Committee for Risk Assessment

RAC

Annex 1

Background document

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

fenamiphos

ECHA/RAC/CLH-O-0000001374-78-03/A1

EC number: 244-848-1
CAS number: 22224-92-6

Adopted

15 September 2011

CONTENTS

TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name:	**fenamiphos**
EC Number:	**244-848-1**
CAS number:	**22224-92-6**
Registration number (s):	CIPAC 692
Purity:	Minimum content of pure as (excluding inactive isomers): 920 g/kg
Impurities:	Confidential information

Fenamiphos was included in Annex VI to the CLP regulation in 2004 (29. ATP; Commission Directive 2004/73/EC of 29 April). A discussion regarding a change of the classification took place at the TC C&L in November 2006 (Summary record ECB/20/07). The TC C&L discussion was only related to acute toxicity and eye irritation. TC C&L agreed to additionally classify fenamiphos as to acute toxicity and eye irritation. However, the TC C&L conclusion was not implemented in Annex I of Directive EC 67/548 and consequently not included in Annex VI of Regulation EC 1272/2008. Therefore, a proposal for changing the current harmonised classification and labelling was prepared. This proposal focusses on the changes in the classification of fenamiphos as discussed by the TC C&L in November 2006. However, information on all other hazard classes is included as additional information.

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
	fenamiphos	244-848-1	22224-92-6	Acute Tox. 2 Acute Tox. 2 Acute Tox. 2 Eye irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H300 H310 H330 H319 H400 H410	GHS06 GHS07 Dgr	H300 H310 H330 H319 H410		Acute M=100 Chronic M=100	

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	fenamiphos	244-848-1	22224-92-6	T+; R26/28 T; R24 Xi; R36 N; R50-53	T+, Xi, N R: 24-26/28-36-50/53 S: ½-23-26-28-35-36/37-45-60-61	C≥0.25% N;R50-53 0.025%≤C <0.25% N;R51-53 0.0025%≤ C<0.025% R52-53	

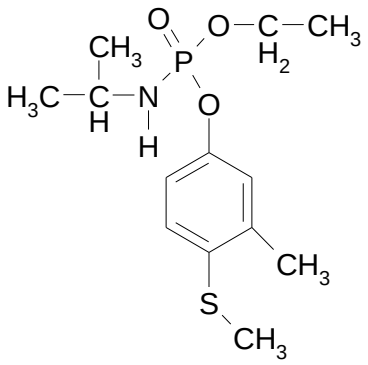
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	ethyl 3-methyl-4-(methylthio)phenyl (1-methylethyl)phosphoramidate
EC Name:	fenamiphos
ISO name:	fenamiphos
CAS Number:	22224-92-6
CIPAC Number:	692
EC Number:	244-848-1
IUPAC Name:	ethyl 3-methyl-4-(methylsulfanyl)phenyl isopropylamidophosphate
applicant's code Number:	SRA 3886

1.2 Composition of the substance

Chemical Name:	ethyl 3-methyl-4-(methylthio)phenyl (1-methylethyl)phosphoramidate
EC Number:	244-848-1
CAS Number:	22224-92-6
IUPAC Name:	ethyl 4-methylthio-m-tolyl isopropylphosphoramidate
Molecular Formula:	$C_{13}H_{22}NO_3PS$
Structural Formula:	
Molecular Weight:	303.4
Typical concentration (% w/w):	-
Concentration range (% w/w):	Minimum content of pure as (excluding inactive isomers): 920 g/kg
Impurities	The identity of the impurities is confidential. The impurities are considered not relevant for classification and labelling.

1.3 Physico-chemical properties

Table 1.3.1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	Colourless crystalline powder with weak characteristic odour	
VII, 7.2	Melting/freezing point	3.2	43-49°C	
VII, 7.3	Boiling point	3.3	Not available (thermal decomposition)	
VII, 7.4	Relative density	3.4 density	1.191 g/cm^3 at 23°C	
VII, 7.5	Vapour pressure	3.6	1.2E-4 Pa at 20°C 2.3E-4 Pa at 25°C	
VII, 7.6	Surface tension	3.10	47.2 mN/m at 20°C	
VII, 7.7	Water solubility	3.8	368 mg/L at 20°C in MilliQ 356 mg/L at 20°C in buffer of pH 4 345 mg/L at 20°C in buffer of pH 7 344 mg/L at 20°C in buffer of pH 9	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	3.30 at 20°C	
VII, 7.9	Flash point	3.11	No data	
VII, 7.10	Flammability	3.13	Not highly flammable	
VII, 7.11	Explosive properties	3.14	Not explosive	
VII, 7.12	Self-ignition temperature		No data	
VII, 7.13	Oxidising properties	3.15	No oxidizing properties	
VII, 7.14	Granulometry	3.5	No data	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No data	
XI, 7.16	Dissociation constant	3.21	No basic or acidic properties	
XI, 7.17	Viscosity	3.22	No data	
	Auto flammability	3.12	Not undergoing spontaneous combustion	
	Reactivity towards container material	3.18	No data	
	Thermal stability	3.19	No data	
	Hydrolitic stability (DT_{50})		Half life at 25°C: at pH 5: 245 days at pH 7: 301 days at pH 9: 235 days	
	Temperature of decomposition		200°C	
	Henry's law constant		9.1E-5 Pa m^3/mol	
	Solubility in organic solvents		n-hexane	27 g/L at 20°C
			xylene	> 250 g/L at 20°C
			dichloromethane	> 250 g/L at 20°C
			2-propanol	> 250 g/L at 20°C

			polyethyleneglycol	> 250 g/L at 20°C
			1-octanol	> 250 g/L at 20°C
			acetone	> 250 g/L at 20°C
			ethylacetate	> 250 g/L at 20°C
			acetonitrile	> 250 g/L at 20°C
			dimethylsulfoxide	> 250 g/L at 20°C

The above data are obtained from the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of the active substance fenamiphos in Annex I of Council Directive 91/414/EEC (DAR November 2007 + final addendum December 2005, RMS The Netherlands). Fenamiphos is included in Annex I of Council Directive 91/414/EEC.

2 MANUFACTURE AND USES

Not relevant for this type of report.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI of Regulation EC 1272/2008

According to table 3.1 of Annex VI (index no 015-123-00-5), fenamiphos is classified as

Hazard class: Acute Tox 2 (minimum classification)
Acute Tox 3 (minimum classification)
Aquatic Acute 1
Aquatic Chronic 1

Hazard Statement: H300
H311
H400
H410

M factor: 100

According to table 3.2 of Annex VI, fenamiphos is classified as

Classification: T+; R28
T; R24
N; R50-53

Risk phrases: R24: Toxic in contact with skin
R28: Very toxic if swallowed
R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Safety phrases:(S1/2): Keep locked up and out of the reach of children
S23: Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer)

S28: After contact with skin, wash immediately with plenty of … (to be specified by the manufacturer)
S36/37: Wear suitable protective clothing and gloves
S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S60: This material and its container must be disposed of as hazardous waste
S61: Avoid release to the environment. Refer to special instructions/Safety data sheets

Specific Concentration limits:

Concentration	Classification
C≥0.25%	N; R50-53
0.025%≤C<0.25%	N; R51-53
0.0025%≤C<0.025%	R52-53

3.2 Self classification(s)

Not relevant for this dossier

4 ENVIRONMENTAL FATE PROPERTIES

The current proposal is a revision of the current entry in Annex VI to the CLP regulation (29 ATP, 2004). The environmental fate properties assessment for fenamiphos is based on the Draft Assessment Report, the Addendum to the Draft Assessment Report and Proposed Decision of The Netherlands prepared in the context of the possible inclusion of the active substance fenamiphos in Annex I of Council Directive 91/414/EEC (DAR November 2003 + final addendum December 2005, RMS The Netherlands). The current assessment did not result in changes in the current classification with regard to the environment. Nevertheless, the assessment is included to provide an overall picture of fenamiphos. Therefore, the information provided below should be regarded as additional.

4.1 Degradation (additional information)

4.1.1 Stability

Hydrolysis

Two hydrolysis studies were performed. In the first study, the hydrolysis of fenamiphos was carried out at 25˚ C at pH 5, 7, and 9. The half life times are summarized in Table 4.1.

The main degradation products were fenamiphos-sulfoxide and fenamiphos-phenol. Fenamiphos-sulfoxide is considered to be a major metabolite detected at all pH levels, fenamiphos-phenol was only found at pH 9. Another metabolite fenamiphos-sulfone was also detected only as a minor metabolite at pH 9.

Table 4.1: DT_{50}s for hydrolysis of Fenamiphos at pH 5, 7 and 9.

Substance	Water type	T [°C]	pH	Duration [d]	Transformation at end [%]	DT_{50} Hydrolysis* [d]	r^2 values
fenamiphos-phenyl-1-^{14}C/^{13}C/^{12}C	sodium acetate	25	5	31	9.7	252	0.76
fenamiphos-phenyl-1-^{14}C/^{13}C/^{12}C	phosphate	25	7	31	7.7	304	0.85
fenamiphos-phenyl-1-^{14}C/^{13}C/^{12}C	borate	25	9	31	9.4	236	0.94

* Recalculated DT_{50} values (20 ˚C)

In the second study, the hydrolysis of fenamiphos, fenamiphos-sulfoxide and fenamiphos-sulfone was studied at pH 4 at a treatment rate of 0.5 mg/L. The half life times are given in Table 4.2. In the fenamiphos treatment fenamiphos-sulfoxide was found as a major metabolite. Under acidic conditions the hydrolysis of fenamiphos is moderately faster than at neutral pH.

Table 4.2: DT_{50}s for hydrolysis of fenamiphos and fenamiphos-based products at pH 4.

Substance	Water type	T [°C]	pH	Duration [d]	Transformation at end [%]	DT_{50} hydrolysis [d]	r^2 values
fenamiphos	sodium acetate	24.5	4	30	11.1	205	0.74
fenamiphos-sulfoxide	sodium acetate	24.5	4	30	13.1	151	0.69
fenamiphos-sulfone	sodium acetate	24.5	4	30	14.7	134	0.76

Conclusion: Fenamiphos is not susceptible to hydrolysis. At relevant environmental pHs (4-7) the DT_{50}s range from 205 -304 days at 25˚C. The most significant degradation product was fenamiphos-sulfoxide. It is concluded that abiotic transformation by hydrolysis is not significant.

Photolysis in water

The photodegradation of fenamiphos in water was investigated in two studies which results are summarized in Table 4.3.

In the first study, the DT_{50} of fenamiphos was estimated to be 3.6 hours under artificial light at 20 °C. Two major metabolites were detected after 24 hours: fenamiphos-sulfoxide and fenamiphos-phenol-sulfonic acid. Fenamiphos-sulfonic acid was detected as a minor metabolite.

In the second study the rate and quantum yield of direct photo-transformation of fenamiphos in water was determined according to the ECETOC method. The quantum yield was 0.232 with a DT_{50} ranging from 2.6 days (30^{th} degree lat. in summer) to >1 year (50^{th} degree lat. in winter).

Photodegradation studies were also performed for the metabolites fenamiphos-sulfoxide and fenamiphos-phenol sulfonic acid, according to the EPA Pesticide Assessment Guideline (Section 161-2) and with the requirements of the EC- and SETAC guidelines. The DT_{50} of fenamiphos-sulfoxide and fenamiphos-phenol-sulfonic acid was estimated as 48 and 768 days, respectively.

Table 4.3 Photolysis of fenamiphos in water

Substance	Water type	T [°C]	pH	Light Source	Wavelength [nm]	Duration [h]	Transformation at end [%]	DT_{50} photo [h]
Fenamiphos-ring-1-^{14}C	Water	27-28	7	artificial light	>300	48	90.0	3.6
Fenamiphos	Water	25		artificial	259-490	30	62%	2.6 -> 1 year

Conclusion: Fenamiphos in aqueous solution degrades rapidly in the presence of light. Fenamiphos sulfoxide is a main transformation product of the photolysis of water. Degradation products of fenamiphos are not susceptible to photodegradation.

Photolysis in soil

Soil photolysis was studied in a sandy loam soil under artificial light (>300 nm) for 48 hours. The temperature corrected DT_{50} value derived from this study is 2.3 hours for the irradiated soil. The major metabolites were fenamiphos-sulfoxide, fenamiphos-sulfone, fenamiphos-phenol sulfoxide. Fenamiphos sulfonic acid was tentatively identified as minor product.

Conclusion: The photolysis study shows a rapid degradation in soil.

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

No data available

4.1.2.2 Screening tests

Ready Biodegradability

No information supplied.

4.1.2.3 Simulation tests

Biodegradation in water/sediment systems

Aerobic water/sediment system

Degradation of (phenyl-1-^{14}C) fenamiphos was tested in water-sediment systems according to EC/SETAC guidelines: one with a sandy sediment and water from a small reclaimed gravel pit (Angler Weiher), the other is a loamy sediment from an artificially dammed pond in the course of the "Hönniger Creek" with strong water currents. The $DT_{50,\ water}$ of fenamiphos was 3.6 in sand and 7.9 in loam. The $DT_{50,\ system}$ was 9.3 and 111, respectively (average 60.2 days). This is indicative that fenamiphos disappears rapidly from the water phase. The $DT_{50,\ system}$ values was 9.3 and 111, respectively (average 60.2 days). Mineralisation reached a maximum of 14.3% in sand and 2.4% in loam (at the end of the study). Bound residue reached a maximum of 48.8% on day 58 in the sandy sediment system and 17.4% in the loamy sediment system.

Major metabolites in water were fenamiphos-sulfoxide with a maximum of 13.7% on day 100 in the loam system, and fenamiphos-sulfoxide phenol with a maximum of 10.8% on day 20 in the sand system. Major metabolite in sediment in water was fenamiphos-sulfoxide with a maximum of 16.8% on day 100. DT_{50} values for the metabolites were not determined.

The results of this study points to the primary degradation of fenamiphos and not ultimate mineralisation. Fenamiphos dissipates rapidly from water into sediment the sediments phase where is undergoes further degradation. Degradation products were observed in both water and sediment.

Table 4.3: DT_{50}s values for fenamiphos in water/sediment systems.

Substance	Soil type	Sediment [%]	T [°C]	pH	OM [%]	Duration [d]	DT_{50} water [d]	DT_{50} sediment [d]	DT_{50} system [d]
(phenyl-1-^{14}C) fenamiphos	sand	30	20	6.9-8.2	1.79	100	3.6		9.3
(phenyl-1-^{14}C) fenamiphos	loam	18	20	6.4-8.2	7.60	100	7.9		111

Biodegradation in soil

Aerobic degradation

The aerobic biodegradation of ^{14}C-fenamiphos was tested in two studies. In the first study, (study a) the rate of degradation was measured in 16 soils at a dose rate of 7.7 mg/kg. In the second study (study b) the aerobic degradation rate of fenamiphos was determined in four soils at dose rates of 0.67 mg/kg. Incubations took place at 16, 20, or 22°C. The DT_{50} values obtained from both studies are summarized in Table 4.4.

In both studies, fenamiphos-sulfoxide, fenamiphos-sulfone, fenamiphos-sulfoxide-phenol and fenamiphos-sulfone-phenol were detected in amounts >10%.

In study a, mineralisation measured as production of CO_2 after 90 days, ranged from 1.1% to 39% of AR at 22°C, and from 0.4% to 23% of AR at 16°C. Non-extractable residues reached values of 19% to 69% of AR at 22°C and 9.1% to 46% of AR at 16°C.

In study b, mineralisation, measured as production of CO_2 after 120 days, ranged from 23% to 52%. Non-extractable residues reached values of 16% and 36% of AR. Fenamiphos was oxidised by a first step to the main degradation product fenamiphos-sulfoxide. This metabolite is successively further degraded to fenamiphos-sulfoxide-phenol and fenamiphos-sulfone. Subsequent degradation via fenamiphos-sulfone-phenol and fenamiphos-sulfone anisole leads to the formation of CO_2.

Table 4.4: DT_{50} values from laboratory studies for fenamiphos and metabolites.

Substance	Study a (dose 7.7 mg/kg) DT50 [days]	Study b (dose 0.67 mg/kg) DT50 [days]	Overall average	range
Fenamiphos	-	0.4, 0.6, 1.0, 1.4 (average 0.85)	0.85	0.4-1.4
fenamiphos-sulfoxide	25, 27, 31, 42, 55, 71, 77, 89, 97, 109 (average 57)	30, 36, 48 (average 38)	53	25-109
fenamiphos-sulfone	6, 13, 15, 68, 46, 53, 60 (average 37)	26, 51 (average 39)	38	6-60
fenamiphos-sulfoxide-phenol	14	-	14	
fenamiphos-sulfone-phenol	10, 22 (average 16)	48, 79 (average 64)	40	10-79

4.1.3 Summary and discussion of persistence

Degradation in water

Fenamiphos is not susceptible to hydrolysis. However, in the presence of artificial sunlight fenamiphos degrades rapidly with fenamiphos sulfoxide as the main transformation product.

The two aerobic water/sediment systems the $DT_{50,water}$ of fenamiphos was 3.6 days and 7.9 days. This is indicative that fenamiphos disappears rapidly from the water phase. The $DT_{50,system}$ resulted in a range of 9.3 days and 111 days (average of 60.2 days). Mineralization reached a maximum of 14.3% and 2.4%. At 58 days mineralisation is less than 28% and less than 24% after 100 days. This indicates that full mineralisation is not reached. The major metabolites were fenamiphos-sulfoxide and fenamiphos-sulfoxide-phenol. DT_{50} values for the metabolites were not determined.

Biodegradation in soil

The overall average DT_{50} of fenamiphos in aerobic soil is 0.85 days, which indicates that the substance biodegrades rapidly in soil. Relatively high DT_{50s} are found for fenamiphos-sulfoxide and

not for the other metabolites. Based on this it is considered that the metabolites are not rapidly biodegradable in soil.

Based on the findings from the water/sediment simulation test and soil fenamiphos appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the levels of mineralisation in the simulation study, fenamiphos is considered not readily biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labelling.

4.2 Environmental distribution (additional information)

4.2.1 Adsorption/desorption

Adsorption of fenamiphos was determined in two studies for a series of soil types. Fenamiphos can be classified as moderately mobile in soil, according to the Koc values. The Koc values of fenamiphos varied between 76.2l L/kg and 1432 L/kg.

4.2.2 Volatilisation

Based on the vapour pressure of 1.2 x 10^{-4} Pa (20°C), fenamiphos is not considered as a volatile substance.

4.2.3 Distribution modelling

4.3 Bioaccumulation (additional information)

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Based on experimentally determined partition coefficient (octanol water) fenamiphos has a logKow value of 3.30 at 20°C.

Classification according to Directive 67/548/EEC

The guidance value for bioaccumulation is logKow ≥ 3.0. In view of this, fenamiphos has a bioaccumulation potential, since it exceeds the value of 3.0.

Classification according to Regulation EC 1272/2008

The guidance value for bioaccumulation is logKow > 4. In view of this, fenamiphos does not fulfil the criteria for bioaccumulation. The bioaccumulation potential is low since the value does not exceed a value of 4.

4.3.1.2 Measured bioaccumulation data

A fish bioaccumulation study for fenamiphos is available in *Lepomis machrochiurus*. The following BCF values were calculated: $BCF_{organism}$ 110 L/kg and T ½ for clearance is 0.22 days.

Bluefish sunfish were exposed to ^{14}C-fenamiphos in a flow-through system at a mean concentration of 0.95 µg/L for a 28-d exposure period followed by a 14d depuration period to study the

elimination. Daily concentrations factors for the uptake phase of this study ranged from 7.6 to 26x for fillet, 14 to 97x for whole fish and 23 to 250x for viscera. An analysis of depuration rates by day 14 of the elimination period showed >95, >98 and >99% depuration in fillet, whole fish and viscera, respectively. Characterisation of ^{14}C-residue was not done and there is no information on metabolites is available.

4.3.2 Terrestrial bioaccumulation

4.3.3 Summary and discussion of bioaccumulation

Fenamiphos has a log Kow of 3.30. However, a BCF value of 110 in fish was obtained in a bioaccumulation study. This data suggest that fenamiphos has a low potential for bioconcentration and bioaccumulation. The value of 100 fulfils the criterion for bioaccumulating potential conform Directive 67/548/EEC, since it exceeds the value of 100. However it does not exceed fulfil the criterion for Regulation EC 1272/2008, since it does not exceed the value of 500.

4.4 Secondary poisoning

Assessment of the potential for secondary poisoning

5 HUMAN HEALTH HAZARD ASSESSMENT

The current proposal is a revision of the current entry in Annex VI to the CLP regulation (29 ATP, 2004). The summaries included in this proposal are partly copied from the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of the active substance fenamiphos in Annex I of Council Directive 91/414/EEC (DAR November 2003 + final addendum December 2005, RMS The Netherlands). Some details of the summaries were not included when considered not important for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR and its addenda. No references to individual mammalian studies are included to protect the privacy and integrity of the individual (Article 14 of Directive 91/414). These references are available in the DAR and its addenda. Fenamiphos was also discussed in the TC-C&L in November 2006 (Summary record ECB/20/07). The conclusions of this discussion can be found in Annex 1.
To provide an overall view of the substance, we have also included information related to the hazard classes that do not need to be changed. Only the information related to acute toxicity and eye irritation results in a classification proposal that differs from the current classification. Information regarding the other toxicological endpoints should be regarded as additional.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Absorption

Absorption of radioactivity after oral administration of radiolabelled fenamiphos (0.3-3 mg/kg bw) in rats was nearly complete and very rapid.

Distribution

In rats given 3 mg radiolabelled fenamiphos/kg bw by gavage, autoradiography showed that within 0.5 h, radiolabel was distributed throughout the body, except for compact bone structures, the spinal marrow, and the brain, indicating minimal ability to cross the blood-brain barrier. The highest concentrations were seen in the contents of the stomach, some segments of the small intestine, the bladder as well as the kidney, indicating a high renal excretion. High concentrations were also found in the liver. Blood, lungs, salivary glands, parotids, hypophysis, and tissues with large amounts of connective tissue also had relatively high concentrations of radiolabel. Lower concentrations were found in the lymph, adrenal gland, and spleen. Low concentrations were observed in the muscles, fatty tissues, pancreas, and thymus. At 48 h, most of the levels in tissues and plasma were below the limit of quantification in rats given 0.4 mg/kg bw.

Metabolism

In rats, identified metabolites covered more than 93 % of the total radioactivity. The main groups of metabolites, comprising 80 % to 96 % of the recovered radioactivity, were the fenamiphos-phenols (methylthiometacresol-derivatives (MTMC), M11, M12, M13) in different stages of oxidation at the sulphur atom and their respective sulphuric acid conjugates. Metabolic pathway in rats was oxidation of the thioether to the sulfoxide and sulfone, de-arylation to yield the methyl thioether phenol (or its sulfoxide and sulphide), and potential dealkylation of the ethyl, isopropyl, or isopropylamino moiety of the phosphate ester.

In urine and faeces, metabolites of toxicological relevance were detected in amounts of 0.3 to 1.3 % (fenamiphos-sulfoxide, M01) and of 0.4 to 0.7 % (desisopropylfenamiphos-sulfoxide, M07). Parent compound or other oxidised and/or desisopropylated compounds were not detected above the limit of detection.

Excretion

Excretion of radioactivity after oral administration of radiolabelled fenamiphos was nearly complete and very rapid. After 48 h, > 96% of the recovered radiolabel had been excreted by rats orally treated with 0.3 or 3 mg/kg bw, with 40-80% of the radiolabel being excreted renally within 4 h of treatment. Faecal elimination accounted for only 1.5-3.7% of the recovered radiolabel. The small amounts found in the faeces after intravenous administration indicate that a small amount of biliary excretion occurs. Only a very low fraction (<<0.1% of the total recovered radioactivity) was excreted via pulmonary ventilation (measured after a single oral dose of 3 mg/kg bw in males only). From 2 hours after administration of 3 mg radiolabeled fenamiphos to rats, radiolabel was also found in the region of the hair follicles, suggesting slight elimination via this route.

In the first 4-8 h after administration, urinary excretion appeared to be slightly faster in males than females after oral dosing, and faster after 3 than after 0.3 mg/kg bw in females only. Prior treatment with unlabelled fenamiphos resulted in a slightly faster urinary excretion in both males and females. There were no indications of accumulation of the parent compound or its metabolites.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Two acute oral studies were available.
In the first study, performed according to OECD 401, doses of 1, 4, 5, 5.6, 6.3, 10 and 100 mg/kg bw in males and 1, 5, 6.3 and 8 mg/kg bw in females were used. Clinical signs were observed at doses ≥ 1 and 4 mg/kg bw in females and males, respectively, and included palmospasms, laboured breathing, apathy, diarrhoea, clonic cramps, piloerection, isolated cases of spastic gait and bloody eyes. These symptoms, which were mainly moderate in intensity, subsided within a few hours. Apathy persisted up to the third day. Mortality occurred at doses ≥ 5 and 5.6 mg/kg bw in females and males, respectively. Pathology revealed dark, patchy, distended lungs with fluid and grey stipples; dark livers; patchy, pale or dark spleens; patchy kidneys; reddened renal pelvis; reddened glandular stomach, covered with ulcer like foci; and slightly reddened small intestines, well supplied with blood.
The second study was a limit study with a dose of 25 mg/kg bw, performed according to OECD 423. All animals died within 10 minutes. Palmospasm, dyspnea, and swollen buccal regions were observed. Additionally, in one animal each, chromodacryorrhea and increased salivation occurred. The liver had dark-red discoloration and the lungs were slightly collapsed.

Table 5.1 Acute toxicity, LD_{50} values

Test substance	LD_{50}	Species	Vehicle
SDF 1291	6.0 mg/kg bw in males 6.1 mg/kg bw in females	Rat	PEG E 400
SRA 3886	< 25 mg/kg bw in females	Rat	Water + Cremophor EL 2% v/v

In addition, in an acute oral neurotoxicity screening study, rats were given fenamiphos by gavage (0.37, 1.52, or 2.31 mg/kg bw). Four males and one female of the top dose group died. Erythrocyte ChE activity was significantly lower (>20%) in males at all dose levels and in females at ≥ 1.52 mg/kg bw. No effects on brain ChE were found. Forelimb strength was significantly reduced in males and females of the top dose group, as well as hindlimb strength in males.

In a delayed neurotoxicity following acute oral administration fenamiphos was administered twice by intubation to 30 Leghorn hens at 25 mg/kg bw at a 21-day interval. The hens treated with

fenamiphos received atropine intramuscularly at 100 mg/kg bw before treatment and subcutaneously at 30-50 mg/kg bw 7, 24, or 30 or 48 h after treatment. Fourteen animals died during the acute phase of intoxication after the 1st or 2nd treatment. Body weight was decreased during the week following the 1st treatment. All animals showed staggering gait, ruffled feathers, reduced activity, flaccid, drooping wings, spasmodic state, difficult breathing in some cases, sternal and laternal recumbency and salivation one day after the 1st and 2nd treatment. The birds showed no impairment of motor co-ordination indicative of delayed neurotoxicity. Histological examination showed no changes indicative of delayed neuropathy.

In a neurotoxic esterase activity study following acute oral administration in hens (25 mg/kg bw, under atropine protection), neurotoxic esterase activity in central and peripheral nerve tissue was not inhibited.

5.2.2 Acute toxicity: inhalation

Two acute inhalation studies were available.
In the first study (not according to OECD) fenamiphos was dissolved and the solution (57, 62, 100 and 155 mg/m^3 for males, 57, 62, 100, 155 and 191 mg/m^3 for females) was aerosolised into dynamic flow inhalation chambers. Rats were exposed for a period of 4 hours (nose-only). The animals were kept under observation for 14 days. Clinical signs were observed in all animals and included muscle twitching, cramps (at lethal concentrations), inactivity, stiff gait, dirty hair coat, drowsiness, breathing disorders. Mortality occurred at doses ≥ 62 and 100 mg/m^3 in females and males, respectively. Since no data on particle size and distribution were available, the study is acceptable as supportive study only.
In the second study (in accordance with OECD 403) actual concentrations of 63.6, 64.7, 92.1, 243.1 and 510. 8 mg/m^3 were applied to rats (nose only). The MMAD of the aerosol particles in the atmosphere ranged from 1.31-1.44 μm at different concentrations (geometric standard deviation ranged from 2.12-2.41). Clinical signs were observed in all dosed animals and included piloerection, hair-coat ungroomed, bradypnea, laboured breathing pattern, dyspnea, irregular breathing pattern, reduced motility, limp, tremor, fasciculations, giddiness, high-legged gait, prostration, exophthalmos, miosis, corneal opacity, chromodacryorrhea, red encrustations of the nostrils, salivation, pallor, emaciation and periorbicular red stains. Mortality occurred at doses ≥ 64.7 and 63.6 mg/m^3 in females and males, respectively. Pathology revealed less collapsed lungs with dark-red discolorations, bloated intestines, pale parenchymatous organs and corneal opacity.

Table 5.2 Acute toxicity, LC_{50} values

Test substance	LC_{50}	Species	Vehicle
SRA 3886	0.1 mg/L/4 h in males and females*	Rat	1:1 ethanol:lutrol
SRA 3886	0.065 mg/L/ 4h in males 0.079 mg/L/ 4h in females	Rat	1:1 PEG 400: ethanol

* only acceptable as supportive data, as adequate skin contact can not be ensured since the test substance was only liquefied and then applied (i.e. at room temperature the substance will be solid again).

5.2.3 Acute toxicity: dermal

One acceptable dermal study was available, with applied doses of 25, 35, 40, 45, 50, 65, 75, 100, 125, 1000 mg/kg bw in males and 25, 50, 75, 100, 125, 1000 mg/kg bw in females. Fenamiphos was dissolved, emulsified, and suspended in Lutrol (warm) and applied under occlusive conditions to non-fasted male and female rats for an exposure duration of 24 hours. The treatment volume was 0.05 – 2 mL/kg bw, but no information on the application surface is provided. The recovery period

was 14 days. All treated animals showed symptoms of toxicity (not specified). Mortality was observed at doses ≥ 75 and 45 mg/kg bw in females and males, respectively.

Table 5.3 Acute toxicity, LD_{50} values

Test substance	LD_{50}	Species	Vehicle
SRA 3886	72 mg/kg bw in males 92 mg/kg bw in females	Rat	Lutrol, warm

5.2.4 Acute toxicity: other routes

No data available.

5.2.5 Summary and discussion of acute toxicity

Fenamiphos is considered very toxic to rats after acute oral (LD_{50} 6 mg/kg bw) and inhalation (LC_{50} 0.065 mg/L) exposure and toxic by acute dermal exposure (LD_{50} 72 mg/kg bw). Therefore, according to 67/548/EEC, fenamiphos should be classified as T+; R26 because the LC50 is below the limit of 0.25 mg/L, as T+; R28 because the oral LD50 is below the limt of 25 mg/kg bw and as T; R24 because the dermal LD50 is within the limits of 50 – 400 mg/kg bw. According to EC 1272/2008, fenamiphos should be classified as Cat 2; H300 (limits 5 – 50 mg/kg bw, oral), H310 (limits 50 – 200 mg/kg bw, dermal) and H330 (limits aerosol 0.05 – 0.5 mg/L).

An additional classification with R39 is not considered necessary for fenamiphos, since the oral study showed that the clinical effects were reversible. However, both after acute oral and inhalation exposure, function-impairing clinical signs were observed, including palmospasms, dyspnea, laboured breathing, bloody eyes and apathy (no specified information for clinical effects dermal exposure was available). In addition, in an acute oral neurotoxicity screening study in rats significantly reduced erythrocyte ChE activity (>20%) was observed in males at all dose levels and in females at ≥ 1.52 mg/kg bw. These effects fulfil the criteria for STOT SE Cat1; H370. However, these effects are only seen at dose levels close to the dose levels that cause mortality. Also, the same effect probably also causes the mortality. Therefore, classification with STOT SE Cat1; H370 is considered a double classification for the same effect. Therefore, classification for STOT SE is not proposed.

The classification of fenamiphos was discussed by the TC-C&L in November 2006 (Summary record ECB/20/07). The TC-C&L agreed with the proposed classification for T+; R26/28 and T; R24.

5.3 Irritation

5.3.1 Skin (additional information)

Only one skin irritation study was performed. The study was considered unacceptable due to the fact that adequate skin contact can not be ensured in this study. Therefore, no conclusions can be drawn from this study.

5.3.2 Eye

In an eye irritation study (no OECD guideline) male rabbits received a single application of 0.1 mL of fenamiphos technical (purity 90.7%) into the conjunctival sac. At 24 hours 0.1 mL of 2 %

fluorescein sodium solution was used for examination. Midriasis was observed 10 min. after application. It recovered to normal on day 2 to 3. General effects observed included salivation, rhinorrhoea, licks, increased respiration, cyanosis and slight convulsion. These changes appeared 3-4 h after application and disappeared 6 h after application. In three additional animals, where the eyes were rinsed, no effects on the eyes were observed.

Table 5.4: Results eye irritation study

Scores observed after	24 hours	48 hours	72 hours	96 hours	168 hours	10 days
Cornea/opacity	1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0
Iris	1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1	0, 1, 1, 1, 1, 1	0, 1, 1, 1, 0, 1	0, 0, 0, 1, 0, 1	0, 0, 0, 0, 0, 0
Conjunctiva redness	1, 1, 1, 1, 1, 1	0, 1, 1, 1, 1, 1	0, 1, 1, 1, 1, 1	0, 1, 1, 1, 0, 1	0, 0, 1, 0, 0, 0	0, 0, 0, 0, 0, 0
Conjunctiva chemosis	1, 1, 0, 1, 1, 1	0, 0, 0, 0, 0, 0	0, 0, 1, 0, 0, 0	0, 0, 0, 1, 0, 1	0, 0, 0, 0, 0, 1	0, 0, 0, 0, 0, 0
Conjunctiva discharge	2, 2, 1,1, 1, 1	0, 0, 1, 0, 0, 1	0, 0, 1, 0, 0, 0	0, 0, 0, 1, 0, 0	0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0

5.3.3 Respiratory tract

No data available.

5.3.4 Summary and discussion of irritation

The skin irritation study was also not acceptable. However, no skin effects were found in an acute dermal study, nor in two repeated dose dermal studies (conform OECD-guideline 404). It can therefore be concluded that classification for skin irritation is considered not necessary.

Fenamiphos is considered irritating to eyes: irititis occurred within 24 hours after exposure in all animals (score 1) and persisted for at least 48 hours. In addition, corneal opacity was observed in all animals (score 1) after 24 hours, which lasted at least until 168 hours. Fenamiphos should therefore, according to 67/548/EEC, be classified as Xi; R36 because significant ocular lesions (irititis score 1) occurred within 72 hours and persisted for more then 24 hours. According to EC 1272/2008, fenamiphos should be classified as irritating to eyes Cat 2; H319, because corneal opacity and irititis (score 1) was observed in all animals (except for 1 animal, which had a score of 0 for irititis at 72 hours), calculated as the mean score following grading at 24, 48 and 72 hours and reversible within 21 days.

The classification of fenamiphos was discussed by the TC-C&L in November 2006 (Summary record ECB/20/07). The TC-C&L agreed with the proposed classification for Xi; R36 and no classification for skin irritation.

5.4 Corrosivity

No corrosive effects were observed in the acute or repeated dermal studies.

5.5 Sensitisation (additional information)

5.5.1 Skin

A guinea pig maximization test was performed in accordance with OECD 406. Twenty males were included in the test group, 10 in the control group. An intradermal induction was used with 1% fenamiphos (based on range-finding studies) after one week followed by the topical induction with 25% fenamiphos, which was performed for 48 h. Three weeks after the intradermal induction, a topical challenge was conducted with 12 and 25% fenamiphos for 24 h. Two animals of the test group died after intradermal induction. The macroscopic examination revealed paleness of the liver, lungs and kidneys and the stomach was filled with liquid.

Although only in 18 animals a topical challenge was administered, further testing is not required, due to the high toxicity of fenamiphos. It is concluded that fenamiphos is not a skin sensitiser.

Table 5.5: Results GPMT study

	Test substance group				Control group			
	Test substance patch		Control patch		Test substance patch		Control patch	
Challenge	48h	72h	48h	72h	48h	72h	48h	72h
12%	0/18	0/18	0/18	0/18	0/10	0/10	0/10	0/10
25%	0/18	0/18	0/18	0/18	0/10	0/10	0/10	0/10

Another GPMT study, which can only be accepted as supportive because the number of animals was too low (10/dose/group), also did not show sensitising properties of fenamiphos.

5.5.2 Respiratory system

No data available.

5.5.3 Summary and discussion of sensitisation

Fenamiphos does not have sensitising properties in a guinea pig maximisation test. No classification is necessary for sensitization.

5.6 Repeated dose toxicity (additional information)

5.6.1 Repeated dose toxicity: oral

The results of the relevant subacute, subchronic and chronic oral toxicity studies are summarized in Table 5.6.

Table 5.6: Summary of repeated dose oral toxicity data

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
Diet* Fenamiphos Purity: unknown	28 days No OECD	Rat, Sprague Dawley 6/sex/dose	Males: 0, 0.1, 0.3, 0.9, 2.9, 9.1 mg/kg bw/day; Females: 0, 0.1, 0.3, 0.9, 2.7, 9.3 mg/kg bw/day	At highest dose: slight degree of tremor of limbs and exophthalmos; lower body weight (10-15% decrease in week 1) and food consumption (19-30% decrease in week 1); lower level of glucose in males (-29%); **brain ChE inhibition ≥20% (females)**. From 2.9 (males) or 2.7 (females) mg/kg	9.3	2.7

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				bw: erythrocyte ChE inhibition ≥20%.		
Diet BAY 68 138 Purity 82%	3 months No OECD	Rat, Wistar 15/sex/dose treated, 30/sex in control group	Doses equivalent to 0, 0.2, 0.4, 0.8, 1.6 mg/kg bw/day	At 1.6 mg/kg bw/day: signs of cholinergic stimulation during first two months (not further specified). **Inhibition of erythrocyte ChE activity (> 20%) at 0.8 mg/kg bw/day (male and female).** Slightly increased absolute liver weights males at ≥ 0.8 mg/kg bw/day	0.8	0.4
Diet, cholinesterase study Fenamiphos techn Purity 89%	3 months No OECD	Rat, Fischer 344 20/sex/dose	Males: 0, 0.03, 0.045, 0.072 mg/kg bw/day; Females: 0, 0.035, 0.053, 0.084 mg/kg bw/day	No toxicologically significant, treatment-related effects were observed.	-	0.07
Diet, subchronic neurotoxicity study SRA 3886, Purity 95.5-95.7%	15 weeks FIFRA 82-5	Rat, Wistar Hsd Cpb:WU 12/sex/dose	Males: 0, 0.06, 0.61, 3.1 mg/kg bw/day; females: 0.08, 0.8, 4 mg/kg bw/day	At top dose: reduced body weight gain in males; muscle fasciculations in females during weeks 1 to 3. At ≥ mid dose: reduced erythrocyte ChE activity in males and in week 4 and 15 in females. **Slightly decreased brain ChE was (<20%) in females at mid and top dose and in males at top dose.**	0.8	0.08
Diet, cholinesterase study Fenamiphos Purity: 89%	100 days No OECD	Dog, Beagle 4/sex/dose	Doses equivalent to 0, 0.015, 0.025, 0.042 mg/kg bw/day	No toxicologically significant, treatment-related effects were observed.	-	0.042
Diet Fenamiphos techn Purity 88.3-89%	1 year OECD 452	Dog, Beagle 4/sex/dose	Males: 0, 0.03, 0.089, 0.31 mg/kg bw/day; Females: 0, 0.03, 0.083, 0.35 mg/kg bw/day	**Brain ChE activity significantly reduced (<20%) in females at 0.35 mg/kg bw/day**. mild, transient anaemia in males at 0.35 mg/kg bw/day (decreased erythrocyte counts: 11-19%, haemoglobin: 7-15%, haematocrit: 7-15%, increased MCV: 4-5%) Inhibition erythrocyte ChE activity (>20%) at males 0.35 mg/kg bw/day. Erythrocyte ChE activity compared to pre-treatment values: significant decrease males and females (>20%) at ≥ 0.083 mg/kg bw/day.	0.35	0.083
Diet, supplemental study Fenamiphos techn Purity 88.3-89%	6 months OECD 452	Dog, Beagle 4/sex/dose	0, 0.011 mg/kg bw/day	No toxicologically significant, treatment-related effects were observed.	-	0.011
Diet BAY 68 138 Purity unknown	2 year No OECD	Dog, Beagle 4/sex/dose	Males: 0, 0.015, 0.029, 0.063, 0.15, 0.31 mg/kg bw/day; Females: 0, 0.014, 0.036, 0.06, 0.17, 0.34 mg/kg bw/day	Top dose: erythrocyte count decreased (~10%) in males and females, absolute and the relative pancreas weight increased (23%) in males. **Decreased erythrocyte ChE activity (>20%) at ≥ 0.15 mg/kg bw/day.**	0.15	0.06
Diet*	2 year	Rat, Wistar	Males: 0, 0.17, 0.56, 1.7 mg/kg	Top dose: mild muscle twitching during first six weeks;	1.7	0.56

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
BAY 68 138 Purity unknown	no OECD	40/sex/dose treatment groups, 80/sex in control group	bw/day; Females: 0, 0.23, 0.76, 2.2 mg/kg bw/day	**slight increase in mortality rate females (15/40 vs 23/80); erythrocyte ChE activity inhibited by up to 60%; thyroid weights females increased (absolute 11%, relative 11%).** At 0.76 mg/kg bw/day: thyroid:body weight ratios females increased (15%).		
Diet, combined chronic/oncogenetic study Fenamiphos techn Purity 89.3%	2 year in acc OECD 451	Rat, Fischer 344 50/sex/dose main group, 20/sex/dose satellite group	Males: 0, 0.1, 0.5, 2.5 mg/kg bw/day; Females: 0, 0.1, 0.6, 3.4 mg/kg bw/day	Top dose: increased incidence of rough coat (34/50 vs. 13/50) and alopecia (12/50 vs. 3/50) in females vs controls; decrease in body-weight (~3% males, 5-15% females); **decreased brain ChE activity males (14%);** decreased liver weight (males 11%, females 20%); increased lung weight (males 25%, females 21%); increased relative lung weight (males 40%, females 76%); increased relative kidney weight (females 20%); increase in mottled or dark red lungs; higher incidences of non-neoplastic inflammatory lesions in the nasal, laryngeal, and lung tissues. Inhibited erythrocyte ChE activity (>20%) at ≥0.5 mg/kg bw/day.	2.5	0.5

Critical effects are presented in bold
*supportive study only

Short term dietary administration of fenamiphos to rats (0, 1, 3, 10, 30 and 100 mg/kg food for 4 weeks, equal to 0.1, 0.3, 0.9, 2.9 and 9.1 mg/kg bw/day in males and 0.1, 0.3, 0.9, 2.7 and 9.3 mg/kg bw/day for females) resulted in lower body weight (10-15% decrease in week 1) and food consumption (19-30% decrease in week 1) in the top dose group, especially in the first two weeks. In addition, decreased plasma glucose was observed in top dose males (-29%). Erythrocytes ChE inhibition was ≥20% at 30 mg/kg food for both sexes and brain ChE inhibition was ≥20% at 100 mg/kg food for females.

In a subchronic neurotoxicity study in hens (0, 1, 3, 10, or 30 mg/kg food, equal to 0, 2, 5, 16, or 26 mg/kg bw/day, for 30 days) food consumption and the average body weight and growth was depressed in birds at the top dose. There were no indications of delayed neurotoxicity.

After administration of fenamiphos (0, 4, 8, 16 or 32 mg/kg food, equivalent to 0.2, 0.4, 0.8, or 1.6 mg/kg bw/day) for three months in rats, males and females at the highest dose showed signs of cholinergic stimulation during the first two months (not further specified). Erythrocyte ChE activity was decreased (> 20%) in animals at 16 mg/kg food and above, with peak inhibition (56%) at 16 mg/kg food by week 8. Absolute (but not relative) liver weights in males were slightly increased at 16 or 32 mg/kg food (13 and 14% respectively). In another 3 months dietary study with rats (0, 0.37, 0.57, or 0.91 mg/kg food, equal to 0, 0.03, 0.045, or 0.072 mg/kg bw/day for males and 0, 0.035, 0.053, or 0.084 mg/kg bw/day for females) no biologically significant ChE activity inhibition had occurred. Also in a 3 months dietary study in dogs (0, 0.6, 1.0, or 1.7 mg/kg food, equivalent to 0, 0.015, 0.025, 0.042 mg/kg bw/day) erythrocyte and brain ChE activities were unaffected.

In a semichronic neurotoxicity study, fenamiphos was administered in the diet to rats for 15 weeks at dietary concentrations of 0, 1, 10, or 50 mg/kg food, equal to 0, 0.06, 0.61, or 3.1 mg/kg bw/day

in males and 0.08, 0.8, or 4 mg/kg bw/day in females. Body weight gain was lower in males at the top dose. Muscle fasciculations were observed at the top dose in females during weeks 1 to 3. In the functional observation battery (week 4) no behavioural changes corresponding to the muscle fasciculations in females were observed at the top dose. No treatment-related effects were seen in motor and locomotor activity testing. At ≥ 10 mg/kg food erythrocyte ChE activity was lower in week 15 in males and in week 4 and 15 in females. Brain ChE was slightly decreased (<20%) in females at 10 mg/kg food and above and in males at 50 mg/kg food.

After administration of fenamiphos to dogs for 1 year (0, 1, 3, or 12 mg/kg food, equal to 0, 0.03, 0.089, or 0.31 mg/kg bw/day in males and 0, 0.03, 0.083, and 0.35 mg/kg bw/day in females) brain ChE activity was non-significantly decreased in males but significantly reduced (although <20%) in females at 12 mg/kg food. Males at this dose also had mild, transient anaemia characterised by significantly decreased erythrocyte counts (11-19%), haemoglobin concentrations (7-15%), and haematocrit (7-15%), with a concomitant increase in mean corpuscular volume (4-5%). When erythrocyte ChE activity was compared to the control group at the same day the inhibition of erythrocyte ChE activity was >20% at 12 mg/kg food. At lower doses no toxicologically relevant inhibition was observed. This was mainly because the pre-treatment values of the control group were ~10% lower than the pre-treatment values in the treated groups. When erythrocyte ChE activity was presented compared to pre-treatment values, a statistically significantly decrease was observed in both males and females with >20% at 3 and 12 mg/kg food; however, the activity in the controls and dogs at 1 mg/kg food was variably decreased during the course of the study. Therefore, the data on erythrocyte ChE inhibition were not easily interpretable and a benchmark calculation was conducted for male and female rats at all time points. The dose where 20% erythrocyte ChE inhibition was observed was estimated. There were no differences between males and females and the benchmark dose at day 98 was 2.93 mg/kg food (95% confidence interval: 2.52-3.49), at day 189 was 3.06 (2.65-3.62), at day 280 was 3.05 (2.65-3.60), and at day 361 was 3.33 (2.86-4.00). Based on the effects on brain ChE activity in females at 0.35 mg/kg bw/day, this dose is the LOAEL.

Fenamiphos administered to rats in the diet for two years (0, 3, 10 and 30 mg/kg food, equal to 0.17, 0.56 and 1.7 mg/kg bw/day for males and 0.23, 0.76 and 2.2 mg/kg bw/day for females) resulted in mild muscle twitching during the first six weeks of treatment at 30 mg/kg food. A slight increase in the mortality rate of the female rats at 30 mg/kg food was observed. Thyroid weights were increased in females at 30 mg/kg food (absolute 11%, relative 11%), and at 10 mg/kg food (relative 15%). In animals at 30 mg/kg food, plasma and erythrocyte ChE activity was inhibited by up to 60%.

In another 2 year study in rats doses of 0, 1.7, 7.8, or 37 mg/kg food, equal to 0, 0.1, 0.5, or 2.5 mg/kg bw/day for males and 0, 0.1, 0.6, or 3.4 mg/kg bw/day for females were administered. Additional groups of 10 rats of each sex were given 0 or 37 mg/kg food fenamiphos for one year. An increased incidence of rough coat (34/50 vs. 13/50) and alopecia (12/50 vs. 3/50) was observed in females at the high dose. A statistically significant decrease in body-weight was seen in male (~3%) and female (5-15%) rats at the high dose throughout the study, although no treatment-related effect on feed consumption was seen. Erythrocyte ChE activity was statistically significantly inhibited (>20%) at ≥ 7.8 mg/kg food. A statistically significant decrease in brain ChE activity was observed in male rats at the high dose at termination (14%) and in animals of each sex at interim sacrifice after one year of treatment (>20%). A statistically significant decrease in liver weight (males 11%, females 20%) and an increase in lung weight (males 25%, females 21%) in animals of each sex at 37 mg/kg food were observed. In addition, statistically significant increases in the relative weights of the lung (males 40%, females 76%) in both males and females at the high dose at the end of the study were observed; females at the high dose also had significantly increased

relative kidney weights (20%). At interim sacrifice, females had statistically significantly increased relative weights of kidneys. An increase in mottled or dark red lungs was observed in rats of both sexes at 37 mg/kg food. Statistically significantly higher incidences of non-neoplastic inflammatory lesions were observed in the nasal, laryngeal, and lung tissues of rats receiving 37 mg/kg food fenamiphos in the diet when compared with controls. The study authors suggested that the inflammation was causally related to the increased secretory activity of airway mucosa induced by continuous cholinergic stimulation.

Groups of pure-bred beagle dogs were fed fenamiphos in the diet at levels of 0, 0.5, 1, 2, 5, or 10 mg/kg food (equal to 0, 0.015, 0.029, 0.063, 0.15, or 0.31 mg/kg bw/day for males and 0, 0.014, 0.036, 0.06, 0.17, and 0.34 mg/kg bw/day for females) for two years. The number of erythrocytes was lowered by ~10% in both males and females at the highest dose throughout the study. At the highest dose in males both the absolute and the relative pancreas weight was increased by 23%. Significant dose related inhibition of erythrocyte ChE activity at ≥ 5 mg/kg food.

5.6.2 Repeated dose toxicity: inhalation

A summary of repeated dose inhalation toxicity data is presented in Table 5.7.

Table 5.7: Summary of repeated dose inhalation toxicity data

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	Effects	LOAEL (mg/L/d)	NOAEL (mg/L/d)
Nose only* SRA 3886 Purity 89.8%	5 days No OECD	Rat, TNO/W 74 10/sex/dose	0, 0.3, 0.6, 3.3, 4, 9, 28 mg/m^3 4h/day	Muscle twitching, inactivity, and stiff gait at 4 and 9 mg/m^3 in females and males, respectively. **Depressed erythrocyte ChE activity in males: > 20% at ≥ 9 µg/L; in females > 20% at ≥ 4 µg/L.**	4 µg/L	3.3 µg/L
Nose only SRA 3886 Purity 92.2%	3 weeks No OECD	Rat, TNO/W 74 10/sex/dose	0, 0.03, 0.25, 3.5 mg/m^3 6h/day, 5 days/week	No toxicologically relevant effects were observed.	-	3.5 µg/L

Critical effects are presented in bold
*supportive study only

In a subacute inhalation dose-range finding study fenamiphos was dissolved in a mixture of ethanol and Lutrol and the solution was aerosolised into the dynamic flow inhalation chambers. Since no data on particle size and distribution were available and several parameters as food consumption and haematology were not analysed, the study can only be used as supportive. The clinical signs were characterised by typical signs of cholinesterase activity depression i.e. muscle twitching, inactivity, and stiff gait. The cholinesterase activities were depressed in a dose-related manner. Erythrocyte ChE activity after the 5th exposure in males was inhibited by more than 20% at ≥ 9 µg/L; that in females was depressed by more than 20% at ≥ 4 µg/L. Erythrocyte ChE activities were back to pre-exposure levels 72 h after the 5th exposure. No effects on body weight gain and gross pathology were observed.

In a 3 week inhalation study rats were exposed to fenamiphos diluted with a 1:1 mixture of ethanol and polyethylene glycol 400 for aerosolisation in a dynamic flow inhalation chamber at doses of 0, 0.03, 0.25, or 3.5 µg/L. Of the particles 98% was less than ≤ 3 µm. No toxic signs or effects on mortality, body-weight gain, haematology, urinalysis, or clinical chemistry were seen. In females reduction of erythrocyte ChE activity was found at 3.5 µg/L (<20%). The maximum erythrocyte ChE inhibition was already observed after the fifth exposure. Brain ChE activity was not affected

by treatment with fenamiphos. There were no gross or histopathological changes or effects on organ weights.

5.6.3 Repeated dose toxicity: dermal

A summary of repeated dose dermal toxicity data is presented in Table 5.8.

Table 5.8: Summary of repeated dose dermal toxicity data

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	Effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
Dermal SRA 3886 Purity 89.8%	3 weeks No OECD	Rabbit, NZW 3/sex/dose intact skin, 3/sex/dose abraded skin	0, 0.5, 2.5 or 10 mg/kg bw/day 6h/day, 5 days/week	Top dose: **decreased body-weight gain (32% for males, 47% for females); inhibition of brain ChE females with abraded skin (21%) and intact skin (22%).** All groups, including controls: slight erythema at the abraded skin sites during initial week. At 2.5 mg/kg bw/day: decrease in brain ChE activity in females abraded skin. When groups were combined: erythrocyte ChE activity significantly depressed in male and female rabbits at 10 mg/kg bw/day. Brain ChE activity depressed for >20% in females at 10 mg/kg bw/day.	10	2.5
Dermal SRA 3886 Purity 95.2%	4 weeks OECD 410	Rat, HsdCpb:WU 5/sex/dose	0, 2.5, 10, 40 mg/kg bw/day 6h/day, w1-3 5days/week, w4 7days/week	No treatment-related systemic clinical signs were observed	-	40 mg/kg bw

Critical effects are presented in bold

In the first dermal study, an aqueous formulation of fenamiphos was applied to a clipped dorsal area of 6 rabbits/sex/dose at doses of 0, 2.5, or 10 mg/kg bw/day for 6 h per day, five days per week for three weeks. Two additional groups were similarly treated at 0 and 0.5 mg/kg bw/day. The skin of half of the animals was abraded. Necropsy was performed 24 to 48 hours after the final treatment. Macroscopic and histopathological examinations and brain ChE activity were determined after necropsy. No signs of toxicity or mortality were observed. Body-weight gains were decreased in animals of each sex at 10 mg/kg bw/day by 32% for males and 47% for females. Slight erythema was observed in all groups, including the control group, only at the abraded skin sites during the initial week, which cleared by day 7. There were no apparent differences in haematological, urinary, or clinical chemical parameters between test and control groups. Gross necropsy, histopathology, and organ weight measurements showed no remarkable changes in comparison with controls. At 2.5 mg/kg bw/day, only in the females with abraded skin a decrease in brain ChE activity was observed. The values for erythrocyte ChE were not affected at this dose. In the highest dose group the inhibition of brain ChE with abraded skin was 21 % (therefore the effect was not dose related). Formally, it may not be appropriate to combine the data of the groups with intact and abraded skin. However, given the small group size, and the fact that both groups showed similar responses, the results were combined. Accordingly, erythrocyte ChE activity was significantly depressed in male and female rabbits at 10 mg/kg bw/day. Brain ChE activity was depressed for >20% in females at 10 mg/kg bw/day.

In the second study, fenamiphos was formulated in polyethylene glycol 400 and applied to the dorsal skin (20.3-30.25 cm2) of groups of rats at concentrations of 0, 2.5, 10 and 40 mg/kg bw for 6

hour/day. No treatment-related systemic clinical signs or deaths were observed in males and females. No effects on food intake and body weight development were noted up to 40 mg/kg bw/day. No local skin reddening and skin thickness was observed in the dose groups up to 40 mg/kg bw/day. Erythrocyte ChE activity was significantly increased in males at the highest dose (13%). No effects on brain ChE were observed.

5.6.4 Other relevant information

From the administration, distribution, metabolism and excretion studies some evidence is available that fenamiphos does not easily cross the blood-brain barrier. Therefore, besides data regarding brain ChE activity, data regarding erythrocyte ChE activity are as well considered toxicologically relevant. Plasma cholinesterase inhibition is not considered to be toxicologically relevant. Effects on plasma cholinesterase are therefore not mentioned in the study descriptions.

5.6.5 Summary and discussion of repeated dose toxicity:

Increased mortality was observed in a 2 year dietary study (supportive study) in rats at 2.2 mg/kg bw/day (NOAEL 0.76 mg/kg bw). However, in another 2 year study in rats where even higher doses were used, no mortality was observed. The main effect following repeated oral, dermal and inhalation administration of fenamiphos to rats and dogs is the inhibition of cholinesterase activity, which at higher dose levels may lead to endogenous cholinergic overstimulation including typical cholinergic symptoms. Plasma ChE was found to be the most sensitive parameter which, however, is regarded to have no toxicological relevance. Erythrocyte ChE inhibition was observed in all studies, even more than inhibition of brain ChE activity. This is probably because of the limited ability to cross the blood-brain-barrier. However, when the JMPR ’98 criteria for cholinesterase inhibition are followed, where possible limit values should be based on inhibition of brain cholinesterase instead of erythrocyte cholinesterase. The dog seemed the most sensitive species for effects on brain cholinesterase activity. The LOAEL for erythrocyte ChE inhibition in the one-year dog study was 0.083 mg/kg bw/day, the NOAEL 0.03 mg/kg bw/day. The LOAEL for brain ChE inhibition in the one-year dog study was 0.35 mg/kg bw/day, the NOAEL 0.083 mg/kg bw/day. In addition to the inhibitory effects on ChE, slight effects on the red blood system (reduced values for haemoglobin, haematocrit, red blood cell counts and concomitant increase in MCV) were seen following semi-chronic administration of fenamiphos to dogs (at 0.31 mg/kg bw/day).

Also during chronic administration of fenamiphos to rats inhibition of cholinesterase activity was the most sensitive parameter. The NOAEL for inhibition of brain cholinesterase was 0.5 mg/kg bw/day, and the LOAEL 2.5 mg/kg bw/day. Somatic toxic effects such as slightly lower body weight gain and inflammatory lesions in lungs and airways were seen only at a clearly toxic dose level (2.5 mg/kg bw/day). Slightly lower body weight gain was the main toxic effect also in mice together with lower relative and absolute organ weights for spleen and ovaries. Chronic inhalation or dermal studies were not available.

Inhibition of cholinesterase and related clinical effects were observed in most repeated dose studies at dose levels below the limits for classification with R48 or STOT RE Cat 1. However, as this effect is also seen after single exposure at comparable dose levels and the substance is already classified for acute toxicity, classification with R48 or STOT RE Cat 1 is not considered necessary.

5.7 Mutagenicity (additional information)

5.7.1 In vitro data

Several *in vitro* mutagenicity assays are performed with fenamiphos.

In an Ames test with doses up to 12.5 mg/plate, fenamiphos did not induce point mutations in S. typhimurium, neither with nor without metabolic activation. In addition, a gene mutation assay (HGPRT) in CHO-K_1-B4H_4 cells was negative, as well as an unscheduled DNA synthesis assay.

Two *in vitro* cytogenic assays were performed in human lymphocytes. In the first, 100 µg/ml fenamiphos induced 9.5% metaphases with aberrations (excluding gaps) without metabolic activation, compared to 1.0% in the control group. With metabolic activation, an increase in metaphases with aberrations was only observed at highly cytotoxic levels (mitotic index <0.1%). However, the dose levels in combination with metabolic activation were not appropriate, since at 100 µg/ml toxicity was not observed and at 400 µg/ml haemolysis was observed. In the second assay, no increase in cells with chromosome aberrations was found without metabolic activation between fenamiphos and control values. In the presence of S9, a dose related increase in metaphases with aberrations excluding gaps was observed at the highest dose (10% metaphases with aberrations excluding gaps vs. 3.5% in the control group). At lower concentrations no increase in cells with chromosome aberrations were observed.

In addition, a mouse lymphoma test was performed, with doses up to 200 µg/mL. The positive result in the chromosome aberration study in human lymphocytes without metabolic activation at a dose level of 100 µg/ml could not be confirmed in this assay. Fenamiphos did not demonstrate a mutagenic or clastogenic potential in this assay.

Table 5.9: Results *in vitro* mutagenicity assays

Indicator cells	Endpoint	Results		Activation		Dose range
		- met act	+ met act	Tissue	Inducer	
S typhimurum	Frame shifts, bp substitutions	-	-	Rat liver	Aroclor 1254	0-12.5 mg/plate 0-2 mg/plate
CHO-K_1-BH_4	Sister chromatoid exchange	-	-	Rat liver	Aroclor 1254	0-130 µg/ml (-S9) 0-230 µg/ml (+S9)
Human lymphocytes	Chromosome aberration	+ (100 µg/ml)	n.a.	Rat liver	Aroclor 1254	0-400 µg/ml
Human lymphocytes	Chromosome aberration	-	+ (350 µg/ml)	Rat liver	Aroclor 1254	0-100 µg/ml (-S9) 0-350 µg/ml (+S9)
mouse lymphoma cells L5178Y TK +/-	gene mutation	-	-	Rat liver	Aroclor 1254	10-200 µg/mL with 3 h exposure (+/- S9); 5-100 µg/mL with 24 h exposure (- S9) solvent: DMSO.
V79 chinese hamster cells	Sister chromatoid exchange*	-				0-20 µg/ml
Rat primary hepatocytes	Unscheduled DNA synthesis	-				0-299 µg/ml

* Supportive study only

5.7.2 In vivo data

A dominant lethal study with fenamiphos was performed in mice. No induction of dominant lethal effects in mouse germ cells was observed.

In addition, a micronucleus test was performed in mice, in which the bone marrow was sampled 16, 24 and 48 h after dosing. The PCE/NCE ratio was unaffected at the highest dose. However, since

the test substance was given i.p., it is assumed that the test substance has reached the bone marrow. Fenamiphos was not mutagenic in this assay

Table 5.10: Results *in vivo* mutagenicity assays

Endpoint	Species	Animal number	Results	Dose range
Dominant lethal effects in germ cells	Mouse	50 males/dose	-	0 or 5 mg/kg bw (oral)
Micronuclei in bone marrow cells	Mouse	5/sex/dose	-	0 or 25 mg/kg bw (ip)

In a mouse micronucleus assay, mice were orally dosed twice with 0, 0.625, 1.25 or 2.5 mg/kg bw fenamiphos, 24 h apart, and the bone marrow was sampled once, 6 h after the second dose. However, the PCE/NCE ratio was unaffected at the highest dose, and the assay was considered unacceptable, since this result indicates that fenamiphos was not able to reach the bone marrow.

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

Fenamiphos was not genotoxic in a number of *in vitro* genotoxicity studies including the bacteria microsome assay (Ames test) for point mutations, the HGPRT assay for forward mutations in cultured Chinese hamster ovarian cells, the unscheduled DNA synthesis assay in rat primary hepatocytes and the sister chromatid exchange assay in Chinese hamster V79 cells. The compound showed positive test results for clastogenicity in the chromosomal aberration assay in human lymphocytes. Exclusively in the first study a positive result was obtained at one single dose without activation. In the second study a positive result was observed only with metabolic activation at a dose level with high cytotoxicity. Independent repeat assays were not submitted. These positive results in human lymphocytes were not confirmed in a mouse lymphoma assay. Fenamiphos was not mutagenic in the *in vivo* dominant lethal test for germ cell chromosomal and dominant gene mutations. Futher, two micronucleus tests were available. The first (oral) study was not acceptable since there were no indications that the test substance had reached the bone marrow (no change in PCE/NCE ratio, and based on the results from the ADME study) and the sample time was too short. The second test in which the test substance was given i.p. was negative.

Based on the available *in vitro* and *in vivo* tests, fenamiphos is considered not genotoxic.

5.8 Carcinogenicity (additional information)

5.8.1 Carcinogenicity: oral

In an oncogenicity study, mice were given fenamiphos in the diet (equal to 0, 0.3, 1.4, or 7.4 mg/kg bw/day for males and 0, 0.3, 1.8, or 8.8 mg/kg bw/day for females) for 20 months. Survival was

comparable in all groups, with only a marginal decrease at the high dose. The survival at 20 months was <50% in all groups, including controls. No treatment related histopathological findings, including neoplasms, were observed.

In a combined chronic toxicity/carcinogenicity study in accordance with OECD 451, rats were fed diets containing fenamiphos (equal to 0, 0.1, 0.5, or 2.5 mg/kg bw/day for males and 0, 0.1, 0.6, or 3.4 mg/kg bw/day for females) for two years. No effects on survival were noticed. No treatment-related neoplastic lesions were observed during histopathological examination.

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

There was no evidence of treatment-related oncogenicity in the long-term oral mouse and rat studies. No oncogenic effects were observed up to 7.4 mg/kg bw/day in mice and 2.5 mg/kg bw/day in rats, the highest doses tested. No data were available regarding carcinogenic effects after dermal or inhalation exposure. In addition, no human carcinogenicity data were available. Based on the oral studies it is concluded that fenamiphos does not need to be classified for carcinogenicity.

5.9 Toxicity for reproduction (additional information)

5.9.1 Effects on fertility

In a two-generation study of reproductive toxicity, performed in accordance with OECD 416, rats (30/sex/dose) received fenamiphos in the diet at concentrations of 0, 2.5, 10, or 40 mg/kg food for 70 days before mating (0.17, 0.64, or 2.8 mg/kg bw/day for males and for females 0.20, 0.73, or 3.2 mg/kg bw/day in the premating period, 0.17, 0.64, and 2.82 mg/kg bw/day in the gestation period and 0.39, 1.48, 5.85 mg/kg bw/day in the lactation period). After weaning, 30 F1 animals/sex/dose were treated for 70 days and then bred to produce the second generation (F2); treatment was continued throughout mating, gestation, and lactation. F0 and F1 females were killed after their pups had been weaned or on day 24 of gestation. The males were killed after the last litters were delivered. There were no treatment-related deaths or clinical signs of toxicity in the parental animals. The absolute and relative ovarian weights of F0 females were reduced at all dose levels (absolute 9, 8, and 23%, and relative by 13, 11, and 20% at 2.5, 10 and 40 mg/kg food respectively),

but were unaffected in F1 females, except for a 9% decrease in absolute ovaries weight at 40 mg/kg food. Since there was no dose-related decrease in ovarian weights in the F0 females, only the effects at 40 mg/kg food are considered treatment-related. Nevertheless, no effects were observed on oestrous cycles, mating, fertility, and gestation indices. The NOAEL for reproductive toxicity was 40 mg/kg food, equal to 2.8 mg/kg bw/day, based on the absence of reproductive effects at the highest dose tested.

Another 2-generation study in FB30 rats was performed. However, individual data were not reported and data on body weights were presented in graphs only. In addition, the pathology report the generation of animals was not specified. Furthermore, only limited indices of reproduction were reported. Therefore, the study is considered not acceptable.

5.9.2 Developmental toxicity

In a two-generation study of reproductive toxicity, performed in accordance with OECD 416, rats (30/sex/dose) received fenamiphos in the diet at concentrations of 0, 2.5, 10, or 40 mg/kg food for 70 days before mating (0.17, 0.64, or 2.8 mg/kg bw/day for males and for females 0.20, 0.73, or 3.2 mg/kg bw/day in the premating period, 0.17, 0.64, and 2.82 mg/kg bw/day in the gestation period and 0.39, 1.48, 5.85 mg/kg bw/day in the lactation period). After weaning, 30 F1 animals/sex/dose were treated for 70 days and then bred to produce the second generation (F2); treatment was continued throughout mating, gestation, and lactation. F0 and F1 females were killed after their pups had been weaned or on day 24 of gestation. The males were killed after the last litters were delivered. Results are summarized in table 5.11

Table 5.11: Results two-generation study of reproductive toxicity

Dose (mg/kg food)	**0**		**2.5**		**10**		**40**		dr
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
F0 animals									
Mortality (n=30)		1							
Clinical signs	No toxicologically relevant effects								
Body weight gain								dc[1]	
Food consumption								dc[1]	
Ery ChE									
inhib %[2] week 8			2	6*	22*	25*	54*	56*	dr
sacrifice			-3	4	6	15*	39*	44*	dr
Brain ChE									
inhib %[2] sacrifice			-8	-10*	-9	0	1	21*	
Organ weight									
Ovaries				d[a], dc[r]		d[a], dc[r]		dc[a,r]	
Pathology									
Macroscopy									
Salivary gland, oedema	1	0	1	0	0	0	4	7*	
Microscopy									
Salivary gland, oedema	1		1				4	6*	
Salivary gland, inflammation			1				2	5*	
Salivary gland, vacuolar degen.	1		1				4		
F1 pups									
Litter size	No toxicologically relevant effects								
Survival index	No toxicologically relevant effects								
Sex ratio	No toxicologically relevant effects								
Body weight							dc	dc	
Ery ChE									
inhib %[2] day 4			-4	-11	-3	-4	7	0	
day 21			1	3	8	2	31*	40*	
Brain ChE									
inhib %[2] day 4			-9	0	-6	1	-2	-6	
day 21			0	0	-4	1	1	5	
Pathology									
Macroscopy	No toxicologically relevant effects								
F1 animals									
Mortality						1			
Clinical signs	No toxicologically relevant effects								
Body weight gain					d		dc	dc[3]	

Food consumption									dc[1]	
Ery ChE										
inhib %[2]	week 8			6*	4	14*	15*	48*	44*	dr
	sacrifice			1	3	16*	36*	48*	49*	dr
Brain ChE										
inhib %[2]	sacrifice			-2	4	-3	6*	6*	29*	
Organ weight										
Ovaries										
Pathology										
Macroscopy		No toxicologically relevant effects								
Microscopy		No toxicologically relevant effects								
F2 pups										
Litter size		No toxicologically relevant effects								
Survival index		No toxicologically relevant effects								
Sex ratio		No toxicologically relevant effects								
Body weight								dc	dc	
Ery ChE										
inhib %[2]	day 4			4	2	0	10	11	9	
	day 21			-3	-9	-10	-10	25*	27*	
Brain ChE										
inhib %[2]	day 4			-10	-1	-3	5	3	2	
	day 21			-5	2	-4	2	2	7	
Pathology										
Macroscopy		No toxicologically relevant effects								

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative organ weight
* statistically significantly different compared to the controls
[1] during lactation period only
[2] a negative value indicates an increase in ChE activity
[3] during premating, gestation, and lactation period

There were no treatment-related deaths or clinical signs of toxicity in the parental animals. In F0 and F1 dams at 40 mg/kg food, statistically significant reductions were seen in body-weight gain during lactation (by 72 and 65%) and food consumption (by up to 11 and 19%). F1 and F2 pups also had significant reductions in body-weight gain beginning on day 7 of lactation. Erythrocyte ChE activity was significantly inhibited in females at doses ≥ 10 mg/kg food but only at 40 mg/kg food in F0 and F1 males. At 40 mg/kg food, brain ChE activity was significantly inhibited in F0 and F1 females. Erythrocyte ChE activity was inhibited by > 20% in males and females of both generations at 40 mg/kg food on day 21. Brain ChE activity was not affected in pups.
Sex ratio, and pup viability indices were unaffected. Gross pathology and histopathology showed an increase in oedema of the salivary glands at 40 mg/kg food in both males and females of the F0 generation. No such effects were observed in the F1 generation. The NOAEL for parental toxicity was 2.5 mg/kg food, equal to 0.17 mg/kg bw/day, on the basis of decreased body-weight gain in males and inhibition of erythrocyte ChE activity in both males and females. The NOAEL for developmental toxicity was 10 mg/kg food, equal to 0.64 mg/kg bw/day, on the basis of decreased pup body weights during lactation and in addition inhibition of erythrocyte ChE activity.

In a teratogenicity study, female rats (25/dose) were given fenamiphos in a 0.5% aqueous Cremophor emulsion (0, 0.3, 1, or 3 mg/kg bw/day by gavage) on days 6-15 of gestation. On day 20 of gestation, the dams were narcotised with carbon dioxide and the foetuses were removed. Eighteen dams receiving 3 mg/kg bw/day showed signs of toxicity (trembling and recumbency), and two died. Weight gain was reduced (15%) during treatment in high dosed dams in comparison with controls. Average placental weight of high dose animals was significantly lower than in controls (8%). Treatment did not affect litter size, number of resorptions, number of foetuses, average foetal weight, sex ratio, incidence of alterations in development, or the type or number of malformations. The most frequent manifestations were nodulations on ribs, which were found in two foetuses from one litter of a dam at 0.3 mg/kg bw/day and in four foetuses of three litters of dams at 1 mg/kg bw/day. The other malformations observed were general oedema, abdominal fissure, and anophthalmia in one foetus at 0.3 mg/kg bw/day. No malformations were observed in

foetuses at the high dose. Based on clinical signs, decreased body weight gain, and decreased placenta weights at 3 mg/kg bw/day, the NOAEL for maternal toxicity is 1 mg/kg bw/day. The NOAEL for developmental toxicity is 3 mg/kg bw/day, based on the absence of developmental effects at the highest dose tested.

In a second teratogenicity study, female rats were given fenamiphos at doses of 0, 0.25, 0.85, or 3 mg/kg bw/day by gavage on days 6-15 of gestation. Five dams from each group were killed on day 16 in order to measure plasma, erythrocyte, and brain ChE activities; the remaining dams were killed on day 20 of gestation and necropsied grossly. Six dams at 3 mg/kg bw/day died between days 7 and 14 of gestation. Clinical signs of toxicity, such as tremors, salivation, lachrymation, urine staining, and hypoactivity, were seen to varying extents in the survivors. Body-weight gain (38%) and food consumption (10-17%) were significantly reduced throughout treatment at this dose. Gross necropsy revealed no treatment-related abnormalities, and gestational parameters were unaffected. Foetal body weights were unchanged. Two major malformations were observed. In the control group, one foetus had rhinocephalic with cyclopia, displaced pinnae, agnathia and astomia. At 0.85 mg/kg bw/day, one foetus had exencephaly and possessed an omphalocele and supernumerary appendages. These malformations are considered spontaneous in origin. Variations of the hyoid body were significantly increased at 0.25 and 3.0 mg/kg bw/day. However, the increase was not dose-related and was within the laboratory historical control range (2-32%). When the hyoid body variations were expressed as percentage of litters effected, toxicologically relevant effects were observed at the highest dose only. At day 16, erythrocyte ChE activities were >20% reduced in dams at 0.85 mg/kg bw/day and higher. By day 20, erythrocyte ChE was still significantly reduced at 3 mg/kg bw/day. Brain ChE activity was reduced non-significantly and not in a dose related manner. Foetal brain ChE activity was unaffected. The NOAEL for maternal toxicity was 0.25 mg/kg bw/day, based on decreased erythrocyte ChE activity at day 16 at 0.85 mg/kg bw/day. The NOAEL for developmental toxicity was 0.85 mg/kg bw/day, based on the increase in hyoid body variations at 3 mg/kg bw/day.

In addition, a teratogenicity study in rabbits is available. Female rabbits were given fenamiphos orally at doses of 0, 0.1, 0.3, or 1 mg/kg bw/day on days 6-18 of gestation. Dams given doses ≥ 0.3 mg/kg bw/day showed signs of toxicity, with decreased body-weight gain (34 and 49% for 0.3 and 1.0 mg/kg bw/day respectively), bloody nasal discharge, and white, mucoid ocular discharge. At 1.0 mg/kg bw/day decreased gravid uterine weight was observed (20%). Treatment did not affect the number of litters, number of pups per litter, pregnancy rate, the number of corpora lutea, implantations, or gross abnormalities. Mean foetal weight was slightly depressed at 1 mg/kg bw/day (7%). One dam at 0.3 mg/kg bw/day aborted one dead pup, and two dams at 1 mg/kg bw/day aborted eight dead pups and had seven late resorptions. In addition, one dead foetus was found in each of two litters at the high dose. The most common developmental variation observed was the left carotid arising from the innominate, which occurred at doses ≥ 0.1 mg/kg bw/day. A dose-related response was not observed. This anomaly was not seen in the controls and in only one of 31 litters (3.2%) of historical controls at the laboratory where the study was performed. Based on the total set of information, this effect is not considered to be related to treatment. An increased incidence of accessory skull bones was also seen in all treated groups. A significant increase in the incidence of chain-fused sternebrae was seen at 1 mg/kg bw/day, and this anomaly was also seen at 0.3 mg/kg bw/day. These skeletal anomalies were found at maternal toxic doses only, and are probably due to the maternal toxicity. Two foetuses in one litter at the high dose had aortic arches with a common truncus, which was considered to be a major malformation. Other skeletal malformations, which occurred at doses ≥ 0.3 mg/kg bw/day, included fused ribs, scoliosis, absent vertebrae (thoracic, lumbar, sacral, and caudal), and bipartite or malformed centra. These anomalies occurred in only one or two foetuses in single litters. Furthermore, several of the anomalies were

clustered within a single foetus, indicating that they were not likely to be related to treatment. The NOAEL for maternal toxicity was 0.1 mg/kg bw/day, based on decreased body weight gain and clinical signs at 0.3 mg/kg bw/day. The NOAEL for developmental toxicity was 0.3 mg/kg bw/day, based on decreased foetal weight and skeletal findings at 1.0 mg/kg bw/day.

Finally, another teratogenicity study in rabbits was performed. However, because of the problems of homogeneity questions remain about the doses actually administered. Therefore, the study is acceptable as a supportive study only. In this study, rabbits were given fenamiphos as single daily doses of 0, 0.1, 0.5, or 2.5 mg/kg bw/day by gavage on days 6-18 post coitum. On day 28 post coitum the foetuses were removed. Four females at 2.5 mg/kg bw/day died as a result of treatment. Treatment-related signs of toxicity (salivation and dyspnoea) were observed in these females and in five other females at the high dose. Ataxia was seen in two females that died, and diarrhoea was observed in another. No signs of toxicity were found in animals at 0, 0.1, or 0.5 mg/kg bw/day. A statistically significant decrease in mean food consumption (29%) and a reduction in body-weight gain (56%) were observed during treatment in does at the high dose when compared with controls. Food consumption was significantly increased in this group after treatment (13%). No treatment-related or significant difference was observed between treated and control animals with regard to the mean numbers of implantations, corpora lutea, live or dead foetuses, or resorptions. The pre-implantation loss was increased at the highest dose (10.9 vs. 3.3% of corpora lutea). In general, in a teratogenicity study, pre-implantation loss is not related to treatment, because implantation occurs before treatment starts. Since the days of gestation were counted from mating and not corrected with one day, treatment might have influenced pre-implantation loss. In foetuses, no effect that could be attributed to treatment was seen in sex ratio, body weight, external or internal malformations, skeletal abnormalities, or development. One foetus at the high dose had encephalocele with reduced brain size. A number of skeletal changes unrelated to treatment were seen in foetuses at all doses. The NOAEL for maternal toxicity was 0.5 mg/kg bw/day, based on mortality, clinical signs, decreased body weight and food intake at 2.5 mg/kg bw/day. The NOAEL for developmental toxicity is 0.5 mg/kg bw/day, based on the increase in pre-implantation loss at 2.5 mg/kg bw/day, because the days of gestation were not corrected.

Table 5.12: Summary of developmental studies with fenamiphos

Study type/Route/ Test material	**Duration Method/ Guideline**	**Species/ strain/ sex/ no. per group**	**Dose levels/ frequency of dosing**	**Maternal LOAEL/ NOAEL (mg/kg bw/d)**	**Developmental NOAEL/ NOAEL (mg/kg bw/d)**
2 generation study via diet Fenamiphos techn Purity 88.3-89%	2 generations OECD 416	Rat, CD Sprague Dawley 30/sex/dose	0.17, 0.64, or 2.8 mg/kg bw/day for males and for females 0.20, 0.73, or 3.2 mg/kg bw/day in the premating period, 0.17, 0.64, and 2.82 mg/kg bw/day in the gestation period and 0.39, 1.48, 5.85 mg/kg bw/day in the lactation period	NOAEL: 0.17 LOAEL: 0.64	NOAEL: 0.64 LOAEL: 2.8
Teratogenicity study by gavage SRA 38886 Purity 92.5%	Gestation period No OECD	Rats, Long Evans (FB 30) 25 dams/dose	0, 0.3, 1, or 3 mg/kg bw/day on days 6-15 of gestation	NOAEL: 1 LOAEL: 3	NOAEL: 3 LOAEL: -
Teratogenicity study by gavage Nemacur Purity 88.7%	Gestation period Main acc OECD 414	Rat, Crl:CD BR 33 dams/dose	0, 0.25, 0.85, 3 mg/kg bw/day on days 6-15 of gestation	NOAEL: 0.25 LOAEL: 0.85	NOAEL: 0.85 LOAEL: 3
Teratogenicity	Gestation period	Rabbit, NZW	0, 0.1, 0.3, 1 mg/kg	NOAEL: 0.1	NOAEL: 0.3

Study type/Route/ Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	Maternal LOAEL/ NOAEL (mg/kg bw/d)	Developmental NOAEL/ NOAEL (mg/kg bw/d)
study by gavage Nemacur Purity 88.8%	No OECD	20 dams/dose	bw/day on days 6-18 of gestation	LOAEL: 0.3	LOAEL: 1
Teratogenicity study by gavage* SRA 38886 Purity 91%	Gestation period OECD 414	Rabbit, Chinchilla 16 dams/dose	0, 0.1, 0.5, 2.5 mg/kg bw/day on days 6-18 of gestation	NOAEL: 0.5 LOAEL: 0.3	NOAEL: 0.5 LOAEL: 1

* supportive study only

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

In a 2 generation study in rats, although ovarian weight was reduced in F0 females, this was unaffected in F1 females, except for a 9% decrease in absolute ovaries weight at the top dose. In addition, no effects were observed on oestrous cycles, mating, fertility, and gestation indices. It is therefore concluded that fenamiphos does not affect fertility. Classification is thus not necessary.

In three acceptable teratogenicity studies in rats and rabbits, teratogenic effects were not observed. In rat pups, an increase in hyoid body variations was observed, although this was not dose-related and within the laboratory historical control range. Only at the highest dose, the effects were considered toxicologically relevant, however, at this dose maternal toxicity was also observed. In rabbits, skeletal anomalies were found, as well as a slight decrease in foetal pup weight, but again at maternal toxic doses only. In addition, in the 2 generation study in rats, body weight gain of the pups (F1 and F2) was reduced at maternal toxic doses. Furthermore, erythrocyte ChE activity was reduced in F1 and F2 animals at the top dose.

In conclusion, although some toxic effects on development were observed, this was always at a dose that also caused maternal toxicity and therefore probably due to the maternal toxicity. Classification is not needed.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of report.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

According to the results of the tests on explosive properties (EEC Method A14) with the technical active substance (purity 95.4%), fenamiphos is not explosive (Eberz, 1999) (DAR B.2.1.22 (IIA 2.13)). Therefore, it can be concluded that fenamiphos has no explosive properties and does not require classification for explosivity.

6.2 Flammability

According to the results of the tests for flammability and auto-flammability (EEC Method A10 and EEC Method A16) with the technical active substance (purity 95.4%), fenamiphos is not highly flammable and is not undergoing spontaneous combustion (Eberz, 1999) (DAR B.2.1.20 (IIA 2.11)). Therefore, classification for flammability is not required.

6.3 Oxidising potential

According to the results of the tests for oxidising properties (EEC Method A17) with the technical active substance (purity 95.4%), fenamiphos has no oxidising properties and does not require classification (Eberz, 1999) (DAR B.2.1.23 (IIA 2.15)).

7 ENVIRONMENTAL HAZARD ASSESSMENT

ECHA's Committee for Risk Assessment (RAC) has developed this opinion after entry into force of the 2nd ATP to Regulation EC 1272/2008 in March 2011. On request of the Commission the RAC has scrutinised decisive information on environmental hazard assessment, focusing only on necessary amendments for classification according to the criteria introduced by the 2nd ATP.

As there is already an existing Annex VI entry for the environmental hazard classification of fenamiphos (table 3.1: H400, H410, M=100; table 3.2: N;R50-53, SCL: C ≥ 0.25% N;R50-53 / 0.025% ≤ C <0.25% N;R51-53 / 0.0025% ≤ C <0.025% R52-53), the dossier provided the data on environmental hazard just for information, and no comments during public consultation referred to this hazard class and its underlying information.

The submitted dossier provides only sparse information about the aquatic toxicity tests with fenamiphos, far from comparable to the standard requirement of robust study summaries (RSS). Therefore RAC consulted the original study reports from the two decisive studies, namely the acute daphnia test denoted as Irvita Study R-18525 (2005), and the 21d chronic daphnia study under flow-through conditions identified as Surprenant Study 98431 (1988), as described in section 7.1.1.2.

While the complete presented information apparently justifies the existing hazard classification, RAC applied particular scrutiny to the aforementioned studies for verifying adequate M-factors and the chronic hazard category in accordance with the new criteria of the 2nd ATP to Regulation EC 1272/2008.

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

Only reliable and validated ecotoxicity tests accepted for risk assessment from Draft Assessment Reports were used.

7.1.1.1 Fish

Short-term toxicity to fish

The acute toxicity of fenamiphos and metabolites to fish are summarised in Table 7.1. The lowest 96-h LC50 for mortality for fish (*Lepomis macrochirus)* was 0.0093 mg/L. The toxicity of metabolites in fish is lower than that of the parent compound.

Table 7.1 The acute toxicity to fish.

Fenamiphos						
Substance	**Species**	**Method**	**Purity (%)**	**Duration [h]**	**LC50 mg/L**	**Remark**
Fenamiphos	*Lepomis macrochirus*	Static	96.2	96	0.0093	EPA 721-1; OECD 203
Fenamiphos technical grade	*Cyprinodon variegates*	Flow-through	88.7	96	0.017	
Fenamiphos-metabolites						
Substance	**Species**	**Method**	**Purity (%)**	**Duration [h]**	**LC50 mg/L**	**Remark**
Fenamiphos-sulfoxide-phenol	*Onchorhynchus mykiss*	Static		96	>100	EPA
	Lepomis macrochirus	Static		96	>100	EPA

Fenamiphos-sulfone-phenol	*Onchorhynchus mykiss*	Static		96	>100	EPA
	Lepomis macrochirus	Static		96	>100	EPA

Long-term toxicity to fish

The chronic toxicity of fenamiphos technical (purity 88.7%) on early life stages of the rainbow trout was tested according to EPA guidelines. The 91-days NOEC for growth of 0.0038 mg/L was reported. No information is available for the chronic toxicity of the metabolites.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of fenamiphos and major metabolites are summarised in Table 7.3.

Table 7.3 The acute toxicity of fenamiphos and metabolites to aquatic invertebrates.

Fenamiphos					
Substance	**Species**	**Method**	**Duration [h]**	**EC50 mg/L**	**Remark**
Fenamiphos	*Daphnia magna*	Static	48	0.00106	OECD 202 Irvita Study R-18525
Fenamiphos-metabolites					
Substance	**Species**	**Method**	**Duration [h]**	**EC50 mg/L**	**Remark**
Fenamiphos-sulfoxide	*Daphnia magna*	Static	48	0.015	OECD 202
Fenamiphos-sulfone	*Daphnia magna*	Static	48	0.0035	OECD 202; Annex V, C2 (EEC) guidelines
Fenamiphos-sulfoxide-phenol	*Daphnia magna*	Static	48	94	OECD 202
Fenamiphos-sulfone-phenol	*Daphnia magna*	Static	48	18.2	OECD 202

The acute test with *Daphnia magna* (Irvita, 2005) has been conducted according to standard test guidelines (EU Testing Method C.2 and OECD Test Guideline 202) and in compliance with the standards of Good Laboratory Practice. Fenamiphos was tested as technical grade with 95.7% active ingredient (BD section 1.2 on substance ID states minimum purity of 920 g/kg [which should read ≥ 92% w/w]). Considering the rapid photolytic degradability of fenamiphos, the actual test was conducted in darkness. Safelight conditions were applied during media preparation and observations. At test beginning, LC-MS/MS measured concentrations ranged 74...86% of the nominal concentrations. After 48h at test termination, the measured concentrations ranged 81...91% of the initial measured concentrations, with exception of the medium level treatment (65% of initial concentration, i.e. 1.15 µg/L measured for nominal 2.07 µg/L treatment). For test evaluation the measured concentration levels were expressed as geometric means.

The concentration effect curve was very steep with no effect up to 0.939 µg/L, 90% immobile animals at the next treatment level of 1.43 µg/L, and 100% immobilisation at higher test concentrations. Hence, the calculated **EC50 of 1.06 µg/L** has a quite broad 95% confidence interval, ranging 0.943...1.43 µg/L (profile likelihood method). At the first measurements after 24h test duration, the EC50 was 2.48 µg/L (95% confidence interval 2.23...3.34 µg/L), with no effect at the concentration causing 90% immobilisation after 48h test duration, thus showing a pronounced increase of fenamiphos toxicity during the course of the test.

Long-term toxicity to aquatic invertebrates

The chronic study with *Daphnia magna* (Surprenant, 1988) has been operated according to the "Protocol for Conducting a Flow-Through Life Cycle Toxicity Test with *Daphnia magna* following FIFRA Guide Lines, SLS Protocol #091087/DM-LC.FIF" and in compliance with the standards of Good Laboratory Practice. Diluter stock solutions were prepared with ^{14}C-Fenamiphos Technical (99.6% active ingredient) and acetone as solvent. Maximum acetone concentration was 24 µL/L in solvent control and highest treatment level, flow rate was approximately six aquarium volumes per 24h equalling a 90% test solution replacement rate of ca. 6h. Weekly radiometric analyses for ^{14}C-fenamiphos established proper diluter system function throughout the 21d test period and mean measured concentrations which ranged 100...114% and averaged 106% of nominal levels. Weekly HPLC analyses of the highest test concentration (0.47 µg/L nominal) rendered 0.59 µg/L (standard deviation: ± 0.086) fenamiphos, i.e. 125% of the nominal level.

Survival rates of control treatments after 21d were 95% (pooled; control 98%, solvent control 93%), well fulfilling the 80% validity criterion of OECD Test Guideline 211 (2008), whereas the cumulated numbers of 49 offspring per female (pooled; control 46, solvent control 53) did not meet the criterion of the recent guideline requirements (≥ 60 offspring per surviving parent animal). No parent animal survived in the highest treatment level (0.49 µg/L mean measured), while survival rates in all other treatment levels did not differ statistically ($P \leq 0.05$) from the control survival rates. Apart from the highest treatment level, neither reproduction was affected, yielding 49...68 offspring per parent animal in all other treatments.

The most sensitive endpoint has been growth, measured as individual body lengths. The study report stated that at 0.24 µg/L mean measured fenamiphos concentration (i.e. the highest treatment level with unaffected survival rates), the mean body length of 4.2 mm was significantly ($P \leq 0.05$) lower than in controls with a mean length of 4.6 mm (pooled; control 4.5 mm, solvent control 4.7 mm); the mean lengths in the other three treatment levels (0.032, 0.066, 0.12 µg/L) were 4.5 mm, statistically not different from the pooled controls. The study report concludes a NOEC of 0.12 µg/L (mean measured).

A statistical re-evaluation of the raw data listed in the study report reveals however the following results:

Both control and solvent control are normally distributed (Shapiro-Wilks-Test), and an F-test confirms variance homogeneity. However, a t-test reveals that the controls show significantly ($p < 0.01$) different body length means and should not be pooled. This is also confirmed by non-parametric tests as Levene-, U-, and Kruskal-Wallis- tests. Nevertheless, statistical evaluation confirms that the mean of the pooled control differs significantly from at least one of the four 0.032, 0.066, 0.12, and 0.24 µg/L treatments means (Kruskal-Wallis-Test, $p << 0.001$), and that both the 0.24 µg/L and the 0.066 µg/L treatments show significantly different body length means than the pooled control (level of significance $\alpha = 0.0125$, multiple U-test). Applying the same evaluation procedure with reference to the solvent control only, which is adequate according to statistical state-of-the-art processing, reveals that all four treatment means are significantly different ($p < 0.0125$). Hence no NOEC can be derived for body length reduction in this 21d study as the lowest treatment level differs already significantly from the solvent control. The LOEC = 0.032 µg/L.

Table: *Daphnia magna* mean body lengths [mm] of adults after 21d exposure to fenamiphos

	mean [mm]	coefficient of variation [%] (all single values)	reduction of body length compared to solvent control [%]
control	4.53	4.7	
solvent control	4.67	4.0	
[*pooled control*	*4.59*	*4.6*]	
0.032 µg/L	4.55	3.3	2.6
0.066 µg/L	4.45	3.9	4.7
0.12 µg/L	4.53	3.3	3.0
0.24 µg/L	4.24	3.5	9.2
0.49 µg/L	-	note: no adults survived in this treatment level	

During its further discussion RAC concluded that despite the statistical significance there is no clear concentration-response relation and the biological relevance of the body length reductions below 5 % is not sufficient for classification purposes, and the 9.2 % reduction at 0.24 µg/L is borderline. With a view to the other parameters, i.e. survival (no significant effect up to 0.24 µg/L, 100% mortality at 0.49 µg/L) and reproduction (no significant effect up to 0.24 µg/L; for the 0.49 µg/L treatment, the percentage of reduction could not be calculated as 'cumulated offspring per surviving female' due to the 100% mortality of parent animals), some uncertainty remains about the precise effect threshold. However RAC concludes that for classification purposes it is sufficient to confirm the evidence for this threshold being above 0.12 µg/L and below 0.49 µg/L.

7.1.1.3 Algae and aquatic plants

The toxicity of fenamiphos and metabolites to algae are summarised in Table 7.4. The lowest EC_{50} for growth to algae (*Scenedesmus subspicatus)* for fenamiphos was 11.90 mg/L. Fenamiphos is more toxic to algae than the metabolites.

Table 7.4 The chronic toxicity of fenamiphos and fenamiphos-metabolites to algae.

Fenamiphos								
Substance	**Species**	**Method**	**Duration [h]**	**EC_b50 mg/L**	**NOE_bC mg/L**	**EC_r50 mg/L**	**NOE_rC mg/L**	**Remark**
Fenamiphos technical grade	*Scenedesmus subspicatus*	Static	96	3.8	0.35	11.90	1.10	OECD 201
Fenamiphos-metabolites								
Substance	**Species**	**Method**	**Duration [h]**	**EC_b50 mg/L**	**NOE_bC mg/L**	**EC_r50 mg/L**	**NOE_rC mg/L**	**Remark**
Fenamiphos-sulfoxide	*Scenedesmus subspicatus*	Static	96	> 100	10	> 100	> 100	OECD 201; ISO N84
Fenamiphos-sulfone	*Scenedesmus subspicatus*	Static	96	25.0	10	45.7	18	OECD 201; ISO N84

7.1.1.4 Sediment organisms

Based on nominal concentrations in water phase.

The toxicity of fenamiphos and fenamiphos-sulfoxide to *Chironomus riparius* was tested in a static system for 28 days, in accordance with the BBA proposal of 1995 and draft OECD guideline 219. The results are summarised in Table 7.5.

Table 7.5 The chronic toxicity of fenamiphos and fenamiphos sulfoxide to sediment organisms.

Fenamiphos							
Substance	**Species**	**Method**	**Duration [days]**	**EC_{50ER*} mg/L**	**$NOEC_{ER}$ mg/L**	**$NOEC_{DR**}$ mg/L**	**Remark**
Fenamiphos technical grade	*Chironomus riparius*	Static	28	0.020	0.01	> 0.02	OECD 219: BBA proposal
Fenamiphos-metabolites							
Substance	**Species**	**Method**	**Duration [days]**	**EC_{50ER*} mg/L**	**$NOEC_{ER}$ mg/L**	**$NOEC_{DR**}$ mg/L**	**Remark**
Fenamiphos-sulfoxide	*Chironomus riparius*	Static	48	0.095	0.058	0.058	OECD 219; BBA proposal

*ER = emergence rate; **DR = development rate

The chronic toxicity of fenamiphos and fenamiphos sulfoxide to sediment organisms.

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of report.

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

7.2.1.2 Toxicity to terrestrial plants

7.2.1.3 Toxicity to soil micro-organisms

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Toxicity to other above ground organisms

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Not relevant for this type of report.

7.3 Atmospheric compartment

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

7.4.2 PNEC for sewage treatment plant

Not relevant for this type of report.

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

Not relevant for this type of report.

7.6 Conclusion on the environmental classification and labelling

Conclusion of environmental classification according to Annex VI to 67/548/EEC

In an acute toxicity studies for both aquatic invertebrates and fish L(E)C_{50}s at concentrations below ≤ 1 mg/L were obtained. Based on studies performed with water/sediment systems and soil fenamiphos appears to be susceptible for primary degradation. The degradation products are however still toxic and therefore classifiable. Fenamiphos has a BCF of 110 and as consequence does fulfil the criteria for bioaccumulation. Based on these findings fenamiphos should be classified with N; 50/53.

Based on the toxicity data for *Daphnia magna* (EC50 0.00106 mg/L) the following specific concentration limits should be applied:

Concentration	Classification
C≥0.25%	N;R50-53
0.025%≤C<0.25%	N;R51-53
0.0025%≤C<0.025%	R52-53

where C is the concentration of fenamiphos in the preparation.

Conclusion of environmental classification according to Regulation EC 1272/2008

In acute toxicity studies for both aquatic invertebrates and fish L(E)C_{50}s at concentrations below ≤ 1 mg/L were obtained. Based on studies performed with water/sediment systems and soil fenamiphos appears to be susceptible for primary degradation. The degradation products are however still toxic and therefore classifiable. Fenamiphos has a BCF of 110 and as consequence does not fulfil the criteria for bioaccumulation. Based on these findings fenamiphos should be classified with the aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410. However, according to Article 27 of CLP and the guidance on regulation EC 1272/2008 (4.1.6), where the hazard statement H410 is used on the label due to classification into Chronic hazard category 1, the hazard statement H400 shall not appear on the label.

Based on the toxicity data for Daphnia magna (EC50 0.00106 mg/L) the M-factor is 100.

Conclusions according to 2nd ATP

The existing Annex VI entry is based on the main facts that fenamiphos is not rapidly degradable according to classification criteria and is very toxic to aquatic organisms with effect concentrations well below 1 mg/L. RAC considers the reported bioconcentration factor (BCF) value equivocal as it is based on radiolabel and hence potentially overestimated, and as no specifications on lipid normalisation are reported. However, the BCF is not decisive for classification under 2nd ATP criteria, as chronic data for all three trophic levels (fish, crustaceans, algae) are available. The 2nd ATP introduced independent application of the acute and chronic classification categories with additional criteria for long-term effects, and requires indicating appropriate M-factors for both classification categories 1.

Acute Category 1 requires the lowest LC50 or EC50 from all three tested trophic levels to be ≤ 1 mg/L. The acute *Daphnia* test with EC50 = 0.00106 mg/L confirms this hazard category. Regarding selection of an appropriate M-factor, this value is very close to the decision criterion 0.001 mg/L and RAC notes the broad 95% confidence interval, the particular analytical deviation just in the key concentration range adding further uncertainty to the steep regression curve, and the pronounced toxicity increase from 24h to 48h test duration. However, based on 0.001 < 0.00106 ≤ 0.01 mg/L, **M = 100**.

Chronic Category 1 requires the lowest NOEC from long-term tests with all three trophic levels to be ≤ 0.1 mg/L for not rapidly degradable substances. The 21d *Daphnia* test with effect thresholds well below 1 µg/L thus confirms hazard category Chronic 1, and for 0.0001 < NOEC ≤ 0.001 mg/L a corresponding **M = 100**.

Under DSD criteria, the basis for the acute M-factor above corresponds to SCL (specific concentration limits) as follows:

Concentration	Classification
C≥0.25%	N; R50-53
0.025%≤C<0.25%	N; R51-53
0.0025%≤C<0.025%	R52-53

where C is the concentration of fenamiphos in the preparation.

This SCL compilation matches the existing entry as in table 3.2 of Annex VI to CLP Regulation EC 1272/2008.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Fenamiphos is an active substance in the meaning of Directive 91/414/EEC and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008 article 36.2).

A corresponding discussion took place at the TC C&L in November 2006 (Summary record ECB/20/07). The TC C&L discussion was only related to acute toxicity and eye irritation. TC C&L agreed to additionally classify fenamiphos as to acute toxicity and eye irritation. Information is available demonstrating the need to revise the existing Annex VI entry (Regulation EC 1272/2008, article 37.1). This includes 2 acute oral studies, 2 acute inhalation studies and 1 acute dermal study, all in rats, as well as an eye irritation study in rabbits.

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of the active substance fenamiphos according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR and the addendum to the DAR. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR and its addenda.

REFERENCES

European Commission. Draft Assessment Report Fenamiphos, prepared by The Netherlands, November 2003.

European Commission. Draft Assessment Report Fenamiphos, prepared by The Netherlands, final addendum of December 2005.

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The chronic toxicity of fenamiphos to *Daphnia Magna* under flow-through conditions, Surprenant, D. C. (29-11-1988), Springborn Life Sciences, Inc. USA, report # 98432, study #274.1287.6168.130.

ANNEX 1

Conclusions of the discussion from the TC-C&L in November 2006 (Summary record ECB/20/07).

Fenamiphos (NL) P239

(Index No: 015-123-00-5, CAS No: 22224-92-6, EC No: 244-848-1)

Current classification in Annex I(29th ATP): T+; R28 - T; R24 - N; R50-53

Proposal: [T+; R26/28 - T; R24 - Xi; R36 -] N; R50/53

ECBI/80/06: Classification proposal from NL

Acute toxicity

The new classification suggested by **NL** with T+; R26 was supported by **BE**, **IRL** and **ES** in written prior the meeting.

NL informed that R26 was based on new study and there was not very much to discuss.

The **TC C&L** agreed to the NL proposal to classify T+; R26 and confirmed the current classification for the other routes of exposure for acute toxicity, i.e. the resulting recommendation from the group was T+; R26/28 – T; R24.

Irritancy

The **NL** expert explained that the classification with Xi; R36 was a borderline for so they were interested to hear other Member States' opinion on this end-points. A score grade 1 was seen in 6 out of 6 rabbits at 24 and 48 hours and in 5 out of 6 animals at 72 hours. The score was 0 in 1 out of 6 animals at 72 hours. The average score over 24, 48 and 72 hours is 0.94 which is just below the limit for classification. However, Annex VI states that classification is warranted when a substance causes significant ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours. In this case, significant ocular lesions (iris lesions equal to 1) occurred within 72 hours after exposure and persisted for at least 24 hours (observations at 24 and 48 hours). Therefore, they considered the criteria to be fulfilled.

DK agreed that as the effect was not reversible during the time period tested they also supported classification.

DE agreed to the others that it was a borderline case, but also in their opinion classification should be applied.

EL, SE and N also explicitly agreed to classification on the same argumentation.

TC C&L thereby agreed to recommend classification with Xi; R36.

IND asked about normal handling and use consideration based on the uses indicated in the dossier.

EL replied that this was hazard assessment, so in this case there was no space for the consideration of the use listed in Annex I to Directive 91/414.

Conclusion:

TC C&L agreed to classify Fenamiphos in accordance with the NL proposal, i.e. with **T+; R26/28 - T; R24 - Xi; R36 - N; R50/53** and Specific Concentration Limits for Environmental effects with M=100. The resulting labelling would then be with the symbols: T+, N, the R-phrases: 24-26/28-36-50/53 and the S-phrases: (1/2-)23-28-36/37-45.