nominal concentrations of fenpyroximate and the resultant mortalities of rats exposed to fenpyroximate via nose-only inhalation in the second study (Hoffman, 1991)

Group	Fenpyroximate concentration (mg/L)				Mortality		
	Analytical [a]	Analytical [b]	Gravimetric [b]	Nominal [b]	Male	Female	Total
I	0.51	0.58	0.65	2.7	3/5	3/4 [c]	6/9 [c]
II	0.20	0.22	0.24	0.53	3/5	1/5	4/10
III	0.096	0.11	0.11	0.23	0/5	0/5	0/10

[a] – Concentration based on percentage of active ingredient
[b] – Concentration based on formulation
[c] – Excludes one accidental death

Table 17: Results of the particle size determination in the second study (Hoffman, 1991)

Group	Mass Median Aerodynamic Diameter (microns)	Geometric Standard Deviation	% of Particles in Diameter ≤ 1 µm	% of Particles in Diameter ≥ 1 µm
I	2.9	2.3	11	94
II	2.5	2.3	15	96
III	3.0	2.2	8.8	94
Mean	2.8	2.3	12	95

Table 18: Summary of acute inhalative toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/L)	Value LD_{50} (mg/L)	Remarks	Reference
OECD 403	Inhalative	Rat, SD CD 5M + 5F	0.067-0.14-0.36-0.78-0.74	Male: 0.33 Female: 0.36 Combined: 0.36	4 h, whole body	Hoffman, G.M. (1989), report no. T-4004
OECD 403	Inhalative	Rat, SD CD 5M + 5F	0.096-0.20-0.51	Male: 0.21 Female: 0.33 Combined: 0.31	4 h, nose only	Hoffman, G.M. (1991), report no. T-4052

5.2.3 Acute toxicity: dermal

Fenpyroximate showed low acute dermal toxicity (LD_{50}, rat: >2000 mg/kg bw). All animals survived throughout the study. No severe dermal effects were seen during the course of the study.

Table 19: Summary of acute dermal toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 402	dermal	Rat, SD 5M + 5F	2000	>2000	Moistened with 0.9% saline	Blaszcak, D.L. (1989), report no. T-4003

5.2.4 Acute toxicity: other routes

No data are available.

5.2.5 Summary and discussion of acute toxicity

Oral LD_{50} of fenpyroximate was between 350 mg/kg bw in rats (245 mg/kg bw in females and 480 mg/kg bw in males) and 500 mg/kg bw in mice.

According to Directive 67/548/EEC Substances and preparations shall be classified as:

"R22 Harmful if swallowed" and assigned the symbol "Xn"

in case following criteria are fulfilled:

LD_{50} per oral, rat: $200 < LD_{50} \leq 2\,000$ mg/kg,

Therefore, classification as harmful, symbol Xn, and risk phrase R22 "Harmful if swallowed" is proposed for fenpyroximate.

According to Regulation (EC) No 1272/2008 a substance is allocated to Acute Tox. 3 if an oral LD_{50} is derived in the following range: $50<LD_{50}\leq300$ mg/kg bw. The LD_{50} in female rats was 245 mg/kg bw. Therefore, Acute Tox. 3 and the Hazard Statement H301: Toxic if swallowed is proposed.

The dermal toxicity was low (LD_{50}>2000 mg/kg bw). Therefore, no classification of dermal toxicity is required.

The acute inhalation toxicity was tested in two studies. In the first study, the LC_{50} of fenpyroximate as active ingredient was 0.33 mg/L in males and 0.36 mg/L in females (0.36 mg/L for combined sexes). In the second study, the LC_{50} was calculated to be 0.31 mg/L for the combined sexes, 0.21 mg/L for the males and 0.33 mg/L for the females. However, fenpyroximate was formulated with 10% dioxosilane (silicon dioxide), the toxicological contribution of this compound for the mortality observed in the inhalation study was investigated and considered to be negligible. The mortality in the studies is due to the active substance and not to the dioxosilane.

According to Directive 67/548/EEC substances and preparations shall be classified as:
"R26 Very toxic by inhalation" and assigned the symbol "T+"
in case following criteria are fulfilled:

LC50 inhalation, rat, for aerosols and particulates: ≤ 0,25 mg/litre/4h.

Consequently, classification as very toxic, symbol T+, and risk phrase R26 "very toxic by inhalation" is proposed for fenpyroximate.

According to CLP regulation substances can be allocated to Acute Tox. 2 based on acute toxicity by inhalation if the following criteria are fulfilled for dustes and mists: 0.05 mg/L < LC50 < 0.5 mg/L. In the submitted studies, dusts have been tested. The experimental exposure period was 4 h. Therefore, no further correction is necessary. Consequently, classification as Acute Tox. 2, H330 "Fatal if inhaled" is proposed.

Proposed classification:

Directive 67/548/EEC:
Xn, R22 Harmful if swallowed
T+, R26 Very toxic by inhalation

CLP Regulation:

Acute Tox. 3, H301 Toxic if swallowed

Acute Tox. 2, H330 Fatal if inhaled

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The Dossier Submitter proposed to classify fenpyroximate as Acute Tox. 3; H301 (Xn; R22) and Acute Tox. 2; H330 (T+; R26) in accordance with the CLP Regulation and Directive 67/548/EEC (DSD), respectively.

The oral LD_{50} of fenpyroximate was between 350 mg/kg bw in rats (245 mg/kg bw in females and 480 mg/kg bw in males) and 500 mg/kg bw in mice.

The acute dermal toxicity was low (LD_{50}>2000 mg/kg bw). Therefore, no classification for acute dermal toxicity is required.

The acute inhalation toxicity was tested in two studies. In the first study, the LC_{50} of fenpyroximate as active ingredient was 0.33 mg/L in males and 0.36 mg/L in females (0.36 mg/L for both sexes combined). In the second study, the LC_{50} was calculated to be 0.31 mg/L for the combined sexes, 0.21 mg/L for males and 0.33 mg/L for females. Although fenpyroximate was formulated with 10% dioxosilane (silicon dioxide) in this study, the observed mortality was considered to be due to the active substance and not to the dioxosilane.

Comments received during public consultation

One MSCA expressed agreement with the proposal.

Assessment and comparison with the classification criteria

Oral toxicity:

According to the CLP Regulation a substance should be classified as Acute Tox. 3 if the oral LD_{50} is derived in the following range: $50<LD_{50}\leq300$ mg/kg bw. The LD_{50} in female rats was 245 mg/kg bw. Therefore, classification as Acute Tox. 3 and the Hazard Statement H301: "Toxic if swallowed" is warranted.

According to DSD substances shall be classified as R22 "Harmful if swallowed" and assigned the symbol "Xn" if the LD_{50} per oral, rat is $200 < LD_{50} \leq 2\,000$ mg/kg. Therefore, classification as harmful (Xn), and the risk phrase R22 "Harmful if swallowed" is warranted for fenpyroximate.

Inhalation toxicity:
According to the CLP regulation, substances can be classified as Acute Tox. 2 by inhalation route if the following criteria are fulfilled for dusts and mists: 0.05 mg/L < LC_{50} < 0.5 mg/L. In the submitted studies, fenpyroximate dusts have been tested, and the LC_{50} values fall within that range. The experimental exposure period was 4 h. Therefore,

no correction factor is necessary. Consequently, classification as Acute Tox. 2, H330 "Fatal if inhaled" is needed.

According to DSD substances shall be classified as R26 "Very toxic by inhalation" and assigned the symbol "T+" if the LC_{50} inhalation, rat, for aerosols and particulates is ≤ 0,25 mg/litre/4h. Consequently, classification as very toxic (T+), and the risk phrase R26 "very toxic by inhalation" is appropriate for fenpyroximate.

5.2.6 Summary and discussion of specific target organ toxicity – single exposure (STOT-SE)

According to Regulation (EC) No 1272/2008, "the information required to evaluate specific organ toxicity comes either from single exposure in humans, such as: exposure at home, in the workplace or environmentally, of from studies conducted in experimental animals."

According to the Guidance to Regulation (EC) No 1272/2008 (13 July 2009), "older acute toxicity studies which tended to only measure lethality as an observational endpoint (e.g. to determine LD50/LD50) will generally not provide useful information for STOT-SE."

The available studies on fenpyroximate are valid according to the data requirements. However, they are considered to provide no sufficient information for STOT-SE.

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

Summary of the Dossier submitter's proposal

The dossier submitter provided no data but noted that "the available studies on fenpyroximate are valid according to the data requirements. However, they are considered to provide insufficient information for STOT-SE."

Comments received during public consultation

One MSCA proposed classification as Xi; R37 "Irritation to respiratory system" under DSD and STOT SE 3; H335 "May cause respiratory irritation", based on the findings observed in acute inhalation studies (Hoffman, 1989 and 1991) and in a subacute inhalation study (Hoffman, 1991) in rats, in which the following signs of reversible respiratory tract irritation were observed: laboured breathing, gasping, rales and the histopathological data from the respiratory system (oedema, reddening and firm lugs, frothy fluid in the trachea and atrophy, desquamation and squamous metaplasia of nasal passage mucosa).

Assessment and comparison with the classification criteria

For fenpyroximate, classification as Acute Tox. 2; H330 (Fatal if inhaled) / T+, R26 (very toxic by inhalation) has already been proposed by the DS. Therefore, an additional classification as STOT SE 3, H335 / R37 would not provide significant additional hazard information.

In two acute inhalation studies, the findings reported were mainly observed in the lethal dose range. Therefore, it is questionable to base the classification for specific target organ toxicity on the results of studies at these extreme doses.

However, the results of the 4-week, short term inhalation toxicity study in rats are also considered to be relevant. According to the protocol of this study, 6 samples of the lungs (from each lobe) and from mainstem bronchi of all animals were examined

histopathologically. No effects of the test substance were observed in these comprehensive investigations. Therefore, the cause of the increased lung weight is questionable. Furthermore, in one comment received during public consultation, squamous metaplasia of respiratory mucosa is mentioned. However, the incidence of this finding was not increased after a 14-day recovery period. Squamous metaplasia is a serious change in the organ structure. It is questionable whether such fundamental transformations can be reversible within 14 days. Furthermore, the incidence of this finding in male animals of the highest dose group was 2. The incidence of this finding in the recovery control group was also 2. Therefore the incidences of the highest dose group are considered to be within the range of those in the control animals.

All in all, RAC considered that the effects described in the inhalation studies did not constitute sufficient evidence to support classification for specific target organ toxicity on the respiratory system.

5.3 Irritation

5.3.1 Skin

No skin irritating potential of fenpyroximate was observed in the rabbit. Neither erythema nor oedema were seen on any of the treated skin sites and untreated control skin sites of each animal at any occasion of observation (1, 24, 48 and 72 hours) after removal of the patches.

Table 20: Summary of skin irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average score 1, 24, 48, 72 h		Reversi-bility yes/no	Results	Remarks	Reference
		Erythema	Oedema				
OECD 404	Rabbit, KBL:NZW 6M	0-0-0-0	0-0-0-0	Not applicable	Not irritating	None	Kosaka, T. (1988), report no. T-4010

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

No evidence for skin irritating potential of fenpyroximate was observed in an OECD TG 404 -compliant study conducted with rabbits (New Zealand White (NZW), 6 males). Therefore, no classification is required.

Comments received during public consultation

None

Assessment and comparison with the classification criteria

All average scores in the submitted study were 0, therefore no classification for skin corrosion/irritation is warranted.

5.3.2 Eye

The eye irritating potential of fenpyroximate was tested in rabbits. Changes due to irritation were found neither in the cornea nor in the iris of any treated eyes. In respect to the conjunctivae all animals showed redness of grade 1 (some blood vessels definitely hyperemic) from 1 to 24 hours and 4 of 6 animals showed redness to 48 hours after the treatment. Chemosis of grade 1 was observed in 6 of 6 animals 1 h after treatment and disappeared by 24 hours after the treatment. All changes due to irritation in the conjunctivae disappeared by 3 days after the treatment in either group.

Information concerning eye irritation in farmers who used fenpyroximate 5 % SC was gathered by Nihon Nohyku (Sano, Y., Nokata, M.: Effects on Fenpyroximate in human. Eyes and skin irritation. Nihon Nohyaku Co. September 1992, unpublished report). Eye irritation was found in 1991 in 23 cases and in 1992 in 3 cases of farmers applying fenpyroximate 5 % SC in citrus field but was not reported in farmers using the formulation in any other crop. The occurrence of eye irritation only during use in citrus fields was considered to be related to the planting conditions of this crop, resulting in a higher exposure to the pesticide spray, in contrast to other crops (e.g. apple). The irritation was primary and recovery was obtained within a short time after application. The incidence of eye irritation in 1992 was lower than that in 1991 in spite of an increase of the amount of fenpyroximate 5 % SC sold, as a greater attention to avoid exposure to fenpyroximate 5 % SC was made popular among farmers and the use of glasses and goggles was recommended.

The following information was submitted in the report:

Spray conditions:

Single use of fenpyroximate 5% SC or tank mix use with one to three further pesticides.

Dilution ratio of fenpyroximate 5% SC: 1000, 1500 or 2000

Volume rate: 800-2000 l/10 a

Applicator: Power sprayer

Condition of eye irritation:

Subjective symptom: Feeling as being of foreign substance in the eyes, being dim, irritation, pain, decreased eyesight, bloodshot eye, weeping

Instances of diagnosis by occultist: Inflammation of cornea and iris, corneal erosion

Table 21: Summary of eye irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Average score 1, 24, 48, 72 h				Reversi-bility yes/no	Results	Remarks	Reference
		Cor-nea	Iris	Redness Conjunctiva	Chemosis				
OECD 405	Rabbit, KBL:NZW 6M	0-0-0-0	0-0-0-0	1-1-0.7-0	1-0-0-0	Yes	Not irritating	None	Kosaka, T. (1988), report no. T-4009

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

Slight eye irritation was observed in an OECD TG 405 –compliant study conducted in rabbits (NZW, 6 males). On the basis of this study, classification would not be warranted.

Method / Guideline	Species, Strain, Sex, No/group	Average score 1, 24, 48, 72 h				Reversible yes/ no	Results	Remarks	Reference
		Cornea	Iris	Redness Conjunctiva	Chemosis				
OECD 405	Rabbit, KBL:NZW 6M	0-0-0-0	0-0-0-0	1-1-0.7-0	1-0-0-0	Yes	Not irritating	None	Kosaka, T. (1988), report no. T-4009

However, there human data showed that eye irritation was observed in workers and farmers. Information concerning eye irritation in farmers who used fenpyroximate 5 % SC was gathered by Nihon Nohyku (Sano *et al.*, 1992). Eye irritation was found in 23 cases in 1991 and in 3 cases in 1992 in farmers applying fenpyroximate 5 % SC in a citrus field but was not reported in farmers using the formulation in any other crop. The occurrence of eye irritation only during use in citrus fields was considered to be related to the planting conditions of this crop, resulting in a higher exposure to the pesticide spray, in contrast to other crops (e.g. apple). The irritation was primary and recovery occurred within a short time after application. The incidence of eye irritation in 1992 was lower than that in 1991 in spite of an increase of the amount of fenpyroximate 5 % SC sold, as there was greater attention to avoiding exposure to fenpyroximate 5 % SC among farmers and the use of glasses and goggles was recommended.

Comments received during public consultation

Three MSCA expressed disagreement with the proposal for eye irritation. The Dossier Submitter agreed with the comments received during public consultation, and therefore classification of fenpyroximate as Xi; R36 is no longer proposed by the Dossier Submitter.

Additional key elements

Up until August 1992, two incidents of eye and skin irritation in workers engaged in manufacturing technical grade fenpyroximate were reported. Both cases occurred when the manufacture of technical grade of fenpyroximate had just begun (case 1: July 1990, case 2: November 1990). Thereafter, irritation considered to be related to fenpyroximate has not been reported. No other adverse effects related to fenpyroximate have been recognised in workers in a factory where fenpyroximate has been manufactured (DAR Fenpyroximate, September, 2005).

Assessment and comparison with the classification criteria

According to the CLP regulation, substances may be classified in category 2 (irritating to eyes) if there is adequate existing human experience which provides evidence that the substance is irritating to eyes. However, as there have only been two incidents reported in workers engaged in manufacturing technical grade of fenpyroximate and these more than 20 years ago, together with the knowledge that the most relevant primary eye irritation study with the active substance fenpyroximate in rabbits was negative, RAC considered that classification as Eye Irrit. 2, H319 (CLP) and Xi; R36 (DSD) is not appropriate.

5.3.3 Respiratory tract

No data available.

RAC evaluation of respiratory sensitisation
Summary of the Dossier submitter's proposal No indication of respiratory sensitization in the acute inhalation toxicity studies.

5.3.4 Summary and discussion of irritation

No skin irritating potential of fenpyroximate was observed in the rabbit. Therefore, no classification is required.

A slight eye irritation was observed in rabbits. On basis of this study a classification would not be necessary. However, eye irritation was observed in workers and farmers.

According to Directive 67/548/EEC substances and preparations shall be classified as:
"R36 Irritating to eyes" and assigned the symbol "Xi"
in case following criteria are fulfilled:

> "Substances or preparations which cause significant ocular lesions, based on practical experience in Humans".

Therefore, classification of fenpyroximate as irritant, symbol Xi, and risk phrase R36 "Irritating to eyes" is proposed.

According to CLP regulation substances are classified in category 2 (irritating to eyes) if there is adequate existing human experience which provides evidence that the substance is irritating to eyes. The submitted data on human effects are considered to be an evidence of the irritating potential.

Proposed classification:

Directive 67/548/EEC: Xi, R36 Irritating to eyes

CLP Regulation: Eye Irrit. 2, H319 Causes serious eye irritation

5.4 Corrosivity

No evidence for a corrosive activity of fenpyroximate was observed in skin and eye irritation studies.

5.5 Sensitisation

5.5.1 Skin

A maximisation test in the guinea pig showed a sensitisation rate of 36 %. No evidence of sensitising potential was observed in a Buehler test.

Table 22: Summary of skin sensitisation

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/Total number of animals	Results	Remarks	Reference
OECD 406, Magnusson-Kligman test	Guinea pig, Crj:Hartley, 25 F Negative Control, 25 F Treatment group, 10 F DNCB 10 F control to DNCB	0/25 (negative control) 9/25 (fenpyroximate technical)	Sensitising	Vehicle: Induction: Water in oil emulsion of Freund´s complete adjuvant in salt solution; Challenge: test compound in white petrolatum	Kosaka, T. (1988), report no. T-4015
OECD 406, Buehler test	Guinea pig, Crj:Hartley, 20 F Negative control, 20 F Treatment group 10 F DNCB 10 F Control to DNCB	0/20 (negative control) 0/20 (fenpyroximate technical)	No evidence of sensitising potential	Vehicle: 50% aqueous dilution of the test material	Teale, H.J. (1990), report no. T-4016

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

In a Magnusson/Kligman test a sensitisation rate of 36% was obtained. The intra-dermal induction concentration was 5%.. Therefore, classification as Skin Sens. 1B (CLP) and R43 "May cause sensitisation by skin contact" (DSD) is proposed. The negative result (0/60) in a second test (Buehler test) is not relevant because there was clear evidence for the sensitising activity of the test substance in the GPMT.

Comments received during public consultation

One MSCA expressed agreement with the proposal.

Assessment and comparison with the classification criteria

Based to the results in the maximization assay (Kosaka, 1988) and considering the classification criteria in the CLP regulation, the test compound fulfills the criteria to be classified as Skin sensitiser Category 1B (H317) (R43 under DSD) since the intradermal induction concentration was 5% and the sensitisation rate was 36%.

5.5.2 Respiratory system

No indication in the inhalation toxicity studies. No further data available.

5.5.3 Summary and discussion of sensitisation

In the Magnusson/Kligman test a sensitisation rate of 36% was obtained. In the Buehler test no animals were sensitized.

Comparison with criteria:

Toxicological result	DSD criteria	CLP criteria[1]
Kosaka, T. (1988): 9/25 (36 %) of the animals positive 5 % intra dermal induction concentration	Adjuvant type test method: ≥ 30 % of the animals positive	**Guinea pig maximisation test** Category 1A: ≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose Categrory 1B: ≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose
Teale, H.J. (1990): 0/20 (0 %) of the animals positive 50 % (% w/w) dermal induction concentration	Other test method: ≥ 15 % of the animals positive	**Buehler assay** Category 1A: ≥ 15 % responding at ≤ 0.2 % topical induction dose or ≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose Categrory 1B: ≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose

In the Magnusson/Kligman test a sensitisation rate of 36% was obtained. The Magnusson/Kligman test is considered to be an appropriate animal test according to Directive 67/548/EEC. Therefore, classification with risk phrase R43 “May cause sensitisation by skin contact” is proposed. The negative result in a second test (Buehler test) is not relevant because the sensitising activity of the test substance was clearly evidenced.

Based to the results in the maximization assay (Kosaka, 1988) and considering the classification criteria in CLP regulation (amended by commission regulation (EU) No 286/2011 of 10 March 2011), the test compound fulfills the criteria to be classified as skin sensitiser category 1B (H317).

Proposed classification:

[1] amended by Commission Regulation (EU) No 286/2011 of 10 March 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures

Directive 67/548/EEC: Xi, R43 May cause sensitisation by skin contact

CLP Regulation: Skin Sens. 1B, H317 May cause an allergic skin reaction

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

The results of the oral repeated dose toxicity studies indicate that the NOEL of fenpyroximate technical when administered for at least 90 days was 20 ppm (corresponding to 1.30 mg/kg/day in males and 1.65 mg/kg/day in females) for rats and the NOAEL in dogs for this time period was < 2 mg/kg/day. A subchronic toxicity study in the dog over one year resulted in a NOAEL of 1.5 mg/kg/day.

Table 23: Summary of repeated oral toxicity

Method/ Guideline	Route of exposure, duration	Species, strain, sex, no/group	Dose levels ppm (mg/kg bw/day)	NO(A)EL ppm (mg/kg bw/day)	LO(A)EL ppm (mg/kg bw/day)	Results, main effects, target organs	Remarks	Reference
OECD 408	Oral, diet, 13 weeks	Rat, SD CD, 10M, 10F	0-20-100-500 M: (0-1.3-6.57-35.22; F: 0-1.65-8.29-38.60)	M: 1.30 mg/kg bw/day, F: 1.65 mg/kg bw/day	M: 6.57 mg/kg bw/day, F: 8.29 mg/kg bw/day	Food intake and bw gain ↓		Aughton, P. (1989), Report-No T-4019
OECD 409	Oral, capsule, 13 weeks	Dog, Beagle, 4M, 4F	(0-2-10-50)	(<2)	(2)	Diarrhoea, emaciation, bw gain ↓, bradycardia, leukocyte count ↓, clin. chemistry		Broadmeadow, A. (1989), Report-No. T-4021
OECD 452	Oral, capsule, 52 weeks	Dog, Beagle, 4M, 4F	(0-0.5-1.5-5-15)	(1.5)	(5)	Diarrhoea, bradycardia, salivation		Broadmeadow, A. (1989), Report-No. T-4022

5.6.2 Repeated dose toxicity: inhalation

A nose only inhalation toxicity study over four weeks in the rat resulted in a NOAEL of 2 mg/m^3.

Table 24: Summary of repeated inhalation toxicity

Method/ Guideline	Route of exposure, duration	Species, strain, sex, no/group	Dose levels mg/m^3	NO(A)EL mg/m^3	LO(A)EL mg/m^3	Results, main effects, target organs	Re-marks	Reference
OECD 412	Inhalation, nose only, 6 hours,	Rat, SD CD, Control	0-2-10-50	2	10	laboured breathing, rales, bw gain ↓, food		Hoffman, G.M. (1991), Report-No. T-

	five days/week, 4 weeks	and highest dose group: 10M, 10F, Other groups: 5M, 5F				consumption ↓, atrophy and metaplasia of nasal passage mucosa, erythrocytes and leukocytes ↑, lung weights ↑		4055

Table 25: Results of particle size determination

Group	Target Concentration (mg/m^3)	Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation	% Particles in Diameter ≤ 1 µm	% of Particles in Diameter ≥ 1 µm
I	0 (control)	0.82	1.5	72	100
II	2	2.8	2.2	9.0	96
III	10	3.2	2.2	6.9	93
IV	50	3.1	2.1	6.4	95

Few sporadic gross lesions were observed during the gross post mortem examinations. Animals killed immediately after a 4-week exposure showed atrophy of the respiratory and olfactory mucosa in the nasal passages of the high dose groups. Squamous metaplasia of the respiratory mucosa was higher in number in mid- and high-dose males and high dose females than in controls. The incidences of these effects found was either lower or not observed among animals which were sacrificed after a 14 days recovery period. Microscopic changes were also seen in the tissues examined. The incidences of these findings were either similar between the control and the treated group, or otherwise occurred sporadically. Because of the low number of effects, the reversibility and no clear evidence of a marked organ dysfunction no classification is required.

Table 26: Incidence of selected mucosal changes in nasal passages (NT_1 – NT_4)

Dose level (mg/m^3)	0		2		10		50	
	Males	Females	Males	Females	Males	Females	Males	Females
NT_1 Respiratory mucosa: squamous metaplasia	1	1	1	0	3	0	2	3
NT_1 Respiratory mucosa: atrophy	0	0	0	0	0	0	1	0
NT_2 Respiratory mucosa: atrophy	0	0	0	0	0	0	1	0
NT_2 Olfactory mucosa: atrophy	0	0	0	0	0	0	0	2
NT_2 Respiratory/olfactory mucosa: desquamation	0	0	0	0	0	0	1	0
NT_3 Respiratory mucosa: atrophy	0	0	0	0	0	0	1	0
NT_3 Olfactory mucosa: atrophy								
NT_4 Olfactory mucosa-. atrophy	0	0	0	0	0	0	2	2
NT_4 Respiratory/olfactory mucosa: desquamation	0	0	0	0	0	0	1	0
Recovery Sacrifice								
NT_1 Respiratory mucosa: squamous metaplasia	2	0					1	1
NT_1 Respiratory mucosa: atrophy	0	0					0	0
NT_2 Respiratory mucosa: atrophy	0	0					0	0
NT_2 Olfactory mucosa: atrophy	0	0					0	0
NT_2 Respiratory/olfactory mucosa: desquamation	0	0					0	0
NT_3 Respiratory mucosa: atrophy	0	0					0	0
NT_3 Olfactory mucosa: atrophy	0	0					0	0
NT_4 Olfactory mucosa-. atrophy	0	0					0	0
NT_4 Respiratory/olfactory mucosa: desquamation	0	0					0	0

5.6.3 Repeated dose toxicity: dermal

A dermal toxicity study over 21 days in rats resulted in a NOAEL of 300 mg/kg bw/day.

Table 27: Summary of repeated dermal toxicity

Method/ Guideline	Route of exposure, duration	Species, strain, sex, no/group	Dose levels mg/kg bw/day	NO(A)EL mg/kg bw/day	LO(A)EL mg/kg bw/day	Results, main effects, target organs	Re-marks	Reference
OECD 410	Dermal, 21 days	Rat, SD, 5M, 5F	0-100-300-1000	300	1000	bw gain and food consumption ↓, liver weight ↑		Wilkinson, G.E. (1992), Report-No.: T-4059

5.6.4 Other relevant information

No data available.

5.6.5 Summary and discussion of repeated dose toxicity:

In the studies on repeated dose toxicity mainly unspecific effects have been observed (decreased body weight gain and food consumption, diarrhoea, emaciation). No substance related mortality was observed. The observed effects are considered to be reversible. There was no clear evidence of a marked organ dysfunction. The effects are unspecific. According to the criteria for non classification concerning specific target organ toxicity (STOT-RE) no classification is required.

No classification for repeated dose toxicity is proposed

Proposed classification:

Directive 67/548/EEC: no classification is proposed

CLP Regulation: no classification is proposed

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

In the repeated dose toxicity studies, mainly nonspecific effects were observed (decreased body weight gain and food consumption, changes in blood chemistry indicated by reduced leukocyte counts, diarrhoea and emaciation). No substance related mortality was observed. The observed effects are considered to be reversible. There was no clear evidence of marked organ dysfunction. According to the criteria for classification concerning specific target organ toxicity (STOT RE) the DS considered that no classification is required.

Comments received during public consultation

One MSCA expressed disagreement and proposed classification as STOT RE 2, H373 "May cause damage to organs through prolonged or repeated exposure" (CLP) and Xn; R48/22 "Harmful: danger of serious damage to health by prolonged exposure if swallowed" (DSD). This was based on the high mortality (50%) observed in females in a 13-week study in dogs at 50 mg/kg bw/day, which occurred within the cut-off value (50 and 100 mg/kg bw/day for DSD and CLP classification criteria, respectively).

Assessment and comparison with the classification criteria

A 13-week and a 52-week oral study with fenpyroximate in dogs were submitted. No spontaneous mortality was observed in either study. In the 13-week study, two female animals of the highest dose group were euthanised (for ethical reasons) during the study after a period of inappetence and body weight loss. There was no specific organ toxicity or evidence of organ dysfunction in the remaining dogs.

Bradycardia and lethargy can be caused by emaciation, diarrhoea, dehydration and starvationand such effects were observed in this study. There was no evidence for neurotoxic effects of fenpyroximate.

In addition, a 13-week oral toxicity study, a 4-week inhalation toxicity study and a 21-day dermal toxicity study with fenpyroximate in rats were submitted. No mortality which could be related to the treatment was observed in these studies.

Two key effects, decreased bodyweight/bodyweight gain and leukocyte counts, which were seen in both dogs and rats, are considered in detail below.

The 13-weeks dog study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg	
	Males	Females
0	12.0 (2.9)	11.6 (3.1)
2	12.4 (3.5)	10.8 (2.3)
10	11.7 (2.6)	9.9 (1.7*)
50	10.8 (1.7*)	8.6 (0.3***)

Dose level (mg/kg bw/d)	0		2		10		50	
	Males	Females	Males	Females	Males	Females	Males	Females
Total leucocyte counts 1000/μL (week 6)	13.2	16.4	14.6	14.1*	14.0	15.0	12.6	10.8***
Neutrophil counts 1000/μl (week 6)	6.0	7.0	7.0	6.8	6.3	6.3	5.4	4.3
Total leucocyte counts 1000/μL (week 12)	15.2	19.6	15.3	15.5	15.3	15.5	15.4	12.8*
Neutrophil counts 1000/μL (week 12)	7.9	11.4	8.2	9.9	8.0	8.7	8.6	6.9
Platelets 1000/μL (week 12)	203	194	198	199	224	218	228	233*
PTTK[#] secs (week 6)	13.9	12.7	13.6	14.2	14.5	13.5	13.3	17.0**
PTTK[#] (week 12)	17.7	14.4	19.3	15.3	15.1	12.9	16.5	17.2

[#]Activated partial thromboplastin time

The 52-week dog study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg			
	Males (day 91)	Males (day 364)	Females (day 91)	Females (day 364)
0	12.4 (3.8)	14.7 (6.1)	11.3 (3.0)	12.8 (4.4)
0.5	12.2 (3.6)	14.0 (5.4)	12.0 (3.5)	13.6 (5.2)
1.5	12.5 (3.6)	14.2 (5.3)	11.5 (3.2)	12.9 (4.6)
5.0	12.9 (3.9)	15.1 (6.1)	11.0 (2.8)	11.8 (3.6)
15.0	10.7 (1.8*)	13.0 (4.0**)	10.5 (2.1)	12.3 (4.0)

There were no treatment-related haematological or ophthalmological findings in this study. A slight but significant lowering of total plasma protein level was observed in males at 15 mg/kg bw/d.

The 13-week rat oral study:

Dose level (ppm)	Bodyweight (bodyweight change) in g	
	Males	Females
0	512 (383)	287 (177)
20	509 (379)	288 (176)
100	459* (327*)	260* (151**)
500	253*** (125***)	177*** (66***)

* P < 0.05; ** P < 0.01; *** P< 0.001

The 4 week-rat inhalation study:

Dose level (mg/m^3)	Bodyweight in g					
	Males			Females		
	Day 1	Week 4	Week 6	Day 1	Week 4	Week 6
0	286.8	394.6	457.6	179.3	238.6	259.6
2	282.0	379.8	-	178.0	230.2	-
10	280.2	379.8	-	175.2	235.6	-
50	282.5	363.6*	443.6	175.7	224.3*	251.2

Dose level (mg/m^3)	0		2		10		50	
	Males	Females	Males	Females	Males	Females	Males	Females

RBC mil/μL (week 4)	8.06	7.73	8.29	7.75	8.51*	7.88	8.67**	7.91
Total leucocyte counts 1000/μl (week 4)	10.2	8.1	10.6	11.2	11.9	11.8	14.6	16.9**
MCV μ^3	55	54	54	54	52*	55	53	55
MCH μg	19.8	20.0	19.6	20.2	18.9*	20.4	19.1	20.2

The 21-day dermal rat study:

Dose level (mg/kg bw/d)	Bodyweight (bodyweight change) in kg							
	Males				Females			
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22
0	275.5	314.3 (38.8)	346.6 (71.1)	336.9 (61.4)	240.4	257.3 (16.8)	270.6 (30.1)	251.0 (10.5)
100	277.4	308.9 (31.5)	344.5 (67.1)	332.5 (55.1)	237.5	249.6 (12.0)	265.1 (27.6)	243.0 (5.5)
300	276.4	301.3 (24.9)	335.9 (59.6)	317.5 (41.2)	241.3	250.6 (9.3)	264.7 (23.4)	245.6 (4.3)
1000	275.3	282.3* (7.0*)	296.4* (21.2*)	270.4* (-4.9*)	240.4	236.7 (-3.8)	237.8* (-2.6*)	212.3* (-28.2*)

Bodyweight and bodyweight changes:

In the 13-week dog study, bodyweight gain was significantly reduced in the females at the highest dose (50 mg/kg bw/d), but there were no significant changes in bodyweight. The same was seen in the 52-week dog study where the males show a significant reduction in bodyweight gain in the highest dose group (15 mg/kg bw/d).

In the 13-week oral rat study a significant reduction in both bodyweight and bodyweight gain were seen in the two highest dose groups, 100 and 500 ppm (~7 and 37 mg/kg bw/d, respectively).

In the 4-week rat inhalation study there was seen a slight but significant reduction in bodyweight in the highest dose group (50 mg/m^3) after 4 weeks of exposure, but this had fully recovered after a 2-week recovery period. In the 21-day rat dermal study, a slight but significant reduction in both bodyweight and bodyweight gain were seen in both females and males in the highest dose group (1000 mg/kg bw/d).

Leucocyte counts:

In the 13-week oral study in dogs there were statistically significant but inconsistent changes in haematology, including total leucocytes counts in females in the highest dose group. The same was seen in the 4-week rat inhalation study in the highest dose group in females.

Comparisons with the classification criteria:

Whether the two dogs in the 13-week oral study would have died if they had not been euthanised cannot be resolved, but these were the only treatment related deaths that were seen among all the animals in the repeated dose toxicity studies.

The changes in the haematology are considered consistent with 3.9.2.8.1.(b) of Annex I to the CLP Regulation, which lists effects that do not justify classification, i.e. "small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance".

The observed effects are considered to be reversible. Overall the proposal of classification STOT RE 2, H373 (CLP) and Xn; R48/22 (DSD) is therefore not supported.

No specific organ toxicity was observed in the carcinogenicity studies. This also indicated to RAC that no classification for specific organ toxicity (STOT RE) was required.

5.7 Mutagenicity

The potential genotoxicity of fenpyroximate was investigated in a series of both in vitro and in vivo studies. All regular end points for genetic damage (point mutations, chromosome damage and DNA-damage and repair) were assessed. Considering all findings, it can be concluded that fenpyroximate is not mutagenic nor genotoxic.

5.7.1 In vitro data

No evidences of genotoxicity have been observed in the in vitro studies.

Table 28: In vitro genotoxicity studies performed with fenpyroximate technical

Study type, Guideline	Test system	Concentrations/ doses	Results	Reference
DNA repair test, not indicated	*Bacillus subtilis* (H17 (rec^+), H45 (rec^-))	With & without S-9: 10, 20, 50, 100, 200, 500 µg/disk	negative	Watanabe, M (1988), Report-No. T-4038
Reverse mutation assay, OECD 471	*Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA 1538) *Escherichia coli* (WP2 uvrA)	With & without S-9: 50, 158, 500, 1580, 5000 µg/plate	negative	May, K. (1989), Report-No. T-4034
Mammalian cytogenetic test, OECD 473	Human lymphocytes	With & without S-9: 1.25, 5, 20 µg/mL	negative	Hodson-Walker, G. (1989), Report-No. T-4036
Mammalian cytogenetic test, OECD 476	Chinese hamster cells (V79)	With & without S-9: 3, 10, 30, 100, 330 µg/mL	negative	Hodson-Walker, G. (1989), Report-No. T-4035
Unscheduled DNA Synthesis, OECD 482	Rat hepatocytes	0.005 – 255 µg/mL	negative	Cifone, M.A. (1989), Report-No. T-4039

5.7.2 In vivo data

There was no evidence of induced chromosomal or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice 24, 48 or 72 hours after oral administration of fenpyroximate, even at a dosage which caused marked clinical symptoms and some evidence of toxicity to the bone marrow.

Table 29: In vivo genotoxicity study performed with fenpyroximate technical

Study type, Guideline	Test system	Concentrations/ doses	Results	Reference
Micronucleus test, OECD 474	Mouse bone marrow erythrocytes	80, 400, 2000 mg/kg bw	negative	Hodson-Walker, G. (1989),

				Report-No. T-4037

5.7.3 Human data

No data available.

5.7.4 Other relevant information

No data available.

5.7.5 Summary and discussion of mutagenicity

No evidences of genotoxicity have been observed. No classification for genotoxicity is required.

Proposed classification:

Directive 67/548/EEC: no classification is proposed

CLP Regulation: no classification is proposed

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

No evidence of genotoxicity has been observed in a battery of OECD TG–compliant tests in bacteria and mammalian cells.

In vivo: There was no evidence of induced chromosomal or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice 24, 48 or 72 hours after oral administration of fenpyroximate, even at a dosage which caused marked clinical symptoms and some evidence of toxicity to the bone marrow.

No classification for genotoxicity is required.

Comments received during public consultation

None

Assessment and comparison with the classification criteria

Since no evidence of mutagenicity was seen in a battery of OECD TG-compliant genotoxicity studies in vitro or in vivo, RAC agreed with the Dossier Submitter that no classification for germ cell mutagenicity was warranted.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

A combined chronic toxicity/carcinogenicity 2-year study was conducted in rats and a carcinogenicity 18-months study was conducted in mice.

Table 30: Summary on long term toxicity and carcinogenicity studies with fenpyroximate

Method/ Guideline	Route of exposure, duration	Species, strain, sex, no/group	Dose levels ppm (mg/kg bw/day)	NO(A)EL ppm (mg/kg bw/day)	LO(A)EL ppm (mg/kg bw/day)	Results, main effects, target organs	Remarks	Reference
OECD 453	Oral/diet 24 months	Rat, SD CD 50M+50F (oncogenicity phase) 30M+30F (toxicity phase)	0-10-25-75-150 (M: 0-0.40-0.97-3.00-6.20, F: 0-0.49-1.21-3.18-8.01)	25 (M: 0.97, F: 1.21)	75 (M: 3.00, F: 3.18)	No evidence of oncogenic potential, bw gain, food and water intake ↓, Clinical chemistry		Aughton, P. (1989); Report No.: T-4023
OECD 451	Oral/diet 18 months	Mouse, Crj:CD-1, 50M+50F	0-25-100-400-800 (M: 0-2.43-9.47-38.02-69.63; F: 0-2.46-10.22-41.46-73.10)	25 (M: 2.4, F: 2.5)	100 (M: 9.5, F: 10.2)	No evidence of oncogenic potential, bw gain, food intake ↓, ovarian atrophy, organ weight changes		Shirasu, Y. (1989); Report No.: T-4026

The NOAEL for chronic toxicity in rats was based on effects on bodyweight gain, food intake and food conversion in dose groups 75 and 150 ppm. There was a temporary decrease of the glucose level in blood in animals receiving 150 ppm. Parameters of urine (low urinary volume, low pH, high specific gravity) were temporary changed in males receiving 150 ppm. Some organ weight differences were observed at 150 ppm. The relative liver weight in females receiving 25 ppm of the oncogenicity phase but not of the toxicity phase was decreased. However, the difference is not considered to be an adverse effect. The NOAEL of the study is considered to be 25 ppm (equivalent to 0.97 and 1.16 mg/kg bw/d for males and females respectively). There was no evidence of any oncogenic potential for fenpyroximate in rats.

In mice, the NOAEL of the study was based on effects on bodyweight and food consumption at 100 ppm. Females in the 800 ppm group showed a slight but significant decrease in segmented form neutrophile in the differential leukocyte count at 52 weeks of treatment. In the 400 ppm and 800 ppm group females showed a significant increase in the overall incidence of ovarian atrophy. Some organ weight differences were observed in the 400 ppm and the 800 ppm dose group. The dietary administration of fenpyroximate to ICR mice at dose levels up to 800 ppm for 18 month revealed no

carcinogenic potential in both sexes. The NOAEL in this study was set at 25 ppm for both sexes, which was equal to 2.4 mg/kg/day in males and 2.5 mg/kg/day in females.

5.8.2 Carcinogenicity: inhalation

No data available.

5.8.3 Carcinogenicity: dermal

No data available.

5.8.4 Carcinogenicity: human data

No data available.

5.8.5 Other relevant information

No data available.

5.8.6 Summary and discussion of carcinogenicity

No evidence of oncogenic potential was observed in rats and mice. No classification of carcinogenicity is required. No specific organ toxicity was observed. Therefore, also no classification of specific organ toxicity (STOT-RE) is required.

Proposed classification:

Directive 67/548/EEC: no classification is proposed

CLP Regulation: no classification is proposed

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No evidence of oncogenic potential was observed in an OECD TG 453–compliant study in rats (doses of 6.2 and 8.0 and mg/kg/d in males and females, respectively) or an OECD TG 451–compliant study in mice (doses of 70 and 73 mg/kg/day, respectively). Therefore no classification for carcinogenicity was proposed by the DS.

Comments received during public consultation

None

Assessment and comparison with the classification criteria

Since no evidence of carcinogenicity was seen in the submitted studies, RAC agreed with the Dossier Submitter that no classification for carcinogenicity was warranted.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

In the two-generation reproduction toxicity study conducted with Sprague-Dawley rats, fenpyroximate technical did not affect reproductive performance. The NOAEL for reproductive performance and fertility was 100 ppm (corresponding to approximately 8 mg/kg bw/day). Based on reductions in bodyweight gain in the adults and in the offspring during lactation the NOAEL for general toxicity toxicity was 30 ppm (equivalent to approximately 2 mg/kg bw/day).

Table 31: Summary of effects on fertility

Method/ Guideline	Route of exposure	Species, strain, sex, no/group	Dose levels ppm	Critical effect	NO(A)EL Parental toxicity ppm	NO(A)EL Reproductive toxicity ppm (mg/kg bw/day)	NO(A)EL offspring toxicity ppm	Reference
OECD 416	Oral/diet	Rat, SD CD, 24M+24F	0-10-30-100	bw gain ↓ during lactation, no effect on fertility	30 (2)	100 (8)	30 (2)	Higgins, C. (1989), Report No.: T-4028

5.9.2 Developmental toxicity

Developmental toxicity studies with fenpyroximate, conducted in Sprague-Dawley rats and in New Zealand White rabbits, showed no evidence of teratogenic effects for fetuses, and no evidence of developmental toxicity in the absence of maternal toxicity.

In the rat developmental toxicity study, the NOAEL for maternal toxicity was 5 mg/kg bw/day based on decreased bodyweights and food consumption at 25 mg/kg bw/day. The NOAEL for developmental toxicity was 5 mg/kg bw/day, based on increased incidence of supernumerary ribs at 25 mg/kg bw/day.

In rabbits a preliminary developmental toxicity study was conducted with only 3 or 4 animals per dose group. Based on depressed bodyweight gain, slightly reduced food and water consumption and reduced faecal output in the high dose group (5 mg/kg bw/day) the NOAEL of maternal toxicity was 2.5 mg/kg bw/day. Increased post implantation loss in two females and smaller foetuses with anomalies of one female were observed in dose group 5.0 mg/kg bw/day. The NOAEL of developmental toxicity was 2.5 mg/kg bw/day.

In the main developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 2.5 mg/kg bw/day based on decreased bodyweight gain and food and water consumption and reduced faecal output at 5.0 mg/kg bw/day.

An increased incidence of slightly folded retinas was observed at 5.0 mg/kg bw/day. The NOAEL of developmental toxicity was 2.5 mg/kg bw/day.

Table 32: Summary of developmental toxicity

Method/ Guideline	Route of exposure	Species, strain, sex, no/group	Dose levels mg/kg bw/day	Critical effect 1) dams 2) fetuses	NO(A)EL Maternal toxicity mg/kg bw/day	NO(A)EL Teratogenicity mg/kg bw/day	NO(A)EL Embryotoxicity mg/kg bw/day	Reference
OECD 414	Oral, gavage, day 6-15 of gestation	Rat, SD CD 22F	0-1-5-25	1) bw, food intake ↓, 2) supernumerary ribs	5	25	5	Higgins, C. (1989) Report No.: T-4030
OECD 414	Oral, gavage, day 6-15 of gestation	Rabbit, NZ white, 4F, goup 1 mg/kg bw/day only 3F	0-1-2.5-5	1) bw gain, food and water intake ↓, Post implantation loss ↑ 2) smaller foetuses with anomalies of one female	2.5	5	2.5	Bailey,G.P. (1989) Report No.: T-4032
OECD 414	Oral, gavage, day 6-19 of gestation	Rabbit, NZ white, 15F	0-1-2.5-5	1) bw gain, food and water intake ↓, 2) slightly folded retinas↑	2.5	5	2.5	King, V.C. (1989), Report No.: T-4033

5.9.3 Human data

No data available.

5.9.4 Other relevant information

No data available.

5.9.5 Summary and discussion of reproductive toxicity

No effects on fertility and no teratogenicity were observed. Developmental effects have only been observed in the highest dose groups together with maternal toxicity and only with small incidence. Therefore, no classification of reproductive toxicity is required.

Proposed classification:

Directive 67/548/EEC: no classification is proposed

CLP Regulation: no classification is proposed

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Fertility:

In a two-generation reproductive toxicity study conducted with Sprague-Dawley rats,

fenpyroximate technical did not affect reproductive performance. The NOAEL for reproductive performance and fertility was 100 ppm (corresponding to approximately 8 mg/kg bw/d). Based on reductions in bodyweight gain in the adults and in the offspring during lactation the NOAEL for general toxicity toxicity was 30 ppm (equivalent to approximately 2 mg/kg bw/d).

Development:
Developmental toxicity studies with fenpyroximate, conducted in Sprague-Dawley rats and in NZW rabbits, showed no evidence of teratogenic effects for foetuses and no evidence of developmental toxicity in the absence of maternal toxicity.

In the rat developmental toxicity study, the NOAEL for maternal toxicity was 5 mg/kg bw/d based on decreased bodyweights and food consumption at 25 mg/kg bw/d. The NOAEL for developmental toxicity was 5 mg/kg bw/d, based on an increased incidence in supernumerary ribs at 25 mg/kg bw/d.

In rabbits a preliminary developmental toxicity study was conducted with only three or four animals per dose group. Based on decreased bodyweight gain, slightly reduced food and water consumption and reduced faecal output in the high dose group (5 mg/kg bw/d) the NOAEL for maternal toxicity was 2.5 mg/kg bw/d. Increased post-implantation loss in two females and smaller foetuses with anomalies from one female were observed in the 5 mg/kg bw/d dose group. The NOAEL for developmental toxicity was 2.5 mg/kg bw/d.

In the main developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 2.5 mg/kg bw/d based on decreased bodyweight gain and food and water consumption and reduced faecal output at 5 mg/kg bw/d.

An increased incidence compared to that of the control group of slightly folded retinas was observed at 5 mg/kg bw/d, which may indicate that a potential for malformations at higher doses has been observed in the highest dose group. The NOAEL for developmental toxicity was 2.5 mg/kg bw/d. The incidence of folded retinas is presented below. Folded retinas are considered a malformation, but the incidence is in the range of historical control data and the findings are only significant in presence of maternal toxicity (bodyweight loss, reduced food and water consumption and reduced faecal output). The observations following sectioning of foetal heads are presented in the table below (percent incidence and number of litters).

Group:	1 (Control)	2 (1 mg/kg bw/d)	3 (2.5 mg/kg bw/d)	4 (5 mg/kg bw/d)	Historical control (mean value)	Historical control (range)
Observation	% incidence (no of litters)					
Unilateral slightly folded retina	8.1 (3)	6.1 (2)	5.9 (2)	25.8 (6) *	9.91	0-33.3
Bilateral slightly folded retina	10.8 (3)	6.1 (2)	14.7 (4)	16.1 (5)	4.82	0-16.7

Comments received during public consultation
None

Assessment and comparison with the classification criteria
No effects on fertility were observed. Where development is concerned, an increased incidence of folded retina compared to that of the control group, which may indicate a potential for malformations at higher doses, was only observed in the highest dose groups together with maternal toxicity. Therefore, RAC considers that no classification for reproductive toxicity is required.

5.10 Other effects

Neurotoxicity / Delayed neurotoxicity studies

In an acute delayed neurotoxicity study in hen administration of fenpyroximate at 5000 mg/kg bw elicited no overt or histopathological change that could be ascribed to a neurotoxic effect of the test material. In contrast the birds treated with tri-ortho-cresyl-phosphate (positive control group) exhibited effects consistent with delayed neurotoxicity.

These results indicated that under the conditions of this study fenpyroximate did not cause delayed neurotoxicity in the hen.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The physico-chemical properties are not relevant for the classification.

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

The acute toxicity of fenpyroximate to fish is summarised in Table 33.

Table 33: Acute toxicity of fenpyroximate to fish

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 203	*Oncorhynchus mykiss*	flow trough	96	LC_{50}	0.00105 m.m.[1)]	Knacker, T. et al. (1992a), Document No.: W-4002
OECD 203	*Lepomis macrochirus*	flow trough	96	LC_{50}	0.002 m.m.[1)]	Dionne, E. (2001), Document No.: W-4055
OECD 203	*Cyprinus carpio*	flow trough	96	LC_{50}	0.0055 m.m.[1)]	Knacker, T. et al. (1992b), Document No.: W-4004

[1)] m.m. … mean measured

The acute study with fish *Oncorhynchus mykiss* can be regarded as the key study for the aquatic toxicity of fenpyroximate and hence for classification and labeling. Therefore the study is presented in more detail below:

Author: Knacker T., Brodesser J., Schallnaß H. (1992)
Report: A study of the acute toxicity to fish (*Oncorhynchus mykiss*) of fenpyroximate under flow-through conditions. Batelle Europe, Frankfurt, Germany.
Report No.: W-4002; unpublished report
Guidelines: OECD Guidelines No. 203 (1984)
US EPA Pesticide Assessment Guideline, Subdivision E, No. 72-1
GLP: yes
Validity: acceptable

Material and methods:

To determine the acute toxicity of fenpyroximate (Batch No. 9005, purity 99.35 %) to rainbow trout, fish were exposed under flow-through conditions over a period of 96 hours. The nominal test substance concentrations were 0.0 (control and solvent control), 0.26, 0.43, 0.71, 1.2, 2.0 and 3.3 µg/L. Acetone was used as solvent for the preparation of stock solutions. Therefore, a solvent control was added to the test system.

After approximately 3, 6, 24, 48, 72 and 96 hours the fish in each test vessel were observed for about 3 to 6 min. Any sublethal effects or changes in the behaviour of the fish which occurred in comparison to the control fish were reported. Probit analysis was used to determine LC_{50}-values and 95 % confidence limits if three or more test substance concentrations caused effects between 0 and 100 %. In case less than three test substance concentrations caused effects between 0 and 100 % or the test was designed that in two consecutive concentration steps 0 and 100 % responses were measured the Arcsin-Transformation was used to determine LC_{50}-values and the binomial test was used to determine the 95 % confidence limits.

Findings:

The nominal concentrations to which the test organisms were exposed were 0.26, 0.43, 0.71, 1.2, 2.0 and 3.3 µg as/L. The analytically determined actual concentrations of the test material in the test solutions at the beginning of the study were found to be within the range of 67 – 75 % with an average of 69.7 % for the active substance fenpyroximate. The analytically determined concentrations of the test material in the test solutions after 96 hours were found to be within the range of 38 – 57 % of the nominal values with an average of 46.8 % for the active substance fenpyroximate. The analytically determined actual concentrations of the test material in the stock solutions were found to be within the range of 87 – 116 % with an average of 97.3 % for the active substance fenpyroximate after 0, 12, 24, 36, 48, 60, 72 and 84 hours of the test period.

Cumulative number of dead fish and percentage of mortality in each test concentration during the test period is summarised in Table 34.

Table 34: Cumulative number of dead fish and percentage of mortality over 96 hours

Time (h)	Cumulative numbers of dead fish (% mortality)							
	Solvent control	Control	0.26 µg/L	0.43 µg/L	0.71 µg/L	1.2 µg/L	2.0 µg/L	3.3 µg/L
0	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
3	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
6	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	4/10 (40)
24	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	3/10 (30)	10/10 (100)
48	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	4/10 (40)	10/10 (100)
72	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	4/10 (40)	10/10 (100)
96	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	5/10 (50)	10/10 (100)

Conclusion:

Based on the actual measured mean concentrations throughout the test (on average 58.3 % of the nominal value), the study resulted in a LC_{50} (96 h) of 0.00105 mg as/L. The 95 % confidence limit for LC_{50} after 96 h was calculated to be 0.00070 - 0.00192 mg as/L. The NOEC was determined to be 0.00041 mg as/L.

Long-term toxicity to fish

The long term toxicity of fenpyroximate to fish is summarised in Table 35.

Table 35: Long-term toxicity of fenpyroximate to fish

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
OECD 204	*Oncorhynchus mykiss*	flow trough	21	NOEC	0.00019 m.m.[1)]	Knacker, T. et al. (1992c), Document No.: W-4013
OECD 210	*Pimephales promelas*	ELS, flow trough	34	NOEC	0.00011 nom growth	Sousa, J. (2001), Document No.: W-4061

[1)] m.m. … mean measured

Author: Sousa J.V. (2001)
Report: Fenpyroximate technical – the toxicity to fathead minnow (*Pimephales promelas*) during an early life-stage exposure
Springborn Laboratories Inc., Wareham, Massachusetts, USA;
Report No: W-4061; WAT 2004-50
Guidelines: FIFRA Guideline No. 72-4
GLP: Yes
Validity: Acceptable

Material and methods:

To determine the toxicity of fenpyroximate (Batch No. 702155, purity 98.6 %; [^{14}C]-fenpyroximate: Batch No. CP-2284, radiochemical purity 99.5 %, specific activity 5.05 mbq/mg) to fathead minnow during an early life-stage, the test substance was added, 24 hours after egg fertilisation, to well water at a range of different concentrations and exposure was continued through 34 days. The test was performed in glass vessels, containing 15 L test solution, under flow-through conditions (turnover rate for one vessel in 24 h: approximately 6.6). Incubation cups, each containing 60 eggs, were distributed to each of the test aquaria when embryos were ≤ 24 hours old. For each concentration two test vessels were set up. The diluter stock solutions used in the definitive test were prepared every 3 to 7 days by combining 1.0 mL of the 431 µg as/L non-radiolabeled fenpyroximate technical stock solution and 1.6 mL of the [^{14}C]-fenpyroximate primary stock in the same flask and bringing to a volume of 25.0 mL with acetone. 0.017 mL/ cycle of this stock solution was delivered in the diluter's mixing chamber and constituted the highest nominal concentration (0.20 µg/L) used in the test. This solution was subsequently diluted to provide the remaining nominal exposure concentrations (0.013, 0.025, 0.050, 0.10 µg/L). The environmental conditions were: Test solution with well water, pH 6.6 - 7.5, temperature 23.1 – 26.4 °C, total hardness as ($CaCO_3$) 34 - 50 mg/L, total alkalinity as ($CaCO_3$) 30-36 mg/L, specific conductance 150 - 210 µmhos/cm, oxygen saturation 67 – 109 %, and a photoperiod of 8 h dark and 16 h light with a light intensity of 80 - 90 footcandles. Acetone was used as solvent for the preparation of stock solutions. Therefore, a solvent control was added to the test system.

Dead and live embryos were counted daily until hatching was complete (exposure day 4). On test day 5 the surviving larvae present in each incubation cup if greater than 40 were thinned to 40 organisms per replicate and placed into their respective exposure aquaria. During the post-hatch exposure period, dead larvae were removed when observed and behaviour and appearance of larvae were observed and recorded daily. At test termination surviving larvae were anaesthetised and

measured and weighed individually. Dissolved oxygen concentration, temperature and pH were measured once daily in each test vessel and the controls throughout the exposure period. Total hardness, total alkalinity and specific conductance were measured weekly in the control, low and high test concentrations. Water samples were taken from one replicate test solution of each treatment level and the control on test days 0, 4, 11, 18, 21, 28 and 34 for total [^{14}C] analysis. The high test concentration was analysed for [^{14}C]-fenpyroximate by HPLC/RAM. The stock was analysed for fenpyroximate by HPLC/UV.

At the termination of the early life-stage exposure, data obtained on organism survival at hatch, larval survival and larval growth (total length, wet weight and dry weight) at test termination were analysed for significant differences between treatment and control organisms. For all statistical analyses conducted either 95 % or 99 % level of certainty was used.

Findings

Analyses were performed on days 0, 4, 11, 18, 21, 28 and 34. Measured concentrations resulted in mean measured concentrations which were 110 % of the nominal levels. The mean measured concentrations of total [^{14}C] defined the treatment levels tested as 0.014, 0.027, 0.056, 0.11 and 0.23 µg/L. Analysis of the quality control samples resulted in measured concentrations which were consistent and ranged from 94.7 to 118 % of the nominal fortified levels (0.0106 to 0.254 µg/L). These results established that the appropriate quality control was maintained during the analysis of the exposure solutions. HPLS/RAM analysis of high concentration resulted in measured concentrations ranging from 53 - 89 % of nominal and indicated that the parent substance accounted for 100 % of the radioactivity present in the solution. Diluter stock analyses (HPLC/UV) ranged from 116 - 125 % of nominal.

Survival of organisms at hatch, larval survival total length, wet weight and dry weight are summarised in Table 36.

- Embryo survival at the different treatment was not statistically different from the survival of the control organisms (90 %).
- Following 30-day post-hatch exposure, larval survival in the different treatment levels ranged from 96 to 100 % and was not statistically different from control organisms (94 %).
- At test termination, there was a significant difference in larval length at the 0.23 µg/L test concentration, compared to the pooled control (31.2 mm).
- Mean wet and dry weight of larvae at the end of the test also showed no statistically significant difference between control and different treatments.

Table 36: Survival of organisms at completion of hatch (test day 5) and survival, total length, wet weight and dry weight of fathead minnow larvae determined at test termination of the early life-stage (30 days post-hatch) exposure to fenpyroximate technical

Mean measured concentration (µg/L)		Survival of organisms at hatch (%)	30 days post-hatch			
			Larval survival (%)	Total length (SD)[a] in mm	Wet weight (SD) [a] in mg	Dry weight (SD) [a] in mg
Control	A	88	95	31.3 (1.4)	290 (40)	71.7 (11)
	B	88	95	31.7 (2.4)	309 (68)	78.2 (19)
	Mean	88	95	31.5 (1.9)	300 (56)	75.0 (15)
Solvent control	A	92	98	31.0 (2.0)	294 (57)	72.3 (14)

Mean measured concentration (µg/L)		Survival of organisms at hatch (%)	30 days post-hatch			
			Larval survival (%)	Total length (SD)[a] in mm	Wet weight (SD) [a] in mg	Dry weight (SD) [a] in mg
	B	90	88	30.9 (2.9)	300 (88)	74.6 (23)
	Mean	91	93	31.0 (2.5)	297 (73)	73.4 (19)
Pooled control		90	94	31.2 (2.2)	298 (65)	74.2 (17)
0.014	A	90	98	31.7 (2.3)	311 (68)	78.5 (18)
	B	90	95	31.7 (1.5)	313 (50)	78.7 (13)
	Mean	90	96	31.7 (1.9)	312 (59)	78.6 (16)
0.027	A	90	100	31.2 (2.0)	298 (58)	72.8 (15)
	B	85	98	31.4 (1.8)	313 (63)	77.0 (16)
	Mean	88	99	31.3 (1.9)	305 (61)	74.9 (15)
0.056	A	92	98	30.9 (2.1)	301 (55)	73.5 (14)
	B	90	100	31.2 (1.7)	300 (51)	72.4 (14)
	Mean	91	99	31.1 (1.9)	301 (53)	72.9 (14)
0.11	A	92	100	30.8 (2.1)	291 (58)	71.7 (15)
	B	87	100	31.3 (1.6)	309 (50)	76.0 (12)
	Mean	89	100	31.0 (1.8)	300 (54)	73.9 (14)
0.23	A	88	100	29.8 (3.6)	280 (95)	68.9 (24)
	B	88	98	31.0 (1.9)	299 (62)	74.4 (17)
	Mean	88	99	30.3 (2.9)[b]	289 (80)	71.6 (21)

a: SD = standard deviation

b: Statistically different from the pooled control based on Williams' Test

Conclusion: Larval length was the most sensitive indicator of the toxicity of fenpyroximate technical to fathead minnow. Therefore the no observed effect concentration (NOEC) for fenpyroximate technical and fathead minnow was determined to be 0.00011 mg/L. The lowest observed effect concentration (LOEC) was 0.00023 mg/L.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of fenpyroximate to invertebrates is summarised in Table 37.

Table 37: Acute toxicity of fenpyroximate to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 202, part I	*Daphnia magna*	static	48	EC_{50}	0.00328 m.m.[1)]	Knacker, T. et al. (1992d), Document No.: W-4021

[1)] m.m. … mean measured

Long-term toxicity to aquatic invertebrates

The long-term toxicity of fenpyroximate to invertebrates is summarized in Table 38.

Table 38: Long-term toxicity of fenpyroximate to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
OECD 202, part II	*Daphnia magna*	Semi-static	21	NOEC reproduction	0.00068 m.m.[1)]	Knacker, T. et al. (1992e), Document No.: W-4034

[1)] m.m. … mean measured

7.1.1.3 Algae and aquatic plants

The toxicity of fenpyroximate to algae and aquatic plants is summarised in Table 39.

Table 39: Long-term toxicity of fenpyroximate to algae and aquatic plants

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 201	*Scenedesmus subspicatus*	static	72	E_rC_{50} E_bC_{50} NOEC	0.00554 nom 0.00344 nom 0.001 nom	Heusel, R. (1992), Document No.: N-4016; A48254

[1)] m.m. … mean measured

7.1.1.4 Sediment organisms

The toxicity of fenpyroximate to sediment dwelling organism is summarised in Table 40.

Table 40: Long-term toxicity of fenpyroximate to sediment dwelling organism

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
BBA Draft guideline 1995	*Chironomus riparius*	static, spiked water	28	NOEC (emergence)	0.01 nom 0.00859 i.m. [1)]	Heusel, R. (1997), Document No.: W-4044; A57599

[1)] i.m. … initial measured concentration

7.2 Terrestrial compartment

Not relevant for this type of dossier.

7.3 Atmospheric compartment

Not relevant for this type of dossier.

7.4 Microbiological activity in sewage treatment systems

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

Fenpyroximate is hydrolytically stable. Fenpyroximate was found to be not readily biodegradable within 29 days in the Modified Sturm test (OECD guideline 301B).

Fenpyroximate has a log Kow of 5.01. In a BCF study, a maximum BCF value of 1601 was obtained based on plateau total radioactive residue in whole fish and average total radioactive residue in water, whereas a kinetic BCF value of 1842 was obtained based on uptake and elimination rate constants. Also the lipid normalized maximum BCF of 870 L/kg ww and BCF kinetic of 1001 L/kg ww (normalized to 5 % lipid content of test fish) are above the trigger of 100/ 500 for not readily biodegradable substances.

The acute toxicity of fenpyroximate to fish and invertebrates is high in the µg/L range with a toxicity of LC_{50} = 1.05 µg/L to fish and of EC_{50} = 3.28 µg/L to aquatic invertebrates.

Fenpyroximate shows also a high toxicity to algae (ErC_{50} = 5.54 µg/L, NOEC = 1 µg/L). The lowest endpoints in long- term studies were observed with fish (35-d early life stage study NOEC = 0.1 µg/L) and aquatic invertebrates (21-d reproduction study NOEC = 0.68 µg/L).

Conclusion of environmental classification according to Directive 67/548/EEC

In aquatic toxicity studies, ErC_{50} values for algae, acute LC_{50} value for fish and EC_{50} value for invertebrates were obtained at fenpyroximate concentrations < 1 mg/L.
Fenpyroximate is not readily biodegradable according to the Modified Sturm test (OECD 301B).
In a BCF study, a kinetic BCF value of 1842 L/kg ww and lipid normalized BCF value of 1001 L/kg ww was obtained based on uptake and elimination rate constants.

Fenpyroximate therefore fulfils the criteria for classification with N; R50/53.

Conclusion of environmental classification according to Regulation EC 1272/2008

In aquatic toxicity studies, ErC_{50} values for algae, acute LC_{50} value for fish and EC_{50} value for invertebrates were obtained at fenpyroximate concentrations < 1 mg/L.
Fenpyroximate is not readily biodegradable according to the Modified Sturm test (OECD 301B).

In a BCF study, a kinetic BCF value of 1842 L/kg ww and lipid normalized BCF value of 1001 L/kg ww was obtained based on uptake and elimination rate constants.

Fenpyroximate therefore fulfils the criteria for classification as aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410.

The acute M-factor for fenpyroximate is 100. This value is based on LC50 value of 0.00105 mg/L obtained for fish *Oncorhynchus mykiss* in a 96-h flow through study. The chronic M-factor is 1000, based on the chronic toxicity data for the fish (35-d early life stage study NOEC = 0.1 µg/L).

RAC evaluation of environmental hazards

Summary of Dossier submitter's proposal

The Dossier Submitter proposed to classify the substance as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) in accordance with CLP, with an M-factor of 100 and 1000, respectively. The corresponding classification according to the DSD is N; R50/53 (with appropriate concentration limits). The proposal is based on acute toxicity to fish (96-h LC_{50} of 0.00105 mg/L) and invertebrates (48-h EC_{50} of 0.00328 mg/L) for the acute CLP and DSD classifications, and a long-term fish toxicity result (34-d NOEC of 0.0001 mg/L for *Pimephales promelas*) for the chronic classification under CLP, together with the fact that the substance is not rapidly (or readily) biodegradable and has a fish bioconcentration factor (BCF) above 500 L/kg.

Comments received during public consultation

One MSCA asked for clarification of the concentration measurements for the fish early life stage (FELS) test with *P. promelas*, as it appeared that they might fall outside of the acceptability criteria. Two MSCAs also queried why a chronic M-factor of 1000 (rather than 100) was used when the long-term fish NOEC was reported as 0.00011 mg/L. The Dossier Submitter replied that three analytical methods had been used in this test, and whilst one of these (HPLC/RAM, used for the highest dose only) suggested a significant loss of concentration (mean 25%) at the highest dose, this finding was not supported by a second method (Liquid Scintillation Counting (LSC), which indicated that concentrations were 110% of nominal for all doses). Given that the methods indicated that concentrations were well maintained in general, the Dossier Submitter preferred to use the nominal concentration of 0.0001 mg/L for classification, and the value of 0.00011 mg/L (a mean measured value using LSC) was referred to in the report in error. In addition, a new fish full life cycle (FFLC) test has become available, with a mean measured NOEC of 0.000063 mg/L (nominal 0.00008 mg/L), supporting the original proposal for the chronic M-factor.

One MSCA agreed with the proposal but highlighted that specific concentration limits (SCLs) should be assigned under the DSD, and a second MSCA pointed out some missing information from the description of physico-chemical properties that are not directly relevant to this opinion.

Additional key elements

A new FFLC test has become available, and the Dossier Submitter provided a short summary as a confidential annex to their response to comments made during the public consultation. A full study report has not been made available, but an EFSA Peer Review report has been finalised (though not yet made publicly available), so it is considered appropriate to include further details for the purposes of this opinion.

Fathead minnows (*P. promelas*) were exposed to radiolabelled fenpyroximate for 264 days under flow-through conditions to a series of five test concentrations, a negative

control (dilution water) and a solvent control (0.0065 mL/L acetone). The method followed FIFRA Guideline 72-5 and OPPTS Number 850.1500. Average recoveries of nominal test concentrations during the course of the study as determined by analytical measurement were 82, 77, 79, 81 and 78 % for the 0.02, 0.04, 0.08, 0.16 and 0.32 µg/L nominal treatments, respectively, with a general trend of lower recoveries at the later phases of the study. Time-weighted (over the entire study period) mean measured concentrations were determined as 0.016, 0.031, 0.063, 0.13 and 0.25 µg/L, respectively. The study began with the exposure of F0 embryos (7.5 hours old), which were reared to adulthood and allowed to reproduce. F1 embryos in the controls and each treatment group were then reared until the juvenile stage. Low reproductive performance was observed in the solvent control and 0.031 µg/L treatment; in both cases some spawning groups had negligible spawning activity. The only treatment-related effect was a reduction in the mean total length of F0 larvae after 30 days exposure, with a LOEC of 0.13 µg/L and NOEC of 0.063 µg/L (based on time-weighted mean measured concentrations). RAC notes that as this effect occurred after 30 days, the mean measured concentration over the 264-day duration of the test might not be a relevant indication of toxicity. The equivalent values expressed on the basis of nominal concentrations are a LOEC of 0.16 µg/L and a NOEC of 0.08 µg/L.

The study results are consistent with the FELS test for the same species reported in the CLH dossier (34-day LOEC of 0.2 µg/L and NOEC of 0.1 µg/L (nominal concentrations), based on the same endpoint of reduced growth).

Assessment and comparison with the classification criteria

Degradability:
Fenpyroximate is hydrolytically stable under standard conditions at pH 4, 7 and 9. The experimental aquatic photodegradation half-life at pH 7 was 1.5 hours according to first order kinetics; the DAR indicates that a major degradant was the Z-isomer of the parent substance (although not relevant for classification, this could be important for the interpretation of the algal toxicity study).

Fenpyroximate failed a test for ready biodegradation (achieving at most 1.5% mineralization in 29 days), although the substance appeared to be inhibitory to microorganisms at the concentration used (17.5 mg/L, which significantly exceeds the measured solubility in pure water of around 0.025 mg/L).

Simulation tests in two aerobic water-sediment systems using the radiolabelled substance indicated rapid elimination from the water phase (with a dissipation half-life of around 3 days) due to a combination of primary degradation and adsorption to sediment (around 40 % of the applied radioactivity was found in the sediment immediately after application). Degradation in sediment was slower, with DT_{50} values of 24 – 28 days. A maximum of 1.9 % mineralization occurred over 105 days, and bound residues were increasingly formed during the study period (up to 28 % after 105 days). No information was provided in the CLH dossier about primary degradant identities, concentrations or properties, although further details are available in the DAR (which mentions three major metabolites, and identifies a data gap for the formation of other possible metabolites). The EFSA opinion indicates that the whole system geometric mean DT_{50} was 28.8 days for the sediment compartment and 1000 days for the water compartment.

The available information indicates that fenpyroximate is neither rapidly degradable (CLP) nor readily biodegradable (DSD) in the aquatic environment.

Bioaccumulation:
Fenpyroximate has a log K_{ow} of 5.01. Measured fish BCF values from one study normalised to a 5% lipid content were 870 L/kg wet weight (steady state) and 1001 L/kg wet weight (kinetic). It is not indicated whether growth correction would have been desirable, but both values exceed the CLP and DSD criteria for bioaccumulation (500 and

100 L/kg, respectively).

Ecotoxicity:

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

Trophic level	Species	Short-term result	Long-term result
Fish	*Oncorhynchus mykiss*	**96-h LC_{50} = 0.00105 mg/L**	21-d NOEC = 0.00019 mg/L
	Pimephales promelas	-	**34-d NOEC = 0.0001 mg/L**
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} = 0.00328 mg/L	21-d NOEC = 0.00068 mg/L
Aquatic algae and plants	*Scenedesmus subspicatus* [*Desmodesmus subspicatus*]	72-h E_rC_{50} = 0.00554 mg/L	72-h NOE_rC = 0.001 mg/L

Note: All values except the long-term *P. promelas* result and algal study were based on mean measured concentrations.

Two freshwater fish species had acute LC_{50} values within a factor of 5 of the most sensitive result, so there appears to be good consistency in acute sensitivity amongst fish species. *O. mykiss* had a similar sensitivity to *P. promelas* in long-term testing (so lack of acute toxicity data for the latter species does not appear to be relevant for the classification proposal). The lowest long-term fish toxicity result is based on nominal concentrations, because analytical measurements showed that test concentrations were well maintained. This result is supported by the results of a FFLC study for the same species reported by the Dossier Submitter in response to the public consultation comments (30-day NOEC of 0.00008 mg/L (nominal) for the same endpoint of reduced growth). Acute sensitivity of both invertebrates and algae appears to be similar to fish. Algae appear to be around an order of magnitude less sensitive than fish or invertebrates for long-term endpoints.

RAC notes that the CLH dossier presents very little information about the invertebrate and algal studies. However, due to the rapid aquatic photolysis, the parent substance may have been significantly degraded over the duration of the algal test. In addition, the substance is used as an acaricide, so the sensitivity of other invertebrate species could be different to *D. magna*. The DAR mentions some additional studies that are not included in the CLH dossier, including a 'microcosm' study of effects on total abundance and community composition of zooplankton in the presence of sediment, which gave an overall 28-day NOEC of 0.001 mg/L.

<u>*Classification according to CLP*</u>

Acute aquatic hazard:
The lowest reliable short-term aquatic toxicity result was a 96-h LC_{50} of 0.00105 mg/L for the fish *Oncorhynchus mykiss*. This is supported by acute toxicity data on two other fish species, an invertebrate and algae. Fenpyroximate is therefore classifiable as:

Aquatic Acute 1 (H400), with an M-factor of 100 ($0.001 < L(E)C_{50} \leq 0.01$ mg/L).

Chronic aquatic hazard:
Fenpyroximate is not considered to be rapidly degradable, and has a fish BCF greater than 500 L/kg. Reliable and relevant long-term aquatic toxicity data are available for all three trophic levels. The lowest value is for *P. promelas*, with a 34-d NOEC of 0.0001 mg/L (supported by a 30-day NOEC of 0.00008 mg/L (nominal) for the same

endpoint of reduced growth from a FFLC study with the same species). These concentrations are below the threshold value of 1 mg/L for non-rapidly degradable substances, leading to classification as:

Aquatic Chronic 1 (H410) and an M-factor of 1000 (0.00001 < NOEC ≤ 0.0001 mg/L).

Classification according to DSD

The lack of ready biodegradation, fish BCF above 100 L/kg and 96-h LC_{50} of 0.00105 mg/L for the fish *Oncorhynchus mykiss* (with a similar value for invertebrates and algae) mean that fenpyroximate fulfils the criteria for classification with N; R50-53. The following specific concentration limits are applicable:

Concentration of fenpyroximate in the mixture, C (w/w)	**Classification of the mixture**
C ≥ 0.25%	N; R50-53
0.025% ≤ C < 0.25%	N; R51-53
0.0025% ≤ C < 0.025%	R52-53

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

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Fenpyroximate is an active substance in the meaning of Directive 91/414/EEC. Following article 36(2) or Regulation (EC) 1272/2008 such substances should normally be subject to harmonised classification.

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