CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Etofenprox

EC Number: **407-980-2**

CAS Number: **80844-07-1**

Index Number:

Contact details for dossier submitter:

Umweltbundesamt GmbH

on behalf of

AT Competent Authority

Federal Ministry of Agriculture, Forestry, Environment and Water Management

Version number: 3 **Date: 22. Dec. 2011**

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Etofenprox;*** ***2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether***
EC number:	***407-980-2***
CAS number:	***80844-07-1***
Annex VI Index number:	***n.a.***
Degree of purity:	***min. 970 g/kg***
Impurities:	The manufacturer has requested that all impurities remain confidential since it may provide an indication on the possible method of manufacturing. Information on impurities is provided in the confidential Annex.

The minimum degree of purity has been derived from the results of a 5-batch-analysis. The concentrations of Etofenprox measured in this study lay in the range of 97.2 to 99.0 % (w/w). After discussion at the Biocides Technical Meeting the experts agreed upon 97.0 % (w/w) as minimum purity.

1.2 Harmonised classification and labelling proposal

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

	CLP Regulation (including criteria according to 2nd	**Directive 67/548/EEC (Dangerous Substances Directive;**

	ATP of CLP)	**DSD)**
Current entry in Annex VI, CLP Regulation	Not currently in Annex VI, table 3.1 of the CLP Regulation	Not currently in Annex VI, table 3.2 of the CLP Regulation
Current proposal for consideration by RAC	STOT Rep. Exp.2; H373 - May cause damage to organs (liver, kidney) H362 – May cause harm to breast-fed children Aquatic acute 1 (M=100) Aquatic chronic 1 (M=1000) H400 – Very toxic to aquatic life H410 – Very toxic to aquatic life with long lasting effects	N; Dangerous for the environment R50-53 SCL: N; R50-53: $C_n \geq 0.25\%$; N; R51-53: $0.025\% \leq C_n < 0.25\%$; R52-53: $0.0025\% \leq C_n < 0.025\%$
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	STOT Rep. Exp.2; H373 - May cause damage to organs (liver, kidney) H362 – May cause harm to breast-fed children Aquatic acute 1 (M=100) Aquatic chronic 1 (M=1000) H400 – Very toxic to aquatic life H410 – Very toxic to aquatic life with long lasting effects	N; Dangerous for the environment R50-53 SCL: N; R50-53: $C_n \geq 0.25\%$; N, R51-53: $0.025\% \leq C_n < 0.25\%$; R52-53: $0.0025\% \leq C_n < 0.025\%$

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

Table 3: Proposed classification according to the CLP Regulation (including criteria according to 2nd ATP of CLP)

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	n.a.	n.a.	currently not classified	data lacking
2.3.	Flammable aerosols	n.a.	n.a.	currently not classified	data lacking
2.4.	Oxidising gases	n.a.	n.a.	currently not classified	data lacking
2.5.	Gases under pressure	n.a.	n.a.	currently not classified	data lacking
2.6.	Flammable liquids	n.a.	n.a.	currently not classified	data lacking
2.7.	Flammable solids	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	n.a.	n.a.	currently not classified	data lacking
2.10.	Pyrophoric solids	n.a.	n.a.	currently not classified	data lacking
2.11.	Self-heating substances and mixtures	n.a.	n.a.	currently not classified	data lacking
2.12.	Substances and mixtures	n.a.	n.a.	currently not	conclusive but not

	which in contact with water emit flammable gases			classified	sufficient for classification
2.13.	Oxidising liquids	n.a.	n.a.	currently not classified	data lacking
2.14.	Oxidising solids	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.15.	Organic peroxides	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	n.a.	n.a.	currently not classified	data lacking
3.1.	Acute toxicity - oral	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
	Acute toxicity - dermal	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	n.a.	n.a.	currently not classified	data lacking
3.4.	Skin sensitisation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for

					classification
3.6.	Carcinogenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	STOT Rep. Exp. 2 H373: May cause damage to organs <or state all organs affected, if known> through prolonged or repeated exposure <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>.	n.a.	currently not classified	
3.10.	Aspiration hazard	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.11.	Risk for breast fed babies	H362 – May cause harm to breast-fed children	n.a.	currently not classified	n.a.
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1 H400: Very toxic to aquatic life Aquatic Chronic 1 H410: Very toxic to aquatic life with long lasting effects.	M=100 M=1000	currently not classified	

5.1.	Hazardous to the ozone layer	n.a.	n.a.	currently not classified	data lacking

[1)] Including specific concentration limits (SCLs) and M-factors

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

Labelling: (Including criteria according to 2nd ATP of CLP)

GHS Pictograms:

Signal word: Warning

Hazard statements:

H362 – May cause harm to breast-fed children

H373 - May cause damage to organs (liver, kidney)

H410 – Very toxic to aquatic life with long lasting effects

Precautionary statements:

P201 - Obtain special instructions before use.

P260 - Do not breathe dust/fume/gas/mist/vapours/spray.

P263 - Avoid contact during pregnancy/while nursing.

P264 - Wash thoroughly after handling

P270 - Do not eat, drink or smoke when using this product

P273 – Avoid release to the environment

P308 + 313 - IF exposed or concerned: Get medical advice/attention

P314 - Get medical advice/attention if you feel unwell.

P391 – Collect spillage

P501 - Dispose of contents/container in accordance with local/regional/ national/international regulation (to be specified).

Proposed notes assigned to an entry: none

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Oxidising properties	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Flammability	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Thermal stability	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Acute toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Repeated dose toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Irritation / Corrosion	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Sensitisation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Carcinogenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification

Toxicity to reproduction – development	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Environment	N; R50-53 Dangerous for the environment; Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	SCL: N; R50-53: $C_n \geq 0.25\%$; N; R51-53: $0.025\% \leq C_n < 0.25\%$; R52-53: $0.0025\% \leq C_n < 0.025\%$;	currently not classified	n.a.

[1] Including SCLs

[2] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Labelling symbol:

Indication of danger:

N - dangerous for the environment

R-phrases:

R50/53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases:

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

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

There is no current classification for Etofenprox according to Annex I of Council Directive 67/548/EEC.

No REACH registration dossier was available for this substance until 23 September 2011.

2.2 Short summary of the scientific justification for the CLH proposal

Human toxicology:

STOT RE, category 2, H373 - May cause damage to organs (liver, kidney): Weight of Evidence evaluation: Classification for H373 is required in case subchronic NOAELs are between 10 and 100 mg/kg bw day. Due to large dosing step in the 90 day rat study the respective LOAEL of 120 mg/kg bw day (liver histology, weight, disfunction) may be well below 100 mg/kg bw (NOAEL at 20 mg/kg bw day). The maternal LOAEL of the developmental neurotoxicity study is with 79 mg/kg bw/day below 100 (transient retardation of gestation weight gain by 14% from day 6 to 10). The LOAEL in the 2-year rat study at 26 mg/kg bw day (liver histopathology effects) and in the 2-year mouse study at 10 mg/kg bw day (kidney histopathology effects) are well below 100 mg/kg bw day, also if multiplied by 2 for accounting the longer exposure duration.

H362 – May cause harm to breast-fed children: Potential for accumulation in fat and haemorrhage effect in lactated rats observed in reproduction toxicity studies. However the observed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight

(No classification for R48/20/21/22 (Danger of serious damage to health by prolonged exposure), is proposed since the guidance value for R48/20/21/22 is 50 mg/kg bw day, which is lower compared to the guidance value of 100 mg/kg bw day for H373, and consequently the overall weight of evidence summarized below in 1.5.3. does not appear sufficient for classification with R48/20/21/22.

No classification for R64 (May cause harm to breastfeed babies) is proposed, since R64 may only be applied in addition to other human health R phrases. No other human health R phrases are applicable.)

<u>Environment:</u>

Acute aquatic toxicity: L(E)C_{50} values: 0.01 – 0.001 mg/L; lowest EC_{50} value (daphnia) =0.0012 mg/L

Chronic aquatic toxicity: NOEC values: 0.01 – 0.00001 mg/L; lowest chronic NOEC (daphnia) =0.000054 mg/L;

Fate & behaviour: not rapidly degradable; logP_{ow} =6.9; BCF >1000

According to the above cited data it is proposed

- To classify the substance with Aquatic Acute 1, M factor =100, since the lowest EC_{50} value =0.0012 mg/L.
- To classify the substance with Aquatic Chronic 1, M factor =1000, since the substance is not rapidly degradable and the lowest chronic NOEC value =0.000054 mg/L.
- To classify the substance with N;R50/53 and to apply SCLs, because all acute L(E)C_{50} values < 1 mg/L and the substance is not readily biodegradable with a log P_{ow} =6.9 and a BCF =2565.

2.3 Current harmonised classification and labelling

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

No current classification and labelling

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

No current classification and labelling

2.4 Current self-classification and labelling

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

No current self-classification and labelling

2.4.2 Current self-classification and labelling based on DSD criteria

Hazard symbol: N

Indication of danger: Dangerous for the environment

Labelling symbol:

Risk phrases: R50/53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Safety phrases: S2 Keep out of the reach of children

S13 Keep away from food, drink and animal feedingstuffs

S27/28 After contact with skin, take off immediately all contaminated clothing, and wash immediately with plenty of water.

S36/37/39 Wear suitable protective clothing, gloves and eye/face protection

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Biocides: No need for justification.

Also conclusion for non-classification for the various endpoints is of utmost importance for European harmonisation. RMS proposals for classification and non-classification were not discussed in detail within the European Biocides Technical Meetings.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

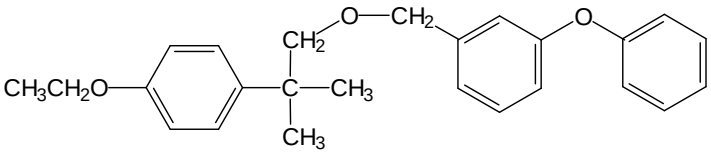
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	407-980-2
EC name:	3-phenoxybenzyl-2-(4-ethoxyphenyl)-2-methylpropyl ether
CAS number (EC inventory):	not attributed
CAS number:	80844-07-1
CAS name:	Benzene, 1-[[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl]-3-phenoxy
IUPAC name:	2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether
CLP Annex VI Index number:	not applicable
Molecular formula:	$C_{25}H_{28}O_3$
Molecular weight range:	376.47 g/mol

Structural formula:



1.2 Composition of the substance

See confidential Annex. (concerns Table 6-8)

Current Annex VI entry: No current Annex VI entry.

1.2.1 Composition of test material

See confidential Annex.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Result	Method	Reference
Melting point	37.4 ± 0.1°C	OECD 102; EEC A.1	Tognucci, 1999
Boiling point	not determinable, degradation at about 200°C	OECD 103; EEC A.2	Tognucci, 1998a
Density	1.172 g/cm^3 at 20.7°C ± 0.1°C	OECD 109; EEC A.3	Tognucci, 1998b
Vapour pressure	8.13 x 10^{-7} Pa at 25°C 2.16 x 10^{-3} Pa at 80°C 7.01 x 10^{-3} Pa at 90°C	OECD 104; EEC A.4	Tognucci, 2000
Henry's Law Constant	0.0136 Pa x m^3/mol at 25°C	calculation	Tognucci, 2000
Physical state	thermodynamically stable state: crystalline solid; metastable state: supercooled liquid		Shimono, 2002a Mirbach, 2006
Physical state	solid (pure) or liquid (manufactured)		Shimono, 2002a
Colour	white (pure) or amber (man.)		Shimono, 2002b
Odour	slight aromatic odour (pure) or aromatic odour (manufactured)		Shimono, 2002c
Absorption spectra	- UV/VIS absorption spectra: similar at pH values from 1 to 12; absorption maximum at 273 nm. - IR, ^{1}H, ^{13}C-NMR and mass spectra in agreement with proposed structure.	OECD 101	Tognucci, 1998c

Solubility in water:	- bidistilled water: 22.5 µg/l - buffer at pH 4: 5.2 µg/l - buffer at pH 9: 12.0 µg/l (measured at 20 ± 0.5°C) Solubility estimated to increase by ca. 4.9%/ °C	OECD 105; EEC A.6	Kunz, 2000 Mirbach, 2004a
Dissociation constant:	not applicable: etofenprox has no sites which can either be protonated or dissociate at pH 3 to 10 (expert statement)		Schmiedel, 1998
Solubility in organic solvents:	- Methanol: 4.9 g/100ml - Ethanol: 9.8 g/100ml - Acetone: 87.7 g/100ml - Ethylacetate: 83.7 g/100ml - Hexane: 66.7 g/100ml - Heptane: 62.1 g/100ml - Xylene: 85.6 g/100ml - Toluene: 86.2 g/100ml - Dichloromethane: 92.4 g/100ml (measured at 20°C ± 1°C) Solubility estimated to increase by ca. 4.9%/ °C	OECD 105	Tognucci, 1998d Mirbach, 2004a
Partition coefficient n-octanol/water:	Log P_{OW} = 6.9 / Log Pow estimated to increase by ca. 1%/ °C	OECD 107 and 117; EEC A.8	Tognucci, 1998e Mirbach, 2004b
Thermal stability:	no decomposition up to 150°C	OECD 113	Tognucci, 1998f

Flammability:	not flammable; no auto-flammability up to the melting point	EEC A.10 EEC A.16	Dublaski, 1991a; Dublaski, 1991b
Flash point:	no flash recorded at temperatures up to 110°C	EEC A.9	Bates, 2001a
Surface tension:	90% aqueous solution: 68.12 mN/m at 20.1°C	EEC A.5	Dublaski, 1991c
Viscosity:	not applicable		
Explosive properties:	not explosive	EEC A.14	Bates, 2001b
Oxidising properties:	not oxidising	EEC A.17	Bates, 2001c

2 MANUFACTURE AND USES

2.1 Manufacture

Biocides: Does not need to be specified for the CLH proposal.

2.2 Identified uses

Product type 08: Wood preservatives

Product type 18: Insecticides

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Property	Result	Method	Reference
Thermal stability:	no decomposition up to 150°C	OECD 113	Tognucci, 1998f
Flammability:	not flammable; no auto-flammability up to the melting point	EEC A.10 EEC A.16	Dublaski, 1991a; Dublaski, 1991b
Flash point:	no flash recorded at temperatures up to 110°C	EEC A.9	Bates, 2001a
Explosive properties:	not explosive	EEC A.14	Bates, 2001b
Oxidising properties:	not oxidising	EEC A.17	Bates, 2001c

1.1 *[Insert hazard class when relevant and repeat section if needed]*

No classification is proposed based on available data.

1.1.1 Summary and discussion of *[Insert physic-chemical hazard class]*

No classification is proposed based on available data.

1.1.2 Comparison with criteria

No classification is proposed based on available data.

1.1.3 Conclusions on classification and labelling

No classification is proposed based on available data.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

A comprehensive evaluation of the absorption, distribution, metabolism and excretion of [^{14}C]-etofenprox has been performed in young adult male and female rats using an approximate 1:1 mixture of [1-^{14}C-propyl]-etofenprox and [α-^{14}C-benzyl]-etofenprox. Single oral doses of 30 and 180 mg/kg and multiple oral doses of 30 mg/kg were employed. Since little or no [1-^{14}C-propyl]-etofenprox and [α-^{14}C-benzyl]-etofenprox was eliminated in expired air, the main experiments were performed without the collection of expired air. Further studies were performed in pregnant and lactating females to evaluate the placental and milk transfer of single oral doses of 30mg/kg etofenprox. The metabolism of [^{14}C]-etofenprox has also been investigated in the dog. An investigative study was also performed to determine if the plant metabolite, 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate (α-CO), was formed *in vivo* by the rat.

Hawkins *et al.* (1985a, document IIIA 6.2/01) demonstrated that single oral dose levels of 30 and 180mg/kg etofenprox are extensively absorbed from the gastrointestinal tract of male and female rats. A minimum of 54.1 and 53.3% administered dose is absorbed at 30mg/kg and 45.8 and 38.1% administered dose at 180mg/kg, in males and females, respectively. Maximum mean plasma concentrations (5.20 / 5.03 μg equiv/mL at 30 mg/kg, 17.3 / 16.4 μg equiv/mL at 180 mg/kg) occur 3 to 5 hours post-treatment in both sexes at both dose levels. The ratios of AUC values for a dose interval of 6 are 3.3 and 3.8 in males and females, respectively. Excretion proceeds rapidly, predominantly via the feces, and is almost complete within 5 days of administration. Fecal excretion amounts to 86.4 - 90.4% dose, whereas urinary elimination amounts to 6.3 - 10.7% administered dose in both sexes at both 30 and 180 mg/kg (see table 3.1.). The bulk of fecal elimination occurs within 72 hours of administration. Tissue distribution is extensive after multiple low doses but brain levels are uniformly low relative to blood plasma concentration. Tissue concentrations peak 4 hours after the last of 7 daily doses, and are highest in fat (94.2 - 101μg equiv/g), adrenal glands (41.4 - 43.4 μg equiv/g), liver (22.3 - 30.5 μg equiv/g), ovaries (23.9 μg equiv/g), and thyroid gland (12.9 - 18.7 μg equiv/g). All other tissues, except for GI tract, showed maximum tissue concentrations ≤ 8.84 μg equiv/g compared with plasma concentrations of 5.39 - 6.93 μg equiv/g. Tissue concentrations decline rapidly in all tissues except fat in which concentrations at 240 hours are 25.0 - 45.2 μg equiv/g, with estimated half-lives of approximately 5 and 8.5 days in males and females, respectively. The results of qualitative whole body autoradiography (QWBA) are consistent with the quantitative findings in all tissues except pancreas. The pancreas of both sexes had relatively high concentrations of etofenprox at 4 hours post-treatment (25.1 / 30.8 μg equiv/g, in males / females), but QWBA suggested very low levels. The discrepancy between the methods of estimation is considered to reflect contamination of the pancreas samples with fat in the quantitative estimation. Etofenprox is transferred via the placenta to the fetus but placental and fetal concentrations are low relative to maternal plasma concentration and elimination from these tissues is rapid. Unchanged etofenprox is actively secreted into maternal milk and is ingested by pups producing a concentration ratio of > 20 (pup stomach contents / maternal plasma). However, transfer to milk decreases markedly on cessation of dosing.

TLC of fecal extracts from animals treated with [1-^{14}C-propyl]-etofenprox or [α-^{14}C-benzyl]-etofenprox indicated that cleavage of the etofenprox molecule is not a significant metabolic process. Unchanged etofenprox occurred at 6.6 / 14% (males / females at 30mg/kg) and 22.6 / 29.0% (males / females at 180mg/kg) administered dose 72 hours after a single oral dose. Two major metabolites of etofenprox accounting for a total of 28.7 – 38.9% administered dose are formed *in vivo* from the O-deethylation of the ethoxyphenyl moiety and by ring hydroxylation of the phenoxybenzyl moiety. Desethyletofenprox occurs at up to 25.1% and 4'-hydroxyetofenprox at up to 13.8% administered dose and are subsequently eliminated in bile and urine as glucuronide or sulphate conjugates. Other than unchanged etofenprox, none of the other components detected in fecal extracts were qualitatively identified. More than 90% of the radioactivity in fat is unchanged etofenprox, with very minor amounts of desethyletofenprox and 4'-hydroxyetofenprox. The major components in liver extracts are unchanged etofenprox, desethyletofenprox and non-mobile radioactivity considered to represent conjugates. Most of the components of urine are non-mobile during TLC but enzyme hydrolysis releases up to 1.5 and 2.0% administered dose of 2 unidentified metabolites.

Table 11a: Mean excretion of radioactivity after a single oral dose of 30 or 180mg/kg [14C]-etofenprox, and AUC values determined from the mean concentrations of radioactivity in the plasma (Hawkins et al., 1985a; main study; see document IIIA 6.2/01, Table A6_2_01-3).

Matrix	Time (hrs post-dose)	% administered dose			
		30mg/kg		180mg/kg	
		Male	Female	Male	Female
Urine	0 - 8	4.5	2.9	1.8	1.6
	8 - 24	4.3	3.6	4.3	3.0
	24 - 48	1.2	0.9	1.4	1.0
	48 - 72	0.4	0.3	0.4	0.5
	72 - 96	0.2	0.1	0.1	0.1
	96 - 120	0.1	0.1	0.1	0.1
	0 - 120	10.7	7.9	8.1	6.3
Cagewash	120	0.1	0.1	0.1	0.1
Feces	0 - 24	38.2	35.7	42.6	45.9
	24 - 48	37.7	38.4	35.1	19.1
	48 - 72	7.7	9.6	8.0	16.9
	72 - 96	3.2	1.6	2.3	7.4
	96 - 120	1.2	1.1	1.0	1.1
	0 - 120	88.0	86.4	89.0	90.4
G. I. tract[a]	120	0.5	0.6	0.4	0.5
Liver	120	0.07	0.04	0.06	0.05
Kidneys	120	0.005	0.004	0.004	0.005
Carcass	120	2.8	2.9	3.8	3.4
Total	0 - 120	102.2	97.9	101.5	100.7
AUC (µg.hr/mL)		93	83	308	315

[a] including contents

Burri (non key study: Burri 2001a) identified 4 metabolites in fecal extracts in addition to unchanged etofenprox. 2-(4-ethoxyphenyl)-2-methylpropyl 3-(4-hydroxyphenoxy)-benzyl ether (4'-OH) occurred at up to 8.84% dose, 3-phenoxybenzyl 2-(4-hydroxyphenyl)-2-methylpropyl ether (DE) at up to 9.17% dose, 3-hydroxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether (DP) at up to 4.65% dose, and 3-phenoxybenzyl alcohol (m-PB-alc) at 0.45% dose. Seven unidentified fractions at 0.10 - 1.72% dose were also apparent. Unchanged etofenprox and 2-(4-ethoxyphenyl)-2-

methylpropyl 3-phenoxybenzoate (α-CO) do not occur in urine, but 2 identified and 4 unidentified metabolites occur. The major metabolite fractions occur at 7.85% dose (unidentified), 1.36% dose (3-phenoxybenzoic acid, m-PB-acid) and 1.97% dose (unidentified). The other unidentified metabolites and 4'-OH-PB-acid occurred at up to 0.36% dose. Fourteen identified and unidentified metabolites can be separated in organic extracts of liver, in total accounting for 25.9% of liver radioactivity. Identified metabolites were DE, DP, m-PB-acid, m-PB-alc and 4'-OH-PB-acid, each of which accounted for 0.8 to 1.5% recovered dose. Nine unidentified metabolites each occurred at 0.8 to 7.1% recovered dose. Although Burri (2001a) did not detect the putative metabolite α-CO in feces, liver, fat and urine, the occurrence of 3-phenoxybenzoic acid and 3-(4-hydroxyphenoxy) benzoic acid in liver and urine suggests that α-CO may be a transient metabolite of etofenprox. Tomoda (1986, non key study) demonstrated the presence of α-CO in both faeces and urine at very low levels (0.0018 and 0.0009% administered dose, respectively), suggesting the presence of the oxidative metabolic pathway, and concluded that α-CO undergoes rapid hydrolysis to form 3-phenoxybenzoic acid (PB-acid).
Burri (non key study: Burri 2001b) demonstrated the presence of the metabolites m-PB-acid and 4'-OH-PB-acid following the dosing of labelled α-CO. These metabolites are also seen following the metabolism of etofenprox and this is taken as evidence that α-CO is a transient metabolite in the metabolism of etofenprox.

With the exception of a slightly lower degree of oral absorption at high dose levels, the biokinetics and metabolism of etofenprox in the rat are not influenced by dose level, dose regimen and sex.

Single oral doses of 30 mg/kg etofenprox are substantially, but not completely, absorbed from the GI tract of the dog (non key study: Hawkins *et. al*., 1985b). The speed of oral absorption is variable but appears to be faster in the female. It is excreted rapidly and predominantly in the feces, in which 89.5% administered dose is excreted. A mean of 86.7% of the total fecal excretion is eliminated during the first 24 hours after administration. Urinary excretion including cagewash accounts for 6.20% administered dose, most of which is eliminated during the first 24 hours. Plasma half lives are in the range 8.6 - 17 hours, assuming first order kinetics. Very high concentrations of radioactivity occur in the bile of both sexes (1036 / 815 μg equiv/g, males / females) indicating the importance of biliary excretion. The highest tissue concentrations occur in the liver (3.1 - 9.6 μg equiv/g wet weight). The rate and routes of elimination are similar in males and females. Unchanged etofenprox is the major component of feces (48.5 - 59.0% administered dose), but it does not occur in bile. Two metabolites occur in feces and bile, resulting from the O-deethylation of the ethoxyphenyl moiety and the ring-hydroxylation of the phenoxybenzyl moiety of etofenprox. In total these metabolites amount to 6.1 / 4.6% recovered dose in feces and 40.5 / 37.3% recovered dose in enzymatically hydrolysed bile, in males and females, respectively. Fat and liver contain >80% and 11 - 18% recovered dose, respectively, as unchanged etofenprox. Most of the components in liver (59 / 56% recovered dose in males / females) are polar compounds.

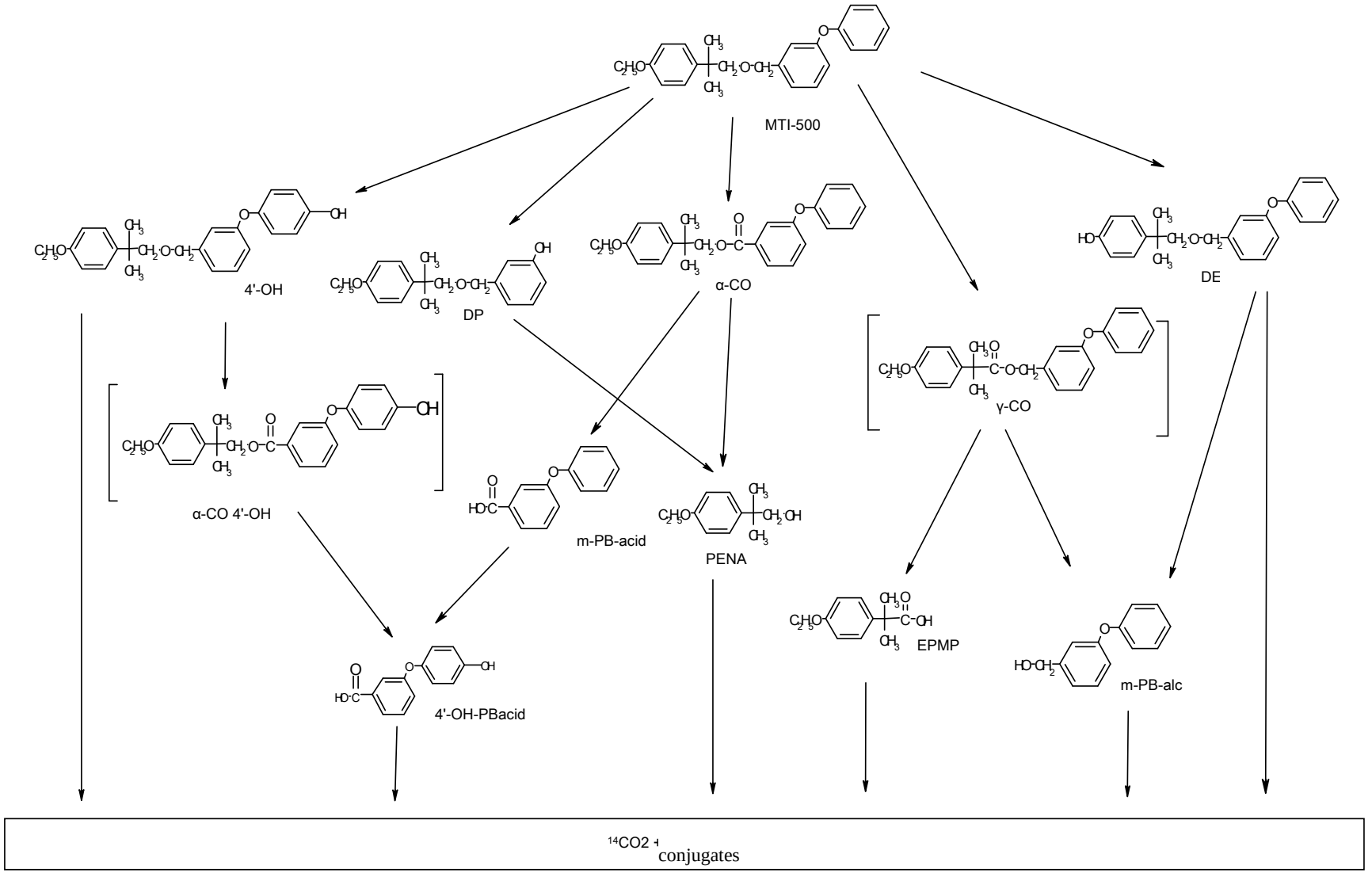
A proposed metabolic pathway in the rat is shown in Figure 3.1. (non key study: Burri et al. 2001)

An *in vivo* dermal absorption study of etofenprox has been performed in the male rat. Direct dermal absorption of etofenprox into the systemic circulation amounts to no more than 5,5% of applied doses up to 250 μg/cm^2. Indirect

absorption, representing etofenprox localized in the skin initially, accounts for a substantially greater proportion of an applied dose, but the maximum total dermal absorption (direct + indirect) amounts to ≤ 27,5% of the applied dose (Thalaker, 1999). Since the integrated direct uptake increased till the last analysed time point of 96h but the actual direct uptake starts decreasing after 38h after washing it would be in line with the guidance on dermal absorption provided by the European Commission document Sanco/222/2000 rev. 6 (November 27, 2002) to include a proportion of the indirect absorption into the direct dermal absorption value. The static levels of etofenprox in the skin (i.e. indirect absorption) from 10 hours to 96 hours suggest very limited mobilisation into the general circulation, at the most 36.9% disappearance (from 10 - 96 hours at 50 µg/cm^2) of skin localised etofenprox. Applying this to the higher indirect absorption value (22.6% - normalised value) of the 250 µg/cm^2 group gives a proportion of 8.33% of applied dose to be added to the (normalized) direct absorption of 5.5%, which amounts to 13,8% of total dermal absorption for the active substance etofenprox. However these absorption data were generated for the active substance and not for the biocidal product. Therefore the assessment of etofenprox - exposure via the product is carried out with a 100% dermal absorption rate. In order to evaluate the effect of the dermal absorption rate on the exposure, an additional calculation was performed employing a 13.8% dermal absorption rate based on the data for the active substance. For the assessment of secondary exposure to etofenprox the dermal uptake rate of 13.8% was used, since it was not expected that solvents and other ingredients will substantially influence the uptake rate of etofenprox from dry wood.

For further details please see the attached study summaries.

Proposed metabolic pathway for Etofenprox in the rat:



4.1.1 Non-human information

See chapter 4.1.

4.1.2 Human information

See chapter 4.1.

4.1.3 Summary and discussion on toxicokinetics

See chapter 4.1.

4.2 Acute toxicity

The acute toxicity of etofenprox has been evaluated using all practicable routes of human exposure that might lead to systemic exposure, and by a number of other parenteral routes. Thus, acute studies have been performed in the rat and mouse by the oral, dermal, subcutaneous and intraperitoneal routes and, in rats only, by inhalation. The acute toxicity of etofenprox has also been investigated in the dog. Since the original acute oral and dermal toxicity studies in the rat were performed more than 20 years ago before the universal adoption of Good Laboratory Practice, limit tests by these routes of administration have been performed according to the latest applicable guidelines. A summary of the acute studies is shown in Table 11b. (key studies highlighted bold).

Table 11b: Summary table of relevant acute toxicity studies

Route	Guideline	Species, strain Sex, No/group	Dose levels Duration of exposure	Result	Reference
Oral	OECD guideline no. 420 (1992) ≡ 92/69/EEC method B.1 bis	Rat, Sprague Dawley, 5 males and 5 females /group	0 and 2000 mg/kg 14 days post-exposure	**LD_{50} > 2000 mg/kg**	**Oda (2003a)** → Document IIIA 6.1.1
dermal	OECD guideline no. 402 (1987) ≡ 92/69/EEC method B.3	Rat, Sprague Dawley, 5 males and 5 females /group	0 and 2000 mg/kg 14 days post-exposure	**LD_{50} > 2000 mg/kg** [a]	**Oda (2003b)** → Document IIIA 6.1.2
Oral	In house methodology, exceeded the requirements for acute toxicity testing in 67/548/EEC	Rat, Sprague Dawley, 10 males and 10 females / group / administration route	20 and 40 mL/kg	LD_{50} > 42.88g/kg*	Hashimoto (1982a)
dermal			2 mL/kg	LD_{50} > 2.14g/kg*	
Subcutaneous			15 and 30 mL/kg	LD_{50} > 32.16g/kg*	
Intraperitoneal			20 and 40 mL/kg 14 days post-exposure	LD_{50} > 42.88g/kg	
Oral	Not applicable -	Mouse, ICR , 10 males and 10	50 and 100 mL/kg	LD_{50} > 107.2g/kg*	Hashimoto (1982b)
dermal			1 and 2 mL/kg	LD_{50} > 2.14g/kg*	

Subcutaneous	no EU regulatory requirement	females / group / administration route	25 and 50 mL/kg	LD_{50} > 53.6g/kg*	
Intraperitoneal			6.25; 12.5; 25 and 50 mL/kg	LD_{50} > 53.6g/kg (M), 13.4g/kg (F)	
			14 days post-exposure		
Inhalation	92/69/EEC (method B.3)	Rat, Sprague Dawley, 5 males and 5 females / group	0 and 5.88 mg/L 14 days post-exposure	**4-hour LC_{50} > 5.88mg/L**	**Jackson, *et al.* (1983)** → Document IIIA 6.1.3
Oral	Not applicable - no EU regulatory requirement	Dog, Beagle, 1 male and 1 female/group	5000 mg/kg 14 days post-exposure	LD_{50} > 5.0g/kg	Harling, *et al.* (1985a)

a…. value used for risk assessment

* The reviewer considers that a proportion of the oral, dermal and subcutaneous administered doses would not have been available for systemic absorption, and the LD_{50} values are lower than the specified values.

Etofenprox exhibits a very low order of acute oral and parenteral toxicity in the rat and mouse, and low acute oral toxicity in the dog. The acute oral and dermal LD_{50} values in rats of both sexes are > 2000mg/kg and no deaths or adverse clinical signs occur at the limit dose level (Oda, 2003a, 2003b). The estimated acute oral LD_{50} value in the dog is > 5000mg/kg (Harling, *et al*, 1985a). The acute 4-hour inhalation LC_{50} value in the rat is > 5.88mg/L (Jackson *et al*., 1983) for a respirable aerosol in air (95.3% of particles < 5.5μm).

For further details please see the attached study summaries.

4.2.1 Non-human information

See chapter 4.2.

4.2.2 Human information

No information available.

4.2.3 Summary and discussion of acute toxicity

See chapter 4.2.

4.2.4 Comparison with criteria

The acute oral LD50 values were above 2000 mg/kg bw, which is above the LD50 range that may lead to classification in CLP category 4 (300 to 2000 mg/kg bw) or DSD category 3 (200 to 2000 mg/kg bw).

The acute dermal LD50 values were above 2000 mg/kg bw, which is above the LD50 range that may lead to classification in CLP category 4 (1000 to 2000 mg/kg bw) or DSD category 3 (400 to 2000 mg/kg bw).

The acute inhalation LD50 values were above 5 mg/L, which is above the LD50 range that may lead to classification in CLP category 4 (dust, mist 1 to 5 mg/L) or DSD category 3 (1 to 5 mg/L).

4.2.5 Conclusions on classification and labelling

No classification necessary.

4.3 Specific target organ toxicity – single exposure (STOT SE)

No specific target organ toxicity was identified, no classification is necessary.

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

Table 12a: Summary table of relevant skin irritation studies

Species, strain Sex, No tested	**Method**	**EU index score* (Mean 24 - 72 hrs)**	**Reversibility yes/no**	**Result**	**Reference**
Rabbit, Japanese White 6 males	92/69/EEC (method B.4), 4-h exposure	0.1	yes	**Non-irritant**	**Kashima (1985a)** → Document IIIA 6.1.4.s

* EU index score = total erythema and edema score at the 24, 48 and 72hr intervals / no. of observation intervals

Table 12b Individual skin irritation and EU index scores.

Animal number	**Individual erythema / edema scores at:**				**EU index score***
	30 minutes	**24 hours**	**48 hours**	**72 hours**	
1	0 / 0	0 / 0	0 / 0	0 / 0	0.0
2	0 / 0	0 / 0	0 / 0	0 / 0	0.0

3	0 / 0	0 / 0	0 / 0	0 / 0	0.0
4	0 / 0	0 / 0	0 / 0	0 / 0	0.0
5	0 / 0	0 / 0	0 / 0	0 / 0	0.0
6	0 / 0	0 / 0	1 / 0	1 / 0	0.6
Total score (erythema + edema)	0	0	1	1	Mean (24 - 72 hrs) 0.1

* EU index score = total erythema and edema score at the 24, 48 and 72hr intervals / no. of observation intervals

For further details please see the attached study summaries.

4.4.1.2 Human information

No information available.

4.4.1.3 Summary and discussion of skin irritation

See chapter 4.4.

4.4.1.4 Comparison with criteria

Etofenprox is non-irritant to skin based on the CLP and DSD classification system, since neither the overall mean index score nor any individual score was greater than or equal to 2.3 (CLP) or 2 (DSD) and inflammation did not persist to the end of the observation period in more than one animal and no pronounced variability was observed between the test animals. Consequently, etofenprox does not require classification with regard to skin irritation according to the CLP Regulation, including the 2nd ATP and not according to DSD criteria.

4.4.1.5 Conclusions on classification and labelling

No classification necessary.

4.4.2 Eye irritation

4.4.2.1 Non-human information

Table 13a: Summary table of relevant eye irritation studies

Species, strain Sex, No tested	Method	Average Score (24 - 72hr)				Reversibility yes/no	Result	Reference
		Cornea opacity	Iris lesion	Erythema	Edema			
Rabbit, Japanese White 6 males	92/69/EEC (method B.5)	0.00	0.00	0.44	0.00	yes	**Non-irritant**	**Kashima (1985b)** → Document IIIA 6.1.4.e

Table 13b: Group mean irritation scores

	Cornea	Iris	Conjunctiva	
			erythema	edema
Score (average of animals investigated)	**0 to 4**	**0 to 2**	**0 to 3**	**0 to4**
60 min	0.00	0.00	1.00	0.17
24 h	0.00	0.00	0.83	0.00
48 h	0.00	0.00	0.50	0.00
72 h	0.00	0.00	0.00	0.00
Average 24h, 48h, 72h	0.00	0.00	0.44	0.00
Area affected	n.a.	n.a.	no data	no data
Maximum average score (including area affected, max 110)	n.a.	n.a.	no data	no data
Reversibility	n.a.	n.a.	c	c
average time for reversion	n.a.	n.a.	48-72 hr	1-24 hr

n.a.: not applicable

c:completely reversible

Table 13c: Individual irritation scores.

Observation	Time (hr) post-dose	Individual irritation scores:						Mean score
		1	2	3	4	5	6	
Corneal opacity	1	0	0	0	0	0	0	0.0
Iris lesion		0	0	0	0	0	0	0.0
Conjunctival erythema		1	1	1	1	1	1	1.0
Conjunctival edema		0	0	0	0	1	0	0.17
Corneal opacity	24	0	0	0	0	0	0	0.0

Iris lesion		0	0	0	0	0	0	0.0
Conjunctival erythema		1	0	1	1	1	1	0.83
Conjunctival edema		0	0	0	0	0	0	0.0
Corneal opacity	48	0	0	0	0	0	0	0.0
Iris lesion		0	0	0	0	0	0	0.0
Conjunctival erythema		0	0	1	1	0	1	0.50
Conjunctival edema		0	0	0	0	0	0	0.0
Corneal opacity	72	0	0	0	0	0	0	0.0
Iris lesion		0	0	0	0	0	0	0.0
Conjunctival erythema		0	0	0	0	0	0	0.0
Conjunctival edema		0	0	0	0	0	0	0.0

For further details please see the attached study summaries.

4.4.2.2 Human information

No information available.

4.4.2.3 Summary and discussion of eye irritation

See chapter 4.4.2

4.4.2.4 Comparison with criteria

Etofenprox produces transient minimal conjunctival erythema in some animals up to 48 hours after application. However, the individual and group mean irritation scores do not meet the criteria for classification as irritating to the eyes (at least in 2 of 3 animals a positive response of corneal opacity or iritis score ≥ 1 or conjunctival redness or oedema score ≥ 2 calculated as the means scores following grading at 24, 48 and 72 hours and which fully reverses within the observation period of 21 days). Therefore, etofenprox does not require classification for eye irritation according to the CLP Regulation 1272/2008, including the 2nd ATP.

The criteria for classification according to DSD are slightly higher (redness score equal to or higher than 2.5), thus etofenprox does also not fulfil the DSD criteria for eye irritation.

4.4.2.5 Conclusions on classification and labelling

No classification necessary.

4.4.3 Respiratory tract irritation

No data available.

4.5 Corrosivity

Etofenprox is not irritating and consequently also not corrosive.

4.6 Sensitisation

4.6.1 Skin sensititsation

4.6.1.1 Non-human information

Etofenrpox was negative in a guinea pig maximization test based on a zero incidence of sensitization (Kobayashi, 1985).

Table 15: Summary table of relevant skin sensitisation studies

Species, strain Sex, No tested	Method	Number of animals sensitized / total number of animals	Result	Reference
Guinea pigs, English Harley, 20 males/group	equivalent to 92/69/EEC (method B.6)	0/20	**No dermal sensitizer**	**Kobayashi, K. (1985)** → Document IIIA 6.1.5

In contrast, all 20 animals treated with DNCB (dinitrochlorobenzene) showed skin reaction grades ranging from grade 1 (mild or loosely scattered erythema) to grade 3 (severe erythema and edema) at the 24, 48 and 72-hour observation periods. Therefore, the sensitization incidence was 100% for the positive control material, DNCB, demonstrating the sensitivity of the animal strain employed to a strong skin sensitizer.

For further details please see the attached study summaries.

4.6.1.2 Human information

No information available.

4.6.1.3 Summary and discussion of skin sensitisation

See chapter 4.6.

4.6.1.4 Comparison with criteria

The guinea pig maximisation test indicates no skin sensitising properties: With intradermal induction of a 20% mixture in corn oil and Freund Adjuvance, 0 from 20 animals scored positive. The criterion indicated in the CLP Regulation table 3.4.4. for category 1B (≥ 30% response at > 1% intradermal induction dose) is not met.

The DSD criteria are less differentiated (for adjuvant test a response of at least 30% of the animals is required). However also according to the DSD criteria no classification is required.

4.6.1.5 Conclusions on classification and labelling

No classification necessary.

4.6.2 Respiratory sensitisation

No information available.

4.7 Repeated dose toxicity

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Table 17a: Summary table of relevant repeated dose toxicity studies

Study **Species / strain** **Sex, No/group** **Dose levels**	**NO(A)EL** **(mg/kg bw/day)**	**LOAEL**[b] **(mg/kg bw/day)**	**Target organs / main effects**	**Reference**
13-week dietary toxicity; Rat / Sprague-Dawley-derived rats (CD strain); 20 males and 20 females /group; 0, 50, 300, 1800, 10800ppm	**20 (males)** [a] **23 (females)**	**120** **142**	Liver, thyroid: ↓ weight gain (F), liver dysfunction (both sexes), hepatocyte enlargement (F), ↑ liver weight (both sexes), ↑ thyroid weight (M) and ↓ T4 (M). At 734/820mg/kg bw/day: ↑ thyroid microfollicles in both sexes and prolonged clotting time in males	**Green *et al.* (1983a)** → document IIIA 6.4.1.1_1
13-week dietary toxicity; Mouse / Swiss mice (CD-1 strain); 20 males and 20 females /group; 0, 50, 500, 3000, 15000ppm	375 (males) [a] 390 (females)	1975 2192	Liver, kidney, hemolymphoreticular system: ↑ mortality, ↓ weight gain, ↓ food utilisation, histopathological alterations in kidneys, liver and lymphoreticular system	Green *et al.* (1983b) document IIIA 6.4.1.1_2

[a] NOAEL considered for risk assessment

[b] lowest observed adverse effect level

For further details please see the attached study summaries.

4.7.1.2 Repeated dose toxicity: inhalation

Table 17b: Summary table of relevant repeated dose toxicity studies

Study **Species / strain** **Sex, No/group** **Dose levels**	**NO(A)EL (mg/kg bw/day)**	**LOAEL[b] (mg/kg bw/day)**	**Target organs / main effects**	**Reference**
13-week inhalation toxicity; Rat / Wistar rats (Crl:COBS WI BR strain; 15 males and 15 females /group; 0, 0.042, 0.21, 1.01mg/L	**> 0.042mg/L (both sexes)**	**0.21mg/L**	Liver, adrenals, thyroid: ↑ liver and kidney weights and minimal increase of cortical thickness in adrenals of females At 1.01mg/L: Minimal hepatocyte enlargement, minimal increase of microfollicles in thyroid and of cortical thickness in adrenals	**Coombs *et al.* (1985)** → document IIIA 6.4.3.1

[a] NOAEL considered for risk assessment

[b] lowest observed adverse effect level

For further details please see the attached study summaries.

4.7.1.3 Repeated dose toxicity: dermal

Table 17c: Summary table of relevant repeated dose toxicity studies

Study **Species / strain** **Sex, No/group** **Dose levels**	**NO(A)EL (mg/kg bw/day)**	**LOAEL[b] (mg/kg bw/day)**	**Target organs / main effects**	**Reference**
4-week dermal toxicity; Rabbit / New Zealand White; 10 males and 10 females /group; 0, 400, 650, 1000mg/kg/day	**> 1000 (both sexes)**	-	No target organs identified. Non-adverse effects: Minor, localized, reversible skin irritation	**Killeen (2000)** → document IIIA 6.3.2

[a] NOAEL considered for risk assessment

[b] lowest observed adverse effect level

For further details please see the attached study summaries.

4.7.1.4 Repeated dose toxicity: other routes

No information available.

4.7.2 Human information

No information available.

4.7.3 Other relevant information

No other relevant information available.

4.7.4 Summary and discussion of repeated dose toxicity

The short-term oral toxicity of etofenprox has been evaluated in the rat and mouse by dietary administration at concentrations up to 15000ppm for 13 weeks. The parenteral toxicity of etofenprox has been investigated in a 4-week dermal study in the rabbit at dose levels up to 1000mg/kg bw/day and in a 13-week study by inhalation in the rat at aerosol concentrations up to 1.01mg/L, the highest technically achievable concentration for 13 weeks.

The short-term oral toxicity of etofenprox has not been investigated in the dog because a 52-week study in this species is available (Harling, *et al.*, 1985b) in which the liver was identified as the only target organ. The NOEL values in this study were 33.4 / 32.2mg/kg bw/day, with LOEL values for minimal hepatic effects of 352 / 339 mg/kg bw/day in males / females, respectively. Since the short-term (13-week) and long-term (104-week) LOEL values in male and female rats were 120 / 142 and 25.5 / 34.3mg/kg bw/day, respectively, the rat is considered to be more sensitive than the dog. Furthermore, the thyroid was not identified as a target organ in the dog. A summary of the short-term toxicity studies is shown in Table 17 (key studies highlighted bold).

The liver and thyroid gland were identified as unequivocal target organs in the rat by oral administration (Green, *et al.*, 1983a). The hepatic response was characterised by hepatocyte enlargement and clinical evidence suggestive of liver dysfunction affecting fat metabolism and, in males only, the synthesis of blood clotting factors. The effect on the thyroid gland was characterised by an increase in the number of thyroid microfollicles in both sexes and reduced levels of circulating thyroxine in males. Similar histomorphological effects in the liver and thyroid occurred after inhalation administration (Coombs, *et al.*, 1985), but there was no clinical evidence of effects on blood clotting time or circulating thyroxine levels. Although adrenal gland weights were increased at the highest dose level in the 13-week oral study, there was no evidence of functional or morphological alterations. In contrast, elevated adrenal weights in the 13-week

inhalation study were accompanied by an increase in adrenal cortical thickness.

The liver was also identified as a target organ in the mouse, which exhibited a similar response to the rat, but at a substantially higher dose level. The kidneys and haemolymphoreticular system were identified as target organs in the mouse at high dose levels (Green, *et al.*, 1983b). The kidneys exhibited cortical scarring, tubular dilatation and widespread tubular basophilia, accompanied by elevated plasma urea nitrogen concentration, suggestive of renal dysfunction. Effects on the haemolymphoreticular system comprised mildly reduced RBC count, haemoglobin concentration and haematocrit values, increased cellularity of the splenic white pulp, lymph node reactivity and reduced thymic cellularity.

Dermal application of etofenprox for 28 days did not produce any evidence of systemic toxicity (Killeen, 2000). However, minor local skin irritation occurred which showed evidence of reversibility.

The lowest NOEL value in short-term toxicity tests is 20mg/kg bw/day, determined in the 13-week oral study in the male rat.

4.7.5 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

See chapter 4.10. and 4.11.

4.7.6 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

See chapter 4.10. and 4.11..

4.7.7 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No classification for R48/20/21/22 (Danger of serious damage to health by prolonged exposure), is proposed since the guidance value for R48/20/21/22 is 50 mg/kg bw day, which is lower compared to the guidance value of 100 mg/kg bw day for H373, and consequently the overall weight of evidence summarized below in 4.8 does not appear sufficient for classification with R48/20/21/22.

No classification for R64 (May cause harm to breastfeed babies) is proposed, since R64 may only be applied in addition to other human health R phrases. No other human health R phrases are applicable.

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4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

See chapter 4.8.2.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

STOT RE category 2, H373 - May cause damage to organs (liver, kidney) is proposed based on a weight of evidence evaluation: Classification for H373 is required in case subchronic NOAELs are between 10 and 100 mg/kg bw day. Due to large dosing step in the 90 day rat study the respective LOAEL of 120 mg/kg bw day (liver histology, weight, disfunction) may be well below 100 mg/kg bw (NOAEL at 20 mg/kg bw day). The maternal LOAEL of the developmental neurotoxicity study is with 79 mg/kg bw/day below 100 (transient retardation of gestation weight gain by 14% from day 6 to 10). The LOAEL in the 2-year rat study at 26 mg/kg bw day (liver histopathology effects) and in the 2-year mouse study at 10 mg/kg bw day (kidney histopathology effects) are well below 100 mg/kg bw day, also if multiplied by 2 for accounting the longer exposure duration.

H362 – May cause harm to breast-fed children: Potential for accumulation in fat and haemorrhage effect in lactated rats observed in reproduction toxicity studies. However these effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

STOT RE category 2, H373 - May cause damage to organs (liver, kidney) is proposed.

4.9 Germ cell mutagenicity (Mutagenicity)

4.9.1 Non-human information

4.9.1.1 In vitro data

Etofenprox has been evaluated in a battery of genotoxicity studies comprising *in vitro* gene mutation assays in bacterial and mammalian cells, *in vitro* and *in vivo* clastogenicity studies, and an *in vitro* unscheduled DNA synthesis assay. A summary of the test battery and results is shown in Table 18 (key studies highlighted bold).

Table 18a: Summary of genotoxicity studies on etofenprox.

Test system / Study	Concentration range or dose levels tested	Result		Reference
		+ S9	- S9	
S. typhimurium (5 strains); *In vitro* gene mutation assay	0, 0 (solvent), 200 - 3200µg/plate (± S9 in both assays)	–	–	**Edwards & Forster (1985)** → document IIIA 6.6.1
Human lymphocytes; *In vitro* cytogenicity test 24-hour exposure, substantial deviations from method (S9 activation less than 1 cell cycle; only 1 harvest time; no repeat experiment)	24-hr: 0 (solvent), 6.25 - 50µg/mL (± S9)	–	–	**Bootman, Hodson-Walker & Dance (1985a)** → document IIIA 6.6.2
Hamster V79 HGPRT$^{+/-}$ cells; *In vitro* gene mutation assay	0 (solvent), 9.75 - 156µg/mL (± S9 in both assays)	– –	– –	**Seeburg & Forster (1985a)** → document IIIA 6.6.3
HeLa S3 cells; *In vitro* UDS assay	0 (solvent), 9.75 - 156µg/mL (- S9) 0 (solvent), 2.44 – 39.0µg/mL (+ S9) in both assays	– –	– –	Seeburg & Forster (1985b)

- unequivocal negative result

For further details please see the attached study summaries.

4.9.1.2 In vivo data

Table 18b: Summary of genotoxicity studies on etofenprox.

Test system / Study	Concentration range or dose levels tested	Result	Reference
Mouse; *In vivo* micronucleus test; 24, 48, 72-hour sacrifices	24-hr: 0, 80, 400, 2000mg/kg 48-hr: 0, 2000mg/kg 72-hr: 0, 2000mg/kg	– – –	**Bootman, Hodson-Walker & Dance (1985b)** → document IIIA 6.6.4

For further details please see the attached study summaries.

4.9.2 Human information

No information available.

4.9.3 Other relevant information

No other relevant information available.

4.9.4 Summary and discussion of mutagenicity

Etofenprox does not produce gene mutations in prokaryotic (Edwards & Forster, 1985) or eukaryotic (Seeburg & Forster, 1985a) cells *in vitro*, either in the presence or absence of a mammalian metabolic activation system. It is not clastogenic in an *in vitro* cytogenetics assay in peripheral human lymphocytes (Bootman, Hodson-Walker & Dance, 1985a). Etofenprox does not influence unscheduled DNA synthesis in cultured human HeLa cells (Seeburg & Forster, 1985b) or in the *in vivo* mouse micronucleus test (Bootman, Hodson-Walker & Dance, 1985b). Despite the absence of an effect on the PCE/NCE ratio in the mouse micronucleus study, there is evidence from the tissue distribution study (Hawkins *et. al*., 1985a, unpublished report no. HRC/MTC 68/84610, document IIIA6.2.1) that a low concentration of etofenprox is widely distributed in the bone marrow after administration of 7 doses of 30mg/kg/day. Therefore, the assay is considered a valid assessment of *in vivo* clastogenic activity.

Based on the absence of genotoxicity in bacterial and mammalian point mutation assays and in an *in vivo* clastogenicity study, an *in vivo* study in germ cells is not required. It is concluded that etofenprox and metabolites do not exhibit primary genotoxic properties at the DNA, gene and chromosome levels of organization in the test systems employed.

4.9.5 Comparison with criteria

See chapter 4.9. The three standard in vitro assays and the in vivo micronucleus assay is clearly negative, no further tests are required and no classification is necessary, neither according to CLP Regulation, nor according to the DSD criteria.

4.9.6 Conclusions on classification and labelling

No classification necessary.

4.10 Carcinogenicity

4.11 Non-human information

4.12 Carcinogenicity: oral

A 52-week dietary toxicity study in the dog and chronic dietary toxicity and carcinogenicity studies of at least 104 weeks duration in the rat and mouse have been performed on etofenprox. The etiology of one specific finding in the rat study was subsequently investigated in a mechanistic study in which the effects of etofenprox on the induction of specific hepatic microsomal enzymes and their influence on pituitary-thyroid homeostasis and thyroid morphology / cytology were examined. A summary of the studies is shown in Table 19a (key studies highlighted bold).

Table 19a: Summary table of relevant carcinogenicity studies:

Study **Species / strain** **Sex, No/group** **Dose levels**	**NOEL** **(mg/kg bw/day)**	**LOAEL** **(mg/kg bw/day)**	**Target organs / main effects**	**Reference**
52-week dietary toxicity Dog / beagle 4 males and 4 females/group 0, 100, 1000, 10000 ppm	**33.4** (m) **32.2** (f) [a]	**352** **339**	Liver: Reversible minimal liver dysfunction, ↑ liver weight, minimal swelling of hepatocytes.	**Harling *et al.* (1985b)** → document IIIA 6.5.2
110-week dietary toxicity / carcinogenicity study; Sprague-Dawley-derived rats (CD strain) 50 males and 50 females/group 0, 30, 100, 700, 4900 ppm	Carcinogenicity > **187** (m) > **249** (f) Thyroid effects: **25.5 (m)** **34.3 (f)** All effects: **3.7** (m) [a] **4.8** (f)	Carcinogenicity - - Thyroid effects: **187** (m) **249** (f) All effects: **25.5** **34.3**	Liver, thyroid: At 25.2mg/kg bw/day: ↑ incidence of eosinophilic hepatocytes (males) At 187 / 249mg/kg bw/day: ↓ weight gain, ↓ food consumption, ↑ liver, kidney, thyroid weights, hepatocyte enlargement, ↑ clotting time (males), ↑ benign neoplastic alterations of thyroid	**Green *et al.* (1986a)** → document IIIA 6.5.1/01
108-week dietary toxicity / carcinogenicity study;	Carcinogenicity: >**547** (m) >**616** (f)	Carcinogenicity: - -	Liver, Kidney: Histopathological alterations in kidneys	**Green *et al.* (1986b)** → document

Swiss mice (CD1 strain) 52 males and 52 females/group 0, 30, 100, 700, 4900 ppm	<u>All effects</u>: **3.1** (m) [a] **3.6** (f)	<u>All effects</u>: **10.4** **11.7**	At 4900ppm: ↑ male mortality, ↓ weight gain, minor haematological effects, ↑ liver weight	IIIA 6.5.1/02
4-week dietary investigative study; Sprague-Dawley-derived rats (Crl:CD(SD)IGS) BR strain) 20 males and250 females/group 0, 1250, 5000, 20000 ppm	**81.2** [b] (m) **90.2** [b] (f)	**316** [c] **380** [c]	1° target organ: liver 2° target organ: thyroid ↑ microsomal protein (m); ↑ hepatic UDPGT (m/f) ↑ serum TSH (m/f) ↓ serum T4 (m) ↑ thyroid proliferation (m) ↑ liver weight (m/f) liver hypertrophy (m/f)	**Smith (2003b)** → document IIIA 6.10

(m) males; (f) f emales

[a] considered for risk assessment as NOAEL

[b] lowest NOEL for the primary effect on liver

[c] primary effect on liver not interpreted not as LOAEL but as LOEL

In the dog, the liver was identified as a target organ (Harling, *et al.*, 1985b), but the hepatic effects were minimal and reversible, and occurred only at dietary concentrations of 10000ppm, equivalent to dose levels of 352mg/kg bw/day in males and 339mg/kg bw/day in females. The effect comprised minor changes in serum clinical chemistry parameters, increased liver weight and, in some female animals, swelling of centrilobular hepatocytes. Since no other treatment-related adverse effects were evident in the study, an NOEL was established as 1000ppm, equivalent to dose levels of 33.4 and 32.2mg/kg bw/day in males and females, respectively.

No further target organs were identified in the long-term studies in rats and mice that had not been identified in short-term toxicity studies. In the rat, the liver and thyroid gland were confirmed as target organs for non-neoplastic effects (Green, *et al.*, 1986a). Cystic follicles occurred at increased incidence in the thyroid of females after prolonged treatment at the highest dietary level of 4900ppm, equivalent to a dose level of 249mg/kg bw/day. Increased height of the thyroid follicular epithelium also occurred at this dose level after 26 weeks of treatment, but not subsequently. In males treated at 4900ppm (187mg/kg bw/day), the thyroid effect was confined to increased weight without histopathological correlate from week 26 to termination. There were no consistent effects on the levels of circulating thyroid hormones, although T_3 activity was reduced by approximately 33% in females at 4900ppm in week 25 only. The hepatic alterations were evident in both sexes at 4900ppm and comprised centrilobular hepatocyte enlargement after 26 and 106 weeks of treatment, but liver weight was increased at all necropsy intervals. Eosinophilic hepatocytes were a further histopathological feature in some animals of both sexes after prolonged treatment at 4900ppm and in males at 700ppm. Blood clotting times were prolonged in males, but not females, at 4900ppm during the first 6 months

of treatment. An NOAEL value for all non-neoplastic effects was established in the rat as 100ppm, equivalent to dose levels of 3.7 and 4.8mg/kg bw/day in males and females, respectively.

In the mouse, the kidneys were identified as the main target organ (Green, *et al*., 1986b). The renal lesion was evident at necropsy as an increased incidence of cortical scarring and pale coloration in both sexes and organ enlargement in males. The histological lesion was characterized by an increased incidence and severity of basophilic and dilated tubules. Dilated/cystic Bowman's capsules, dilated medullary tubules, focal loss of tubules, prominent interstitial papillary tissue and papillary mineralization were associated with the primary renal change. The lesion was confined to animals treated at 4900ppm at 52 weeks but was evident in some animals treated at 100ppm and higher after 104 weeks of treatment. The severity of the renal lesion in males treated at 4900ppm contributed to increased mortality in this group. Other treatment-related effects were confined to animals treated at 4900ppm and comprised reduced weight gain, minor haematological changes and increased liver weight without histopathological correlate. An NOAEL for all non-neoplastic effects was established as 30ppm, equivalent to dose levels of 3.1 and 3.6mg/kg bw/day in males and females, respectively.

Etofenprox did not induce frank carcinogenic effects in either the rat or the mouse, but in the rat, there was an increased incidence of a benign neoplasm of the thyroid, follicular cell adenoma at the highest applied dose of 4900ppm equivalent to dose levels of 186,7 and 249,1 mg/kg bw/day in males and females, respectively. The incidence for males –however- was borderline to statistical significance. Therefore, an NOEL value for thyroid effects in the rat was established as 700ppm, equivalent to dose levels of 25,5 and 34,3 mg/kg bw/ day in males and females, respectively. A NOEL for carcinogenic effects in the mouse was established as >4900ppm, the highest dose level employed, equivalent to dose levels of 546.9 and 615.5mg/kg bw/day in males and females, respectively, since the evidence for carcinogenic effects at this dose level was considered insufficient: Three males at 4900ppm and one male at 700ppm showed a renal neoplasm. However two of the neoplasms at the highest dose level were benign and the statistical evidence was not sufficient.

Smith (2003b) investigated the etiology of the increased incidence of rat thyroid follicular cell adenomas based on the observation that etofenprox produced increased liver weight and hepatic hypertrophy in the rat after short-term (Green, *et al.*, 1983a; Coombs, *et al*., 1985 – see document A 6.4.1/01 and A 6.4.3.1) and long-term administration (Green, *et al.*, 1986a). Specifically, Smith (2003a) investigated the hypothesis that etofenprox produces as primary effect hepatic microsomal enzyme induction, ultimately leading to a secondary effect of increased thyroid follicular cell adenomas mediated by a physiological homeostatic mechanism. The study results, summarised in Table 19b, demonstrate that hepatic microsomal UDPGT activity and circulating TSH concentrations were increased in both sexes after 2 weeks (2w) of treatment.

Although TSH concentrations remained elevated after 4 weeks (4w) of treatment, they returned to normal

concentrations on withdrawal of treatment. Serum T4 concentrations in males were reduced by 44.4 and 23.3% after 2 and 4 weeks of treatment, respectively, but the effect was fully reversible within 4 weeks of treatment withdrawal. Similarly, mild thyroid cell proliferation, demonstrable in males only, was fully reversible after treatment withdrawal. Smith also demonstrated an equivocal increase in thyroid weight and reduced thyroid peroxidase activity.

Table 19b: Summary of findings from 4-week dietary investigative study, Smith (2003b)

Observation	**Effect observed (+) / not observed (-) in:**					
	Males at (ppm):			**Females at (ppm):**		
	1250	**5000**	**20000**	**1250**	**5000**	**20000**
↑ serum TSH concentration	+ (2w/4w)	+ (2w/4w)	+ (2w/4w)	+ (2w/4w)	+ (2w/4w)	+ (2w/4w)
↓ serum T3 concentration	-	-	-	-	-	-
↓ serum T4 concentration	-	-	+ (2w)	-	-	-
↑ microsomal protein	-	-	+ (4w)	-	-	-
↑ hepatic UDPGT (4-MUGT)	-	+ (2w)	+ (2w)	-	-	+ (2w)
↑ hepatic UDPGT (p-NPGT)	-	+ (2w)	+ (2w)	-	+ (2w)	+ (2w)
↓ thyroid peroxidase	± (4w)	± (4w)	± (4w)	± (4w)	± (4w)	± (4w)
↑ hepatic BrdU labelling index	-	-	-	-	-	-
↑ thyroid BrdU labelling index	-	-	+ (2w/4w)	-	-	-
↑ liver weight	-	+ (2w/4w)	+ (2w/4w)	-	-	+ (2w/4w)
↑ thyroid weight	-	-	± (2w/4w)	-	-	± (2w/4w)
Liver hypertrophy	NE	NE	+ (2w)	NE	NE	+ (2w/4w)
↑ hepatic multinucleated cells	NE	NE	+ (2w/4w)	NE	NE	+ (2w/4w)
Thyroid histopathology	-	-	-	-	-	-

(w) weeks

± equivocal treatment-related effect; NE not evaluated

The results are consistent with the hypothesis that the primary effect of etofenprox is on the liver, manifested as increased hepatic microsomal enzyme induction, specifically UDPGT activity. Since UDPGT is known to be a major route of metabolism and elimination of circulating T4, increased circulating TSH concentration is considered to be a secondary, physiological response to reduced circulating T4 concentration. Similarly, the subsequent event observed by Smith (2003a), a mild stimulation of thyroid cell proliferation in males, is also considered to be a secondary, physiological response. There is evidence in the literature that a sustained elevation in circulating TSH concentration can lead initially to hypertrophy of thyroid follicular cells, followed by hyperplasia and ultimately a greater risk of

increased incidence of thyroid adenomas (McClain *et al*., 1988[1]; Marquardt & Schäfer 2004, p1252f[2]). Therefore, the data of Smith (2003a) present consistent support for the contention that the increased incidence of thyroid adenomas in the combined chronic toxicity/carcinogenicity study was a consequence of increased TSH concentration, rather than a direct effect of treatment with etofenprox. Notwithstanding the absence of an effect on circulating T4 concentration and thyroid cell proliferation in female rats, it is concluded that the increased incidence of thyroid adenomas in rats was mediated by an indirect, non-genotoxic mechanism with a clear NOEL for the primary effect on the liver of 81.2mg/kg bw/day. Furthermore the effect is considered less relevant to humans, since the human plasma levels of T4 are much higher and the turn over slower leading to a much more stable T4 concentration and therefore to a reduced positive feedback on TSH synthesis and hypertrophy of thyroid follicular cells.

For further details please see the attached study summaries.

4.12.1.1 Carcinogenicity: inhalation

No information available.

4.12.1.2 Carcinogenicity: dermal

No information available.

4.12.2 Human information

No information available.

4.12.3 Other relevant information

No other relevant information available.

4.12.4 Summary and discussion of carcinogenicity

See chapter 4.10.

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[1] McClain, R.M., Posch, R.C., Bosakowski, T. and Armstrong, J.M. (1988). Studies on the mode of action for thyroid gland tumor promotion in rats by phenobarbital, Toxic. Appl. Pharmacol., 94:254 - 265.

[2] Marquart & Schäfer (editors) (2004). Lehrbuch der Toxikologie. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart; relevant chapter : Diether Neubert, p 1209f, in specific p1252f.

4.12.5 Comparison with criteria

According to CLP a classification for carcinogenicity may be based on strength of evidence (sufficient or limited) and additional considerations.

There was insufficient evidence for carcinogenicity in the mouse study: With three males in the high dose and the one male in the medium dose that a renal neoplasm was observed, however two of the neoplasms at the highest dose level were benign and the statistical evidence was not sufficient.

There was limited evidence for carcinogenicity in the rat study:

There was no significant treatment-related effect on the incidence of follicular carcinomas for either male or female rats.

In males for combined follicular tumors (adenoma and/or carcinoma), there was a significant positive trend with dose (p= 0.009), although in the pairwise comparison there was no significant effect on incidence between the control and the 4900ppm dosage group (p=0.08).

In females for combined follicular tumors (adenoma and/or carcinoma), there was a significant effect on incidence between the control and the 4900 ppm dosage group (p=0.005) and this was supported by a significant trend test for positive trend (p< 0.001). The increased incidence of thyroid follicular tumors in female rats treated with 4900 ppm was due to the increase in follicular adenomas.

Apart from the thyroid follicular tumors mentioned previously there was no deviation from the expected tumor profile for laboratory maintained rats of this strain.

In summary, in the light of the significant trend test for males, the significant though benign effect with females and the thyroid organ weight, marcroscopic and histological alterations it is prudent to assume that at the high doses of 187 (male) or 249 (female) mg/kg bw there is limited evidence of thyroid tumour development in rats.

However additional considerations apply that further reduce the overall level of concern: Results from a mechanistic study are consistent with the hypothesis that the primary effect of etofenprox is on the liver, manifested as increased hepatic microsomal enzyme induction with consequent T4 reduction, TSH increase and finally increased thyroid stimulation. This mode of action is based on an indirect, non-genotoxic mechanism with a clear NOEL, which is furthermore considered of very low relevance for humans due to the different T4 plasma kinetics.

Table 19c : Thyroid gland alterations in the 2-year rat study (Green et al 1986a)

Sex	**Thyroid gland alteration**	**Incidence at (ppm):**				
		0	**30**	**100**	**700**	**4900**
Male	No. animals examined	50	50	50	50	50
	Follicular cell carcinoma	0	0	1	3	2
	Follicular cell adenoma	6	6	4	5	11
	Follicular cell adenoma and/or carcinoma	6	6	5	8	13
Female	No. animals examined	50	50	50	50	50

	Follicular cell carcinoma	0	0	0	2	1
	Follicular cell adenoma	0	3	2	0	9
	Follicular cell adenoma and/or carcinoma	0	3	2	2	9*

In principle the DSD criteria are very similar.

4.12.6 Conclusions on classification and labelling

No classification necessary, neither according to CLP regulation, nor according to the DSD criteria.

4.13 Toxicity for reproduction

4.13.1 Effects on fertility

4.13.1.1 Non-human information

See chapter 4.13.4

4.13.1.2 Human information

No information available.

4.13.2 Developmental toxicity

4.13.2.1 Non-human information

See chapter 4.13.4

4.13.2.2 Human information

No information available.

4.13.3 Other relevant information

No other information available.

4.13.4 Summary and discussion of reproductive toxicity

An extensive evaluation of the reproductive toxicity of etofenprox was undertaken in the rat and rabbit by oral administration. A summary of the reproductive studies is shown in Table 20a (key studies highlighted bold).

Table 20a: Summary table of relevant reproductive toxicity studies

Study / species / dose levels	NO(A)EL (mg/kg/day)	LO(A)EL (mg/kg/day)	Main effects / target organs	Reference
Oral (gavage) developmental/ fertility study; treatment of male P0: 9 weeks prior to mating, mating, 20 days post mating; treatment of females: 2 weeks prior to mating, mating, till day 7 of gestation; sacrifice of all animals at day 20 of gestation, analysis of P0 and F1 animals Rat; 0, 12.5, 250, 5000 mg/kg/day	5000 [a]	> 5000	at ≥ 12,5 ↑salivation and brown staining around mouth	Cozens *et al.* (1985a) → document IIIA 6.8.1.1/1
	250 [b]	5000	slightly lower litter size (not significant)	
	5000 [c]	> 5000	-	
Oral (gavage) developmental/ fertility study: P0 treatment from d6 to d17 of pregnancy; foetal analysis, follow up without treatment to F2 weaning Rat; 0, 12.5, 250, 5000 mg/kg/day	**250 [a]**	**5000**	↓ F0 maternal gestation weight gain (group mean bw 3.6% lower than control)	**Cozens *et al.* (1985b)** → document IIIA 6.8.1.1/2
	5000 [b]	**> 5000**	-	
	250 [c]	**5000**	↓ F1 maternal gestation weight gain (4% lower than control	
Oral (gavage) peri / postnatal study: P0 treatment from d17 of pregnancy to d21 pp; follow up without treatment to F2 weaning Rat; 0, 12.5, 250, 5000 mg/kg/day	250 [a]	5000	at 5000 ↓ F0 maternal gestation weight gain; at ≥ 250 ↑salivation and brown staining around mouth	Cozens *et al.* (1985c) → document IIIA 6.8.1.1/3
	5000 [b]	> 5000	-	
	250 [c]	5000	↑ pup mortality, ↓ weight gain, tremor, haemorrhage, histopathological alterations in kidneys of F1	
Dietary multigeneration study; Rat; 0, 100, 700, 4900ppm	**37 [ad]**	**246**	↓ weight gain, ↑ liver, kidney and thyroid weights.	**Cozens *et al.* (1985d)** → document IIIA 6.8.2
	37 [bd]	**246**	↑ pup mortality (minimal), ↓ pre-weaning weight gain.	

	4.3 [cd]	**30**	↑ liver and kidney weights; kidney lesions at 700ppm; pre-weaning tremors / abnormal gait, histopathological alterations in liver, kidneys and thyroid, and ↑ heart weight at 4900ppm.	
Oral (gavage) developmental toxicity; Rabbit; 0, 10, 50, 250 mg/kg/day	10 [a]	50	↓ weight gain.	Bottomley (1985)
	50 [b]	250	↑ slight post-implantation loss.	
	250 [c]	> 250	-	
Oral (gavage) developmental toxicity; Rabbit; 0, 30, 100, 300 mg/kg/day	**100** [a]	**300**	↓ weight gain / food cons.	**Fisher (2000)** → document IIIA 6.8.1.2
	100 [b]	**300**	↑ slight post-implantation loss and ↓ fetal weight gain.	
	100 [c]	**300**	See above (b)	
Oral (dietary) developmental neurotoxicity study; rat; 28, 79, 238 mg /kg bw/day	**28**[a]	**79**	Transient retardation of gestation weight, at 238: changes in weight gain, increased rearing activity	**Myers (2003)** → document IIIA 6.9.3
	> 238[b]	**> 238**	-	
	28[c]*****	**79**	ocular lesions; at 238: increased pup mortality, subcutaneous haemorrhagic lesions , ↑auditory startle response amplitudes (F); motor activity and latency to peak startle response (M)	

[a] NO(A)EL for effects on parental animals;

[b] NOEL for reproductive effects;

[c] NOEL for developmental and offspring effects;

[d] equivalent to the lowest calculated dose level for either sex

* considered as NOAEL for risk assessment

Although two developmental toxicity studies in the rabbit have been performed and submitted (Bottomley, 1985; Fisher, 2000), the most recent study is considered valid for human risk assessment since it was performed according to a more recent guideline specifying treatment from day 6 to day 28 of gestation. Conversely, the former study is

considered not relevant for human risk assessment, it was performed in groups of animals from different sources.

In the developmental rabbit study from Fisher 2000, embryotoxicity was confined to slightly increased post-implantation loss (10.1% vs. 4.3% in control) and reduced embryofetal weight gain (85% of control). However these effects were only observed in the high dose group of 300 mg/kg bw day that induced severe maternal toxicity in terms of reduced body weight (-10% compared to control), body weight loss (-2.9% from day 6 to 29) and reduced food consumption (-18.9% compared to control). At 300 mg/kg bw day also abortion and/or unscheduled death occurred in 4 dams (compared to 0, 1, 1 in control, low and mid dose). The nature and incidence of fetal malformations did not indicate an effect of treatment at any dose level. Some skeletal variations occurred at higher incidence compared to control, but these were either within the historical control range and without clear dose relationship (unossified 5th sternebra) or were apparent only at the high dose and considered as a consequence of intrauterine growth retardation (unossified talus) or were apparent only in the high dose and of numerically small difference to controls.

In the developmental/fertility rat study (Cozens, *et. al*., 1985b) there were no treatment-related effects at any dose level on the nature and incidence of malformations, visceral anomalies and skeletal variants. Adverse effects on the outcome of pregnancy in this developmental study were confined to reduced maternal gestation weight gain at the high dose of 5000 mg/kg bw day resulting for P0 in 3.6% reduced body weight at day 20 of gestation and 3% at day 21 post partum and for P1 in 4% body weight at day 20 . The physical, behavioral and sexual development of F1 progeny exposed *in utero* during the critical period of organogenesis were unaffected by treatment with etofenprox.

The NOEL values for developmental effects in this rabbit and rat studies were the same as the maternal NOEL values, indicating that the developing embryo is no more susceptible than the maternal animal.

Etofenprox does not produce selective developmental neurotoxicity in F1 progeny at dose levels that produce slight maternal toxicity in terms of transient decrease in weight gain from days 6-10 of gestation in mid and high dose (-14% compared to control, Myers, 2003, document III A 6.9/03). However, slightly impaired pre-weaning survival (offspring mortality between days 14 and 21: 5.7% high dose vs. 0.6% control; but offspring survival indices similar at weaning) and a low incidence of subcutaneous haemorrhagic lesions occur in progeny at the high dose of 238mg/kg bw/day, and low incidences of ocular lesions at the medium dose of 79 mg/kg bw/day. Since the ocular lesions were generally associated with intraocular haemorrhage, they may share a common aetiology with the subcutaneous lesions. Functional developmental effects with a possible relationship to treatment were confined to higher mean auditory startle response amplitudes and reduced habituation in female offspring and a clustering of differences in motor activity and latency to peak startle response in males at the high dose of 238mg/kg bw/day. In contrast histomorphological development of the central and peripheral nerve tissues were unaffected by treatment with etofenprox at the high dose of 238mg/kg bw/day. In summary the NOEL value for developmental effects in this rat study was the same as the maternal NOEL value (low dose 28 mg/kg bw day), indicating that the developing embryo is no more susceptible than the maternal animal.

In the peri/post-natal study, maternal exposure to high oral doses of 5000mg/kg bw/day during the latter part of

gestation and throughout lactation produces tremor, subcutaneous haemorrhage, reduced weight gain, increased neonatal mortality and renal dysfunction accompanied by histopathological alterations in the kidneys in F1 progeny (Cozens, *et al*., 1985c). The main features of the induced renal lesions are cystic collecting ducts, focal fibrosis, cortical scarring and mineral deposits. Renal effects of this nature do not occur at this dose level in the treated maternal animals. The NOEL in F1 progeny in the peri/post-natal study is 250 mg/kg bw/day. Similar renal effects of treatment were confirmed in reared F1 progeny treated at diet concentrations of 4900ppm (267 - 753mg/kg bw/day) in the multigeneration study (Cozens *et. al*., 1985d). Further effects on the F1 progeny identified in this study, comprising tremor, abnormal gait, increased heart weight, hepatocyte enlargement and increased height of the thyroid columnar epithelium, occur at 4900ppm only. However, since a single female offspring at 700ppm also showed cystic collecting ducts extending into the kidney cortex, the NOEL in F1 progeny is equivalent to minimum dose levels of 4,3 / 5,6 mg/kg bw/day in males and females, respectively. The NOEL in parental F_0 animals is equivalent to minimum dose levels of 37 / 44mg/kg bw/day in males and females, respectively, based on increased liver, kidney and thyroid weights at 4900ppm. Fertility and reproductive capacity are unaffected by treatment with etofenprox (Cozens *et al.*, 1985a and 1985d).

Consideration of all reproductive data in rats revealed effects in progeny exposed *in utero* and during lactation that are not evident in adult rats that have not been exposed *in utero*/during lactation: Increased pup mortality, non-specific haemorrhagic lesion (generally subcutaneous but also ocular), renal toxicity, liver/thyroid/renal histopathology, functional neurological effects. Other effects occurring in rat offspring are those that also occur in parental animals, *viz.* changes in thyroid weight and morphology and increased liver and kidney weights.
The relevant NOEL values for rat offspring are presented in the Table below.

Table 20b: Relevant NOEL values for rat offspring

Study	Effect	NO(A)EL (mg/kg bw/day)	LO(A)EL (mg/kg bw/day)
Peri-/post-natal	Increased pup mortality	250	5000
	Haemorrhagic lesions	250	5000
	renal histopathology	250	5000
Multigeneration	Increased pup mortality (F1+F2)	37	246
	Renal histopathology (F1) [e]	4.3 [a]	30
	Ocular/haemorrhagic lesions (F1+F2)	102	744
	Increased liver weight (F1+F2)[e]	12.9 [c]	90
	Increased kidney weight (F2b)[e]	5.6 [b]	40
	Liver/thyroid/(renal) (F1) histopathology [d]	37	279
Developmental neurotoxicity	Ocular lesions	28.4*	79
	Haemorrhagic lesions	79	238
	Increased pup mortality	79	238
	Functional neurological effects	79	238

[a] one animal only with an isolated kidney lesion at 30 mg/kg bw/day;

[b] minimal effect (7.2% increase) in F2b generation adult females only;

[c] minor effect on liver weight (5.8 - 10.2% increase) in F1 and F2 weanling animals but not apparent in adult animals of these generations

[d] in contrast to ([a]) several animals show renal histopathology effects at 279 mg/kg bw/day

[e] considered too conservative values for hazard assessment and classification purposes

* NOAEL considered for risk assessment

For hazard assessment and classification purposes the three NOEL values for the multigeneration study (renal histopathology, increased liver and thyroid weight) marked [e] in the foregoing table, are regarded as not reliable enough since based on one animal only or on minimal and/or transient effects. Renal histopathological alteration in F1 progeny at 30mg/kg bw/day occurred in a single animal and was not accompanied by the inflammatory and degenerative changes seen at higher dose levels. Kidney weight differences at 40mg/kg bw/day were minimal (7.1% higher than controls) and occurred in female F2b progeny only. The kidney weights of F1a, F1b and F2a progeny of both sexes, and of male F2b progeny, were unaffected by treatment. Increased liver weight was minimal (up to 10.2% higher) in weanling F1 and F2 progeny at 90mg/kg bw/day and was transient in nature because increased liver weight was not apparent in F1b and F2b progeny reared to adulthood.

Increased pup mortality was evident in all of these studies. However in the peri-/post- natal study the effect was

significant only at 5000 mg/kg bw/day. Within the multigeneration study the effect was clustered within 2 complete litter losses, both in the high dose group (f: ca. 246 mg/kg bw/day), one litter from F0 females and one from F1b females, all towards the end of lactation. Finally within the developmental neurotoxicity study the effects were (not clustered by complete litter loss, but) clustered in the final week of lactation (in contrast to control pup deaths that occurred throughout lactation) in the high dose group (f: 238 mg/kg bw day) and were marginal (5.7% of pups died compared to 0.6% in control). Because the increased pup mortality occurred in all studies only at relatively high doses above 238 mg/kg bs/day and it was clustered within just 2 litters in the second study and marginal in the third study the effect was considered to be of low level of concern.

Therefore, for hazard assessment and classification the major concerns are ocular lesions at 79 mg/kg bw/day (developmental neurotoxicity study, starting between days 16-21 of age with the majority occurring after weaning; at termination days 63-67; 238/79/28,4/0 mg/kg bw/day: 13/5/2/1 pups of ca. 180 each) and subcutaneous haemorrhagic lesions at 238 mg/kg bw/day (developmental neurotoxicity study, at termination days 63-67; 238/79/28,4/0 mg/kg bw/day: 11/5/1/2 pups of ca. 180 each) and at 5000 mg/kg bw/day (peri-/post natal study, before weaning, around nose) and at 744 mg/kg bw/day (multigeneration study, F1 +F2 at necropsy, ocular and subcutaneus) and functional neurological effects within F1 adults at 238 mg/kg bw/day (higher mean auditory startle response amplitudes and reduced habituation in female offspring and a clustering of differences in motor activity and latency to peak startle response in males) and liver/thyroid/renal histopathological effects at 279 mg/kg bw/day in F1 adults (minor hepatocyte enlargement and vacuolisation and increased height of the thyroid columnar epithelium and renal lesions like primarily cystic collecting ducts, focal fibrosis, cortical scarring and mineral deposits.)
The above described effects were not observed within the F0 generation within the reproductive toxicity studies. However reduced clotting times, hepatocyte enlargement and other histopathological thyroid effects have been observed in rat adults at even lower concentrations of 187 mg/kg bw/day in the 110- week dietary study (Green et al. 1986a) and in the subchronic dietary rat study (Green et al. 1983a) at 120 (hepatocyte enlargement) and 734 mg/kg bw/day (thyroid effects and prolonged clotting time). Severe renal effects were observed in adult mice at 10.4 mg/kg bw/day in the 110-week dietary study (Green et al. 1986b) and at 1975 mg/kg bw/day in the 13-week dietary study. Therefore the above discussed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight. The haemorragic effects, histological liver and thyroid effects and the functional neurological effects are considered minimal. Furthermore all discussed effects were observed only at relatively high doses (above 237 mg/kg bw/day for all effects except ocular haemorrhage at 79 mg/kg bw/day). Thus the described effects are not considered sufficient for classification for developmental toxicity. Nevertheless classification for effects via lactation shall be considered (H362).
The acceptable exposure levels (AEL) are derived from NOAELs below these, thus they cover the discussed effects.

For further details please see the attached study summaries.

4.13.5 Comparison with criteria

Reproductive Toxicity

According to CLP a classification for reproductive toxicity shall be based on a total weight of evidence evaluation for a specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific consequence of other toxic effects (see CLP Regulation, Annex I, point 3.7.2.2.1)

The results of the available developmental and fertility studies in rats and rabbits are summarized above (chapter 4.13.4).

Endpoints for fertility were unaffected by treatment with etofenprox.

With the developmental rabbit study at the high dose of 300 mg/kg bw day severe maternal toxicity was observed and the slight embryotoxicity and slight increase of skeletal variations at this dose were considered to be a consequence thereof. With the developmental rat study no significant developmental effects were observed.

Some effects were present in progeny exposed *in utero* and during lactation that are not evident in adult rats that have not been exposed *in utero*/during lactation. Such effects may indicate a need for classification for developmental toxicity. However these effects were significant only at (partly very) high doses and/or were inconsistent with parallel or subsequent cohorts findings and/or marginal in frequency/severity and/or clustered in two litters and/or were observed also in adults in other (non-reproductive) repeated dose studies and were consequently not considered as specific developmental toxicity but as a consequence of the naturally high ratio of milk uptake to bodyweight. The latter perspective is also supported by toxicokinetic findings indicating a potential for accumulation in fat and active secretion into milk with the consequence of a high concentration ratio between pup stomach content to maternal plasma content (see chapter 4.1.).

Lactation Effects

According to CLP a classification for lactation effects shall be based on a total weight of evidence evaluation based on results from one or two generation studies in animals which provide clear evidence of adverse effects in the offspring due to transfer in the milk or adverse effect on the quality of the milk and/or ADME studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk. Classification in the additional category for effects on or via lactation is considered irrespective of a classification into category 1A, 1B or 2.

The potential for accumulation in fat and active secretion into milk was observed within toxikokinetic studies (see chapter 4.1) and haemorrhage effects in lactated rats were observed in reproduction toxicity studies (see chapter 4.11). The observed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight.

4.13.6 Conclusions on classification and labelling

No classification necessary for category 1A, 1B or 2 with regard to reproductive toxicity.

Classification with “H362: May cause harm to breast-fed children” is proposed.

(No classification according to the DSD criteria for R48/20/21/22 (Danger of serious damage to health by prolonged exposure) is proposed since the guidance value for R48/20/21/22 is 50 mg/kg bw day, which is lower compared to the guidance value of 100 mg/kg bw day for H373, and consequently the overall weight of evidence summarized in 1.5.3. does not appear sufficient for classification with R48/20/21/22.

No classification according to the DSD criteria for R64 (May cause harm to breastfeed babies) is proposed, since R64 may only be applied in addition to other human health R phrases. No other human health R phrases are applicable.)

4.14 Other effects

4.14.1 Non-human information

4.14.1.1 Neurotoxicity

No functional and neurohistopathological effects occur in the rat in response to the oral administration of single doses of up to 2000mg/kg etofenprox and mean dose levels of 604 and 690mg/kg bw/day for 13 weeks, in males and females, respectively (Smith, 2002 and 2003a). Similarly, etofenprox does not produce selective developmental neurotoxicity in F1 progeny at dose levels that produce slight maternal toxicity (Myers, 2003). However, slightly impaired pre-weaning survival and a low incidence of subcutaneous haemorrhagic lesions occur in progeny at 238mg/kg bw/day, and low incidences of ocular lesions at ≥ 79mg/kg bw/day. Since the ocular lesions were generally associated with intraocular haemorrhage, they may share a common aetiology with the subcutaneous lesions. An overall NOEL was established as 28.4mg/kg bw/day. Functional developmental effects with a possible relationship to treatment were confined to higher mean auditory startle response amplitudes in female offspring and a clustering of differences in motor activity and latency to peak startle response in males at 238mg/kg bw/day. In contrast histomorphological development of the central and peripheral nerve tissues were unaffected by treatment with etofenprox at 238mg/kg bw/day, the highest dose level employed. The summary of the available neurotoxicity data is presented in Table 20c. (key studies highlighted bold).

Table 20c: Neurotoxicity data on etofenprox.

Study / species / dose levels	NO(A)EL	LOAEL	Target organs / main effects	Reference

	(mg/kg bw/day)	(mg/kg bw/day)		
Acute (gavage) neurotoxicity; Rat; 0, 25, 125, 500, 2000 mg/kg	> 2000 (neurotoxicity and all effects)	-	No adverse effects, no evidence of neurotoxicity	Smith (2002)
13-week (dietary) neuro-toxicity; Rat; 0, 2500, 5000, 10000 ppm	< 149 (all effects) > 604 (neurotoxicity)	149 -	Increased liver weight No evidence of neurotoxicity	Smith (2003a)
Developmental neurotoxicity; **Rat;** **0, 250, 700, 2100 ppm**	**28.4** (all effects) **79** (functional) **> 238** (histological)	**79** **238** -	Transient retardation of gestation weight, ocular lesions at 81 mg/kg bw/day; ↑ pup mortality, minor functional changes, ocular and haemorrhagic lesions at 238mg/kg bw/day	**Myers (2003)** **→ Doc III A 6.9/03**

4.14.1.2 Immunotoxicity

No information available.

4.14.1.3 Specific investigations: other studies

Not available.

4.14.1.4 Effects on breast fed children

The potential for accumulation in fat and active secretion into milk was observed within toxikokinetic studies (see chapter 4.1) and haemorrhage effects in lactated rats were observed in reproduction toxicity studies (see chapter 4.11). The observed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight.

4.14.1.5 Human information

Comprehensive medical surveillance of male production operatives continually involved in the manufacture of

etofenprox for up to 5 years and 3 months demonstrated the absence of occupational adverse health effects (Yamazaki, 1992, document III A 6.12.1).

The Ohmuta factory of Mitsui Toatsu Chemicals, Inc. was producing 200 - 300t/annum etofenprox technical during the period 1987 – 1992 (exposure period between 11 and 63 months). The production line was operated by 21 male staff who worked in a triple shift pattern. The report documents the health assessments made on the production operatives.
The staff were examined annually for blood biochemistry (GOT, GPT, ϒ-GPT, ALP, TTT, total cholesterol, neutral fat, blood glucose, urea nitrogen and uric acid) and also had an X-ray and ECG recorded. Twice yearly examinations were performed for the following parameters: height, weight, vision, hearing, blood pressure, hematology (RBC, Hb, Ht and WBC), urinalysis (glucose, protein and occult blood) and other medical features (subjective and objective symptoms, lifestyle, family history, past history). Measured values were compared to normal range of values.
Although several different abnormal values were obtained from the 21 operators, there was no consistent pattern suggestive of an effect due to exposure to etofenprox. Individual values falling outside the normal ranges are summarised in the Table 20d below.

Table 20d: Summary of abnormal values in production line staff - etofenprox (January 1987 - March 1992).

ID	Age / sex	Exposure period	Abnormal findings (and dates)
A	43 / M	01.87 - 03.92	Disturbance of vertebral disc (09.88 - 03.90) Neutral fat: 198mg/dL (09.90)
B	41 / M	01.87 - 03.92	No abnormalities detected
C	49 / M	07.87 - 03.92	Disturbance of conjunctiva (11.91 - 03.92)
D	21 / M	04.89 - 03.92	ALP: 263IU/L (11.89) Treated for keratitis (05.87 and 11.91)
E	47 / M	11.87 - 03.92	WBC: 12200/mm^3 (11.89) WBC: 10500/mm^3 (09.90)
F	47 / M	07.87 - 03.92	Treated for duodenal ulcer (05.88 - 05.90) Treated for duodenal ulcer (05.91 - 03.92)
G	48 / M	07.87 - 03.92	Treated for neuralgia (11.88) Ɣ-GPT 110IU/L; GPT 67IU/L; neutral fat:307mg/dL (11.89) Migraine (05.90) GOT 46IU/L; GPT 83IU/L; neutral fat 235mg/dL; migraine (11.90) Migraine (05.91) Ɣ-GPT 107IU/L; GPT 58IU/L; neutral fat:228mg/dL; migraine (11.91) Migraine (03.92)
H	44 / M	02.88 - 03.92	Treated for duodenal ulcer (11.90 - 03.92)
I	41 / M	01.87 - 03.92	No abnormalities detected
J	40 / M	10.87 - 03.92	No abnormalities detected
K	39 / M	10.88 - 03.92	Blood pressure: 138 / 98 (05.88) ALP 69IU/L; neutral fat 206mg/dL; uric acid 8.1mg/dL; blood pressure 158 / 96 (11.89) ALP 71IU/L; neutral fat 274mg/dL; uric acid 8.1mg/dL; blood pressure 150 / 96 (11.90) Blood pressure: 154 / 100 (05.91) ALP 71IU/L; neutral fat 274mg/dL; uric acid 8.1mg/dL (11.91) Treated for gout (03.92)

ID	Age / sex	Exposure period	Abnormal findings (and dates)
L	43 / M	01.87 - 03.92	No abnormalities detected
M	45 / M	01.87 - 03.92	Blood pressure: 150 / 102, treated for hypertension (05.88, 11.91, 03.92) Blood pressure: 142 / 98 - 158 / 108 (11.88 - 11.91) GPT 65IU/L; neutral fat 265mg/dL (11.89) GOT 45IU/L; GPT 60IU/L (11.90)
N	41 / M	01.87 - 03.92	Total cholesterol: 271mg/dL (11.89) Total cholesterol: 271mg/dL; neutral fat 174mg/dL (11.90) Neutral fat: 164mg/dL (11.91)
O	42 / M	01.87 - 03.92	Treated for cholelithiasis (05.88) Treated for allergic rhinitis (05.89) Neutral fat: 188mg/dL (11.89) Neutral fat: 193mg/dL (11.90)
P	37 / M	07.87 - 03.92	No abnormalities detected
Q	35 / M	01.87 - 03.92	No abnormalities detected
R	49 / M	10.87 - 03.92	Under diabetic management and treated for hypertension from 11.88. Blood pressure: 156 / 96 (11.88) Blood pressure: 150 / 106 (05.89) Blood pressure: 134 / 98; neutral fat 179mg/dL; blood glucose 127mg/dL (11.89) Blood pressure: 160 / 100; neutral fat 202mg/dL; blood glucose 176mg/dL (11.90) Blood glucose 194mg/dL (11.91)
S	19 / M	04.91 - 03.92	No abnormalities detected
T	42 / M	01.87 - 03.92	Urinary glucose positive (11.89, 11.90, 05.91)
U	24 / M	04.88 - 11.89	No abnormalities detected

4.14.2 Summary and discussion

See chapter 4.12.

4.14.3 Comparison with criteria

The functional neurological effects in the developemental neurotoxicity study were considered minimal, resulting only with high dose and covered by the study NOAEL based on maternal and covered by the critical NOAEL. The effects are considered insufficient for triggering a classification for reproductive toxicity (for respective discussion see 4.11.). The effects are also considered insufficient for triggering a classification for specific target organ toxicity, repeated exposure (STOT RE), since the LOAEL is above the guidance value of 100 mg/kg bw day for STOT RE category 2. The guidance value for R48/20/21/22 (Danger of serious damage to health by prolonged exposure) is even lower (50 mg/kg bw day), therefore also no classification according to DSD criteria is proposed.

According to CLP a classification for lactation effects shall be based on a total weight of evidence evaluation based on results from one or two generation studies in animals which provide clear evidence of adverse effects in the offspring due to transfer in teh milk or adverse effect on the quality of the milk and/or ADME studies that indicate the likelyhood that the substance is present in potentially toxic levels in breast milk. Classification in the additional category for effects on or via lactation is considered irrespective of a classification into category 1A, 1B or 2.

The potential for accumulation in fat and active secretion into milk was observed within toxikokinetic studies (see chapter 4.1) and haemorrhage effects in lactated rats were observed in reproduction toxicity studies (see chapter 4.11). The observed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight

4.14.4 Conclusions on classification and labelling

Classification with “H362: May cause harm to breast-fed children” is proposed.

(No classification for R48/20/21/22 (Danger of serious damage to health by prolonged exposure), is proposed since the guidance value for R48/20/21/22 is 50 mg/kg bw day, which is lower compared to the guidance value of 100 mg/kg bw day for H373, and consequently the overall weight of evidence summarized in 1.5.3. does not appear sufficient for classification with R48/20/21/22.

No classification for R64 (May cause harm to breastfeed babies) is proposed, since R64 may only be applied in addition to other human health R phrases. No other human health R phrases are applicable.)

5 ENVIRONMENTAL HAZARD ASSESSMENT

Preliminary note: The results of the key studies are highlighted bold in all the tables throughout this chapter.

5.1 Degradation

Table 21: Summary of relevant information on degradation

See single subsections.

5.1.1 Stability

Hydrolysis

Etofenprox is hydrolytically stable in sterile buffer solutions at pH 4, 7 and 9 incubated for 5 days at 50°C in the dark. The metabolite [^{14}C]-α-CO was found to be stable in aqueous buffer acetonitrile solution at pH 4 and 7, but was hydrolysed at pH 9 (35°C DT_{50} 9.6 days; 45°C DT_{50} 2.4 days) to form PENA and m-PBAcid.

Table 21a: Hydrolysis

Guideline	**pH**	**Temperature [°C]**	**Initial TS concentration, C_0 [µg /l]**	**Reaction rate constant, K_h [1/s x 10^5]**	**Half-life, DT_{50} [h]**	**Coefficient of correlation, r_2**	**Reference**
Test substance: **^{14}C-etofenprox**							
OECD 111 (1981); EEC C.7 (1992); OPPTS 835.2110	4, 7 and 9	50	2.659 (pH 4) 2.106 (pH 7) 2.712 (pH 9)	stable	**stable ***	stable	**van der Gaauw (2001)** → Doc III A 7.1.1.1.1/01
Test substance: **^{14}C-α-CO**							
SETAC (March 1995) OECD 111 (1981) EPA OPPTS 835.2110 (1998)	4, 7 and 9	50 45 35 25	22	pH 4: Stable pH 7: Stable pH 9: k = 0.0162/day (extrapolated)	pH 4: Stable pH 7: Stable pH 9: DT_{50} = 42.8 days at 25 °C (extrapolated)	Assuming first order kinetics: at 35 °C: r^2 = 0.977 at 45 °C: r^2 = 0.985	Clayton, McCorquodale & Paterson (2003) → Doc III A 7.1.1.1.1/02

* Rate of degradation too slow to compute a half-life.

Aqueous photolysis

Etofenprox was photo-degraded under simulated sunlight, with DT_{50} values of 4.7 and 7.9 days in sterile buffer solution and natural pond water, respectively. The metabolite α-CO was the major photo-degradate comprising 63.6% and 37.8% of applied radioactivity in sterile buffer and natural water, respectively. A second photo-degradate PENA was also seen but at the lower levels of 12.0 and 14.4% respectively in the

two systems. In the dark control etofenprox was found to be stable. According to these results, direct photo-transformation could be a factor contributing to the disappearance of etofenprox in the aquatic environment.

The photolysis study performed with the metabolite [^{14}C]-α-CO was terminated after 48 and 72 hours due to technical reasons (no significant degradation, indication for inhomogeneous test solution because of low water solubility and high adsorption to glass). However, no significant photo-degradation of [^{14}C]-α-CO occurred in buffered aqueous solution under artificial sunlight during the test phase.

For the risk assessment the DT_{50} of 4.7 days in the sterile buffer solution was used. Conversion to standard European conditions results in a DT_{50} (12°C) of 13.3 days.

Table 21b: Photolysis in water

Guideline	Initial molar TS concen-tration	Total recovery of test substance [% of appl.a.s.]	Photolysis rate constant (k^c_p)	Direct photo-lysis sunlight rate constant (k_{pE})	Reaction quantum yield (ϕ^c_E)	Half-life ($t_{1/2E}$) [days]	Reference
Test substance: **^{14}C-etofenprox**							
SETAC (1995); OECD (97)21; OPPTS 835.2210; JMAFF, 16;	5.24 µg a.s./L	Buffer (pH7): 60.5-103%*, mean 89.35% Pond water: 43.5-108.2%*, mean 86.02% Control: Day 2-7: 111.8 – 85.6%; Day 12: 71.2 and 59.1%; Day 15: 40.4 and 33.5%** (buffer and pond)	Buffer (pH7): - 0.148 Pond water: - 0.087	30° N: - 0.075, - 0.089, - 0.050, - 0.032 40° N: - 0.062, - 0.083, - 0.034, - 0.016 50°N: - 0.047, - 0.073, - 0.018, - 0.0005 (spring, summer, autumn, winter)	- buffer solution (pH 7): Φ = 0.248 - natural pond water: Φ = 0.147	- buffer solution (pH 7): **DT_{50} = 4.7** days (1st order) - natural pond water: DT_{50} = 7.9 days (1st order)	**van der Gaauw (2003)** → Doc III A 7.1.1.1.2 / 01
Test substance: **^{14}C-α-CO**							
SETAC (1995); OECD draft guideline (Aug 2000); EPA, Sub-division N, Paragraph 161-2 (Oct 1982)	not calculated (ca. 23 µg/l)	169.45% after 48 h	not deter-mined	not determined	not deter-mined	the test substance did not undergo photolysis	Clayton, McCorquo-dale (2003) → Doc III A 7.1.1.1.2 / 02

* Values < 75% were not used for DT50 calculation.

** There was no significant degradation observed in these samples

Photo-oxidation of etofenprox in air

The vapour pressure of etofenprox was determined to be 8.13 x 10^{-7} Pa at 25°C and the Henry's Low Constant 0.0136 Pa x m^3/mol at 25°C (Tognucci, 2000, Document III A 3.2). Because of these very low values, no volatilisation and thus no significant amounts of etofenprox are to be expected in air.

Additionally, the photochemical oxidative degradation of etofenprox was calculated using the computer simulation software AopWin. An overall OH rate constant of 62.16 x 10^{-12} cm^3/molecule-sec was determined, resulting in an estimated half-life in air of 2.07 hours (Bates, 2001d, Document III A 7.3.1). According to these results, an accumulation of etofenprox in the air and a contamination by wet or dry deposition is not to be expected.

Photolysis in soil

^{14}C-etofenprox dissipates with a calculated disappearance time DT_{50} of 19.3 days. Up to 10 minor degradation products

were detected, six of which were characterised as α-CO, 4'-OH, DE, m-PB-acid, a mixture of PENA and EPMP and DP. None of the degradation compounds exceeded 7.7% of AR.

The mean recoveries of etofenprox were 98.2 % of AR. The amount of non-extractable radioactivity increased up to 45% of the AR at day 30. The amount of radioactivity evolved as $^{14}CO_2$ amounted to 7.4% after 30 days.

Dissipation of etofenprox was also observed in the dark control with a calculated DT_{50} of 22.2 days. No significant difference in the metabolic pathway was observed in both the irradiated and dark control samples (only one additional radioactive fraction was detected in the irradiated samples).

Disregarding dissipation in the dark control a direct photolysis rate constant of 0.0047 is obtained, yielding in a DT_{50} of 147 days. In general, the main pathways of dissipation of etofenprox in soil are its direct mineralization and binding to soil.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

No data available

5.1.2.2 Screening tests

The biodegradability of etofenprox was investigated in two ready biodegradability studies. In a Closed Bottle test a degradation rate of 17% was reached after 28 days. In this test etofenprox was investigated in concentrations above the water solubility. Therefore a second study (modified Sturm Test) was performed at a low concentration reflecting the low water solubility of the test substance. The DT_{50} for [^{14}C –benzyl]-etofenprox was determined to be less than 2 days, assuming a first order degradation. However, polar metabolites were formed (52.2% AR after 28 days) and only 32% ultimate degradation ($^{14}CO_2$) was measured after 28 days.

Due to the results of both studies etofenprox can be considered as being "not readily biodegradable". The Closed Bottle test was chosen as the key study, due to the fact that no reference substance had been investigated in the modified Sturm test.

An inherent biodegradation test was not considered necessary, since the results of the water/sediment studies show that etofenprox is partially degradable in the aquatic environment.

Table 21c: Biodegradation

Guide-line	Test type[1]	Test parameter	Inoculum			Additional substrate	Test substance concentration	Degradation		Reference
			Type	Concentration	Adaptation			Incubation period	Degree [%]	
OECD 301D (1982) EEC C.4-E (1984)	ready	oxygen consumption	Activated sludge (60% ThOD)	30 mg dry weight/L	No	No	2 mg/L	28 days	**17%**	**Thus, van der Laan-Straat-hof (1992)** → Doc III A7.1.1.2.1/02
OECD 301B (1982) EEC Directive 79/831, Annex V, Part C.4-C	ready	$^{14}CO_2$ evolution	Activated sludge (60% $ThCO_2$)	30 mg dry weight/L	No	No	0.0108 mg/L	28 days	32% $^{14}CO_2$	Thus, van der Laan-Straathof & Keetelaar-Jansen (1993) → Doc III A7.1.1.2.1

1 Test on ready biodegradability according to OECD criteria

5.1.2.3 Simulation tests

Degradation in soil

An aerobic degradation study in 4 soils at 20°C and in one soil at 10°C was performed using a radio-labelled mixture of [2-^{14}C-propyl]etofenprox and [α-^{14}C-benzyl]etofenprox at a minimum expected concentration of 0.3 mg/kg dry soil, assuming an even distribution in the top 10 cm soil layer and 1.0 g/cm^3 soil density (Völkl, 2001 and Völkl, 2002 and 2003 first and second amendment to the report, see document III A 7.2.2.1).

Proposed metabolic pathway: Etofenprox is initially degraded in soil by one of four different routes:

- Oxidation resulting in α-CO
- Hydroxylation of the benzene ring leading to 4'-OH
- De-ethylation resulting in DE
- Cleavage of the ether linkage between the two benzene rings to give DP

Once formed, these four metabolites do not accumulate and degrade to CO_2 (38.2 - 45.6% $^{14}CO_2$ was liberated after 120 days of incubation; n=4) and bound residues incorporate into the organic matter of the soil. It could be shown that the level of bound residues reached its maximum at day 55 in soil I and II (55.8 and 57.0% AR), in soils III and IV with a low organic carbon content the maximum was reached at day 92 (47.9 and 49.9% AR). The amount of bound residues decreased quite slowly (54.5, 52.8, 42.8 and 46.3% of AR at day 120) by further mineralization to carbon dioxide. Also the formation of PENA, EPMP and m-PB-acid could be shown. None of the soil metabolites (except CO_2 and bound

residues) exceeded 10% AR.

Etofenprox is degraded in soil under aerobic conditions at 20°C with $DT_{50\ lab}$ ranging from 7 days to 25 days and $DT_{90\ lab}$ ranging from 22 days to 84 days (first order, n=4). In one soil incubated at 10°C, the DT_{50} was 13 days and the DT_{90} was 41 days (first order).

From the results at 20°C a geometric mean DT_{50} value of 12 days (n=4) was calculated. Conversion to standard European conditions results in a DT_{50} (12°C) of 22.8 days, which was used for further calculations in the risk assessment.

Table 21d: Kinetics of degradation of etofenprox and its degradation products in soil (Völkl, 2001; see document III A 7.2.2.1)

Soil	**Senozan**	**Senozan**	**Gartenacker**	**Georgia**	**Cajon**
Origin	France	France	Switzerland	USA	USA
Soil type (USDA classification)	Silt clay loam	Silt clay loam	Loam	Sandy loam	Sandy loam
Incubation temperature	20°C	10°C	20°C	20°C	20°C
Etofenprox					
DT_{50} (days)	**7**	13	**8**	**14**	**25**
DT_{90} (days)	22	41	28	46	84
Kinetic constant k1 (1/day)	0.1069	0.0556	0.0830	0.0502	0.0275
Correlation coefficient (r)	0.9958	0.9887	0.9964	0.9833	0.9885
α-CO					
DT_{50} (days)	12	34	13	37	45
DT_{90} (days)	40	113	44	122	150
Kinetic constant k1 (1/day)	0.0581	0.0205	0.0529	0.0189	0.0153
Correlation coefficient (r)	0.9341	0.9469	0.9622	0.9587	0.9474
4'-OH					
DT_{50} (days)	14	56	19	29	44
DT_{90} (days)	46	186	63	96	145
Kinetic constant k1 (1/day)	0.0499	0.0124	0.0366	0.024	0.0159
Correlation coefficient (r)	0.9754	0.949	0.9817	0.898	0.9022
DE					
DT_{50} (days)	*****	*	*****	32	41
DT_{90} (days)				105	137
Kinetic constant k1 (1/day)				0.0219	0.0167
Correlation coefficient (r)				0.9711	0.9897
DP					
DT_{50} (days)	24	63	17	43	66
DT_{90} (days)	78	209	56	144	219
Kinetic constant k1 (1/day)	0.0291	0.011	0.0414	0.0160	0.0105
Correlation coefficient (r)	0.9762	0.9706	0.9958	0.9745	0.9559

* Calculation of the kinetic is not possible due to the very low amounts detected (<1% of applied radioactivity)

Degradation in water/sediment systems

The degradation of etofenprox in water/sediment systems was investigated in 3 studies (Lewis, 2001 and 2002 and Mirbach 2005 documents III A 7.1.2.2.2/01, III A 7.1.2.2.2/02). The applied test substance concentration was about 33 µg/100 mL of a mixture of radiolabelled [2-^{14}C-propyl]etofenprox and [α-^{14}C-benzyl]etofenprox corresponding to 200 g a.s./ha (maximum application rate). DT_{50} values for etofenprox of 6.5 days (pond) and 20.1 days (lake) were calculated in the whole system and 2.1 days and 10.4 days in the water phase (first order kinetics, $r^2 > 0.9$; see table 4.1.1.4-1). In an amendment to the first study (Lewis, 2002) dissipation times of 6.5 days (DT_{50}) were reported for the whole system and 1.0 day for the water phase. In an additional study report DT_{50} values of 17.9 days (pond), 32.2 days (lake) and 54.2 days (pond, amendment) for the sediment phase were calculated (Mirbach, 2005).
Immediately after application of etofenprox up to 70.1% were associated with the sediment. This was probably enhanced by the high organic carbon content of both sediments (7.3% pond, 5.1% lake). Only one significant metabolite, identified as 4'-OH, was detected in the water/sediment system. 4'OH was mainly found in sediment extracts in all incubation groups at the maximum levels of 14.4 to 21.4% AR at day 7 and 14, and thereafter, decreasing to ≤10% of AR after 30 days of incubation. All other metabolites were below 10 % AR. The metabolism of etofenprox in water/sediment systems shows also the formation of bound residues (up to 30.8% AR after 99 days of incubation in the lake system and up to 28.9% in the pond at day 30 which decreased to 22.6% at day 59 and 99), that were not detailed characterised, and mineralization to CO_2 (up to 17.8 and 28.2% AR in Emperor Lake and Millstream pond systems).

The DT_{50} values of 4'-OH in the entire system were 29.7 days (pond) and 21.8 days (lake). In an amendment to the first study (Lewis, 2002; pond) a dissipation times of 57 days (DT_{50}) were also reported. In an additional study report DT_{50} values of 55.8 days (pond), 26.4 days (lake) and 86.2 days (pond, amendment) for the sediment phase were calculated (Mirbach, 2005).
The Emperor Lake system was also incubated under light/dark conditions, which resulted in a faster degradation rate for etofenprox (DT_{50} 2.1 days, DT_{90} 7.1 days) and a bit lower rate for 4´-OH (DT_{50} 27.0 days, DT_{90} 87.1 days).

Proposed metabolic pathway: The principal route of degradation of etofenprox is by hydroxylation to 4´OH and further metabolised to EPMP. Etofenprox can also be degraded to α-CO and y-CO and further to m-PB-acid or EPMP. Another minor path involves the cleavage of the ether linkage between the two benzene rings to give DP. The formation of bound residues and mineralization to CO_2 was also shown in the water/sediment study.

In a risk assessment the higher DT_{50} value for the water phase of 10.4 days (Lewis 2001) should be used for safety reasons, since the organic carbon content was high in all tested systems. Conversion to standard European conditions results in a DT_{50} value of 19.7 days.

Table 21e: Degradation of etofenprox in aquatic systems (DT_{50} and DT_{90}, days)

Compound		**Etofenprox**		**4'-OH**		**Reference**
Incubation system		**Mill stream pond**	**Emperor Lake**	**Mill stream pond**	**Emperor Lake**	
Water phase	**DT_{50}**	2.1 [1.0]	**10.4**	Not determined	Not determined	**Lewis (2001** and [2002]) → Doc III A 7.1.2.2.2 / 01 and [/02] Mirbach (2005)
	DT_{90}	7.1 [3.2]	34.5	Not determined	Not determined	
Sediment phase	DT_{50}	17.9 [54.2]	32.2	55.8 [86.2]	26.4	
	DT_{90}	59.4 [180.0]	106.9	185.5 [286.4]	87.8	
Entire system	DT_{50}	6.5 [6.5]	20.1	29.7 [57]	21.8	
	DT_{90}	23.8 [143]	71.0	97.9 [185]	59.8	

1.1.4 Summary and discussion of degradation

See chapters 5.1.1. and 5.1.2.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

An adsorption/desorption screening test was performed in 1999 (Völkel, 1999, document III A 7.1.3). The distribution coefficients were determined, no adsorption isotherms were established. According to the results, etofenprox showed strong adsorption to soil particles. Only a maximum of 2.93% etofenprox could be desorbed.

A soil column leaching study (Warncke, 1998, document III A 7.2.3.2) was also performed, underlining the results obtained in the adsorption screening test, that etofenprox has a very low leaching potential (< 2% of application in the leachate).

For the risk assessment the arithmetic mean value of 10 832 ml/g (n=3; soil to aqueous ratio of 1:5) was used.

Table 21f: Adsorption of etofenprox onto / desorption from soils

Guideline	Soil type	Sand (%)	Clay (%)	Silt (%)	Org. C (%)	pH (KCl)	Adsorbed a.s. [%]	K_a [1]	K_{aOC} [2] [mL/g]	Reference
OECD 106 (soil to aqueous ratio of 1:5)	sandy loam	57.9	15.9	26.2	1.57	7.1	97.7	234	**14923**	**Völkel W. (1999)** → Doc III A 7.3.1
	silt loam	11.8	19.4	68.8	3.80	6.9	98.3	343	**9025**	
	loamy sand	81.9	5.1	13.0	2.29	6.0	97.3	196	**8548**	
								Mean	**10832**	
OECD 106 (soil to aqueous ratio of 1:25)	sandy loam	57.9	15.9	26.2	1.57	7.1	95.3	519	33067	
	silt loam	11.8	19.4	68.8	3.80	6.9	97.0	836	22009	
	loamy sand	81.9	5.1	13.0	2.29	6.0	94.5	434	18968	
								Mean	24681	

[1] K_a = Adsorption coefficient

[2] K_{aOC} = Adsorption coefficient based on organic carbon content

5.2.2 Volatilisation

Table 21g: vapour pressure

Property	Results	Reference
Vapour pressure	8.13×10^{-7} Pa at 25°C 2.16×10^{-3} Pa at 80°C 7.01×10^{-3} Pa at 90°C	**Doc. III-A 3; Study A 3.2**

5.2.3 Distribution modelling

No data available

5.3 Aquatic Bioaccumulation

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

No data available

5.3.1.2 Measured bioaccumulation data

Etofenprox has a potential for bioaccumulation as indicated by its high octanol / water partition coefficient (logPow of 6.9, Tognucci, 1998e).

The bio-concentration in aquatic organisms was studied experimentally. Bioaccumulation factors in a Bluegill sunfish were determined to be 1554, 7213 and 3951in edibles, non-edibles and whole fish, respectively, at test concentrations of 0.18 and 1.08 µg/L The BCF is corrected for a whole body lipid content of 5%, the resulting whole body BCF in fish is 2565. However, the accumulation was reversible with depuration half-life of 9 – 16 days and 95% depuration on day 69.

The bio-concentration in terrestrial organisms was estimated by calculation, according to the TGD on risk assessment.

Table 22a: Measurements of aquatic bio-concentration of [14C]-etofenprox in Bluegill sunfish

Guideline	Expo-sure	Log P_{OW} of a.s.	Initial concentra-tion of a.s.	Steady-state BCF	Uptake rate con-stant	Depurati on rate constant	Depuration time (DT_{50})	Metabolites	Reference
OECD 305 OPPTS 850.1730	Flow-through during 122 days	6.9	Low dose: 0.18 µg/L High dose: 1.08 µg/L	edibles: 1554 non-edibles: 7213 whole fish: 3951 (2565 corrected for a lipid content of 5%)	edibles: 0.235 non-edibles: 0.122 whole fish: 0.170	edibles: 0.061 non-edibles: 0.057 whole fish: 0.044	9 to 16 days	α-CO (1.3%) DE (0.9%) m-PB-acid (3.2 - 4.8%)	**Van Dijk (2002)** → Doc III A 7.4.3.3.1

Table 22b: Estimations on terrestrial bio-concentration

Basis for estimation	log P_{OW} (measured)	Estimated BCF for earthworms	Reference
$K_{ow} \approx 7940000$ (experimental data) and $RHO_{earthworm}$ = 1 $kg_{wwt}.L^{-1}$(default value)	6.9	$BCF_{earthworm} = (0.84 + 0.012K_{ow}) / (RHO_{earthworm})$ = 95281	TGD on risk assessment

5.3.2 Summary and discussion of aquatic bioaccumulation

The bioaccumulation factor corrected for a whole body lipid content of 5% in fish is 2565 in whole

fish.

Aquatic toxicity

5.3.3 Fish

5.3.3.1 Short-term toxicity to fish

In standard laboratory tests etofenprox is highly acutely toxic to fish, as indicated by the LC_{50}-values of 2.7 and 13.0 µg/L for Rainbow trout (*Oncorhynchus mykiss*) and Bluegill sunfish (*Lepomis macrochirus*), respectively.

The 96-hour LC_{50} and NOEC-values of the metabolite α-CO for fish were found to be higher than or equal to the limit concentration of 48 µg/L.

Laboratory studies conducted with etofenprox technical and the metabolite α-CO to assess their toxicity to aquatic organisms are summarised in the following Tables.

Table 23a: Acute toxicity to fish

Guideline	Species	Endpoint / Type of test	Exposure		Results µg a.i./L		Remarks	Reference
			Design	Dura-tion	LC_{50}	NOEC		
Test substance: etofenprox technical								
US EPA Section 72-1	Rainbow trout (*Oncorhyn-chus mykiss*)	Mortality / acute	flow-through	96 hours	**2.7**	**0.66**	5 concentra-tions tested, deaths in all but the two lowest dose groups	**Machado (1995a)** → Doc III A 7.4.1.1/01
US EPA Section 72-1	Bluegill sunfish (*Lepomis macrochiru s*)	Mortality / acute	flow-through	96 hours	13.0	6.9	5 concentra-tions tested, deaths in the two highest dose groups	Machado (1995b)
Test substance: metabolite α-CO								
OECD 203 Directive 92/69/EEC C.1 US EPA OPPTS 850.1075	Rainbow trout (*Oncorhyn-chus mykiss*)	Mortality / acute	flow-through	96 hours	**> 48**	**≥ 48**	No mortality at the limit concentration	**Bätscher (2002a)** → Doc III A 7.4.3.1

5.3.3.2 Long-term toxicity to fish

The chronic toxicity of etofenprox was tested on the Rainbow trout over 21 days and the NOEC was determined to be 3.2 µg/L. The toxicity of etofenprox on the early-life stage of fish was tested with the Zebra fish *(Brachydanio rerio)* and the NOEC determined to be 25 µg/L. (Zebra fish may well be less sensitive to the etofenprox than rainbow trout, which shows an acute LC_{50}-value of 2.7).

Table 23b: Chronic toxicity of etofenprox to fish

Guideline	Species	Endpoint / Type of test	Exposure		Results µg a.i./L (nominal)			Remarks	Reference
			Design	Duration	Effect	NOEC	LOEC		
OECD 204	Rainbow trout (*Oncorhynchus mykiss*)	Mortality, non-lethal effects (e.g. appearance, size and behaviour of the fish), growth / chronic	Semi-static	21 days	mortality	3.2	10*	5 concentrations tested, deaths in the highest dose group	Wilhelmy (1997)
OECD 210, OPPTS 850.1400	Zebra fish *(Brachydanio rerio)*	Mortality, non-lethal effects (e.g. eggs development and hatching rate, hatching time, development juv. fish, etc.)	Flow through	40 days	mortality of larvae and juvenile fish	**25**	**50**	5 concentrations tested, deaths in the highest dose group	**Peither (2005)** → Doc III A 7.4.3.2

* 90%mortality on day 21

5.3.4 Aquatic invertebrates

5.3.4.1 Short-term toxicity to aquatic invertebrates

Etofenprox is highly toxic to *Daphnia magna* with an EC_{50} of 1.2 µg/L.

The 48-hour EC_{50} and NOEC-values of the metabolite α-CO were higher than or equal to the limit concentration of 44 µg/L.

Table 23c: Acute toxicity to aquatic invertebrates

Guideline	Species	Endpoint / Type of test	Exposure		Results µg a.i./L (measured)		Remarks	Reference
			Design	Dura-tion	EC_{50}	NOEC		
Test substance: etofenprox technical								
OECD 202-I EC Directive 92/69/EEC, C.2	*Daphnia magna*	Mobility / acute	static renewal	48 hours	**1.2**	**0.089***	8 concentra-tions tested, treatment related immobilisation in the four highest concentrations	**Gries (2003)** → Doc III A 7.4.1.2/01
Test substance: metabolite α-CO								
OECD 202-I EC Directive 92/69/EEC, C.2 US EPA OPPTS 850.1010	*Daphnia magna*	Mobility / acute	static	48 hours	**> 44**	**≥ 44**	No immobilisa-tion at the limit concentration	**Bätscher (2002b)** → Doc III A 7.4.1.2/02

* based on nominal concentrations and sublethal effects only

5.3.4.2 Long-term toxicity to aquatic invertebrates

The chronic toxicity to *Daphnia magna* was determined in a 21-day reproduction study using [^{14}C]-etofenprox and the NOEC, based on numbers of offspring per adult, was determined to be 0.054 µg a.i./L.

Table 23d: Chronic toxicity of 14C-etofenprox to aquatic invertebrates

Guideline	Species	Endpoint / Type of test	Exposure		Results µg a.i./L (measured)		Remarks	Reference
			Design	Dura-tion	Effect	NOEC		
OECD 202	*Daphnia magna*	Reproduction and mortality / chronic	Semi-static	21 days	Reproduc-tion	**0.054**	5 concentra-tions tested, effects obser-ved in the 2 highest concen-trations	**Groeneveld *et al.* (1993)** → Doc III A 7.4.3.4

5.3.5 Algae and aquatic plants

Etofenprox is less toxic to algae, as shown by E_rC_{50} and E_bC_{50} values exceeding the water solubility (E_rC_{50} and E_bC_{50} >56.25 µg a.i./L).

The metabolite α-CO had no inhibitory effect on the growth of *Pseudokirchneriella subcapitata* up to its water solubility limit in test water (i.e. 42.5 µg/L at 20°C). Accordingly, the 96-hour EC_{50} values for the inhibition of the biomass and growth rate were higher than the mean measured concentration of 53 µg/L.

Laboratory studies conducted with etofenprox technical and the metabolite α-CO to assess their toxicity to algae are summarised in the table below.

Table 23e: Growth inhibition to algae

Guideline	Species	Type of test	Exposure		Results µg a.i./L (nominal)				Remarks	Reference
			Design	Duration	NOE_bC[1]	NOE_rC[2]	E_bC_{50}[1]	E_rC_{50}[2]		
Test substance: etofenprox technical										
OECD 201 Directive 92/69/EEC, C.3	*Pseudokirchneriella subcapitata*	Growth and biomass inhibition	static	72 hours	**56.25**	**56.25**	**> 56.25**	**> 56.25**	6 concentrations tested, no adverse effect on the biomass and the growth rate at the highest concentration	**Gries, Purghart (2003)** → Doc III A 7.4.1.3 /01
Test substance: metabolite α-CO										
OECD 201 Directive 92/69/EEC, C.3 US EPA OPPTS 850.5400	*Pseudokirchneriella subcapitata*	Growth and biomass inhibition	static	96 hours	**≥ 53**	**≥53**	**> 53**	**> 53**	No inhibitory effect at the limit concentration	**Bätscher (2002c)** → Doc III A 7.4.1.3 /02

[1] calculated from the area under the growth curve;

[2] calculated from growth rate;

[3] calculated from the cell density

5.3.6 Other aquatic organisms (including sediment)

Aquatic microbial activity

The toxicity of etofenprox to aquatic microbial activity was measured in laboratory experiment with activated sludge, as described in Table 4.2.1-6. Up to and including the highest tested concentration of 100 mg a.i./L (nominal) the test item etofenprox had no significant inhibitory effect on the respiration rate of activated sludge. However, at 50 and 100 mg a.i./L an increase of 3.4 and 10.3% oxygen consumption compared to the control could be detected. All test concentrations were far above the water solubility limit of Etofenprox.

The 3 hour EC_{50} is therefore greater than 100 mg a.i./L (nominal). The 3-hour NOEC for STP

micro-organisms was determined to be at least 100 mg/L (nominal).

Table 23f: Inhibition of aquatic microbial activity by etofenprox

Guide-line	Inoculum	Endpoint / Type of test	Exposure		Results mg a.i./L		Remarks	Reference
			Design	Dura-tion	NOEC or EC10	EC_{50}		
OECD 209	Activated sludge from predominant-ly domestic wastewater treating plant	Oxygen consumptio n /Bacterial respiration inhibition	Aerobic activated sludge incubated under defined conditions	3 hours	**≥ 100 (nominal)**	> 100 (nominal)	5 concentrations tested, no inhibitory effect on the respiration rate of activated sludge	**Czech P. (2002)** → Doc III A 7.4.1.4

Sediment dwelling organisms

The acute and the chronic toxicity of etofenprox to *Chironomus riparius* was determined experimentally in static water-sediments systems, with application of the test item to the water column. The nominal 10-day EC_{50}-value of etofenprox for survival and body weight of larvae of *Chironomus riparius* was determined to be higher than 20.9 µg/L, the highest concentration tested, and the NOEC was 3.8 µg/L. In this chronic study, the nominal NOEC based on the development rate was also 3.8 µg/L.

The sediment metabolite 4'-OH is less toxic to the invertebrate *Chironomus riparius* than etofenprox to the invertebrate daphia magna (the NOEC 198 times and the EC_{50} < 42 times). The 48-hour LC_{50} of 4'-OH was 50.2 µg/L and the 48-hour NOEC 17.6 µg/L (acute test in static water).

Table 23g: Acute toxicity to sediment dwelling organisms

Guideline	Species	Endpoint / Type of test	Exposure		Results µg a.i./L (nominal)		Remarks	Reference
			Design	Duration	EC_{50}	NOEC		
Test substance: etofenprox technical								
OECD 219	*Chironomus riparius*	survival/ body weight of the larvae	static water/se-diment system	10 days	**>20.9**[1]	**3.8**[2]	3 concentra-tions tested, toxic effects observed at the highest concentration	**Memmert (2002a)** → Doc III A 7.4.3.5.1/01
Test substance: metabolite 4'-OH								
OECD 202 OECD 219 Directive 92/69/EEC C.2 Proposal for a BBA Guideline	*Chironomus riparius*	immobility/ acute	static	48 hours	**50.2**[3]	**17.6**[3]	5 concentra-tions tested, toxic effects observed at the two highest concentra-tions	**Memmert (2002b)** → Doc III A 7.4.3.5.1 / 02

[1] based on the survival rate and the larval body weight, [2] based on a significant reduction in body weight [3] mean measured

Table 23 h: Chronic toxicity of etofenprox to sediment dwelling organisms

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results µg a.i./L (nominal)		Remarks	Reference
			Design	Duration	Effect	NOEC		
OECD 219 Proposal for a BBA Guideline	*Chironomus riparius*	development time/ rate and emergence ratio of midges*	static water/se diment system	25 days	reduced develop-ment rate	**3.8**	3 concentra-tions tested, toxic effects observed at the highest concentration	**Memmert (2002c)** → Doc III A 7.4.3.5.1/03

* not significant

5.4 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

CLP:

Aquatic Acute 1:

Aquatic acute toxicity: L(E)C_{50} values for all three trophic levels are between 0.1 – 0.001 mg/L; Lowest L(E)C_{50} value: EC_{50} (dapnia) =0.0012 mg/L

- ➔ **Classification with Aquatic Acute 1**
- ➔ **M factor = 100**

Studies used:

- Doc. III A7.4.1.1/01: Machado M.W. (1995 a), EPA, Subdivision E, Series 72, § 72-1 -> **LC_{50} = 0.027 mg/L**
- Doc. III A7.4.1.2/01: Gries T. (2003), OECD 202, Part1 (1984) EEC C.2 (1992) -> **EC_{50} = 0.0012 mg/L**
- Doc. III A7.4.1.3/01: Gries T., Purghart V (2003), OECD 201 (1984) EEC C.3 (1992) -> **E_rC_{50} = >0.056 mg/L**

Aquatic Chronic 1:

There are chronic data for all three trophic levels and Etofenprox is not rapidly degradable (17% biodegradation in a ready test; 18, 28 and 35% mineralization in a water/sediment simulation test; hydrolytically stable pH 4-9; photloysis in water DT_{50} =4.7 days, but there are not enough data about the toxic effects of the two major metabolites and contribution to total removal will be quite low;).

Chronic NOEC values for all three trophic levels are between 0.01 and 0.00001 mg/L;

Lowest chronic NOEC value: NOEC (daphnia) =0.000054 mg/L

- ➔ **classification with Aquatic Chronic 1**
- ➔ **M factor = 1000**

Studies used:

- Doc. III A7.1.1.2.1/02: Thus, van der Laan-Straat-hof (1992), OECD 301D (1982) EEC C.4-E (1984) -> **17% degradation in 28 days**
- Doc. III A7.1.2.2.2/01: Lewis C.J. (2001), SETAC (1995) and Dir. 95/36/EC (1995) -> **28 and 18% mineralization in 99 days at 20°C**
- Doc. III A7.1.2.2.2/02: Lewis C.J. (2002), SETAC (1995) and Dir. 95/36/EC (1995) -> **35% mineralization in 100 days at 20°C**
- Doc. III A7.1.1.1.1/01: Van der Gaauw A. (2001), EEC C.7 (1992), OECD 111 (1981) and EPA OPPTS 835.2110 -> **hydrolytically stable at pH 4,7 and 9 at 50°C**
- Doc. III A7.1.1.1.2/01: Van der Gaauw A. (2003), Dirl 95/36/EEC and 94/37/EEC, SETAC

(1995), OECD guidande document (97)21, EPA OPPTS 835.2210 and Japan MAFF Guideline, **16 -> DT_{50} =4.7 days, but not enough data on toxic effects of two major metabolites**

- Doc. III A7.4.3.2: Peither A (2005), OECD 210, OPPTS 850.1400 -> **NOEC (fish) =0.025 mg/L**
- Doc. III A7.4.3.4: Groenefeld A.H.C., Berends A.G., van der Laan J.M.Th., van Dijk N.R.M. (1993), OECD guideline 202 (OECD, 1984 and 1991) -> **NOEC (crustacea) =0.000054 mg/L**
- Doc. III A7.4.1.3/01: Gries T., Purghart V (2003), OECD 201 (1984) EEC C.3 (1992) -> **NOE_rC = (algae) =0.056 mg/L**

DSD:

Acute aquatic toxicity: $L(E)C_{50}$ values for all three trophic levels are between 0.1 – 0.001 mg/L; lowest $L(E)C_{50}$ value: EC_{50} (Dapnia) =0.0012 mg/L; the substance is not readily degradable, the measured $logP_{ow}$ =6.9 and the measured BCF = 2565

R50/53:

➔ **classification with N; R50/53**

➔ **SCL:**

N; R50-53: $C_n \geq 0.25\%$;

N, R51-53: $0.025\% \leq C_n < 0.25\%$;

R52-53: $0.0025\% \leq C_n < 0.025\%$;

Studies used:

- Doc. III A7.4.1.1/01: Machado M.W. (1995 a), EPA, Subdivision E, Series 72, § 72-1 -> **LC_{50} (fish) =0.027 mg/L**
- Doc. III A7.4.1.2/01: Gries T. (2003), OECD 202, Part1 (1984) EEC C.2 (1992) -> **EC_{50} (crustacea) =0.0012 mg/L**
- Doc. III A7.4.1.3/01: Gries T., Purghart V (2003), OECD 201 (1984) EEC C.3 (1992) -> **E_rC_{50} (algae) >0.0056 mg/L**
- Doc III A3.9/01; Tognucci A.; (1998) ; OECD 107 and 117; EEC A8; JMAFF; (HPLC method); $logP_{ow}$ =6.9;
- Doc III A7.1.1.2.1/02: Thus, van der Laan-Straat-hof (1992), OECD 301D (1982) EECC.4-E (1984) -> **17% degradation in 28 days**
- Doc III A7.4.3.3.1: van Dijk A. (2002), OECD 205 (1996) EPA OPPTS 850.1730 (Draft, 1996) -> **BCF = 2565**

5.5 Conclusions on classification and labelling for environmental hazards (sections 5.1

– 5.4)

Proposed classification according to Reg. (EU) No 1272/2008, Table 3.1 and Reg. (EU) No 286/2011(proposed by RMS)

Classification		Justification
Classification	Aquatic acute 1 (M=100)	L(E)C_{50} values ≤1 mg/L for all three trophic levels. Lowest available EC_{50} value =0.0012 mg/L.
	Aquatic chronic 1 (M=1000)	Not rapidly degradable and chronic NOECs for all three trophic levels ≤0.1 mg/L. Lowest available chronic NOEC value =0.000054 mg/L.
Hazard statements	H400 - Very toxic to aquatic life	See above
	H410 – Very toxic to a aquatic life with long lasting effects	See above

Proposed labelling according to Reg. (EU) No 1272/2008, Table 3.1 and Reg. (EU) No 286/2011(proposed by RMS)

Labelling		
GHS Pictograms		 GHS09
Signal words		Warning
Hazard statements		H410 – Very toxic to a aquatic life with long lasting effects
Precautionary statement	Prevention	P273 – Avoid release to the environment
	Response	P391 – Collect spillage
	Storage	-
	Disposal	P501 - Dispose of contents/container in accordance with local/regional/ national/international regulation (to be specified).

Proposed classification and labelling according to Reg. (EU) No 1272/2008, Table 3.2 (proposed by RMS)

Classification		Justification
Hazard symbol:	N	
Indication of danger:	**Dangerous for the environment**	
Labelling symbol:		
Risk phrases	**R50/53** Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment **SCL:** N; R50-53: $C_n \geq 0.25\%$; N; R51-53: $0.025\% \leq C_n < 0.25\%$; R52-53: $0.0025\% \leq C_n < 0.025\%$;	All acute toxicity values are ≤1 mg/L and the substance is not readily degradable. Lowest available EC_{50} value =0.0012 mg/L.
Safety phrases	**S60-61** This material and its container must be disposed of as hazardous waste. Avoid release to the environment. Refer to special instructions /safety data sheets.	According to classification with N; R50-53 and labelling with N; R50/53 S-phrases S60-61 have to be applied on the label.

6 OTHER INFORMATION

No other informations

7 REFERENCES

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A 2.10.1 → B 6.6	Mirbach M.	2004	Etofenprox: estimation of the human exposure to etofenprox used in the wood preservative product SPU-01990-I. Landis Kane Consulting, Report No. 04-alpha-02 Landis Kane Consulting, Document No.500-5-93 not GLP, not published	Y	Mistui Chemicals. Inc.
A 2.10.2 → B 7.1/06	Rathey S.	2005 b	Estimation of the predicted environmental concentrations of etofenprox used in the wood preservative product SPU-01990-I. Landis Kane Consulting, Report No. 04-alpha-04/03 Landis Kane Consulting, Document No.500-7-46 Not GLP, not published	Y	Mitsui Chemicals, Inc.
A 3.1.1	Tognucci A.	1999	Determination of the melting point / melting range of etofenprox RCC Ltd, Report No. 718830 Landis Kane Consulting, Document No: 500-2-01 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.1.3	Tognucci A.	1998 b	Determination of the relative density of etofenprox RCC Ltd, Report No. 692728 Landis Kane Consulting, Document No. 500-2-03 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.2	Tognucci A.	2000	Determination of the vapour pressure of etofenprox RCC Ltd, Report No. 751803 Landis Kane Consulting, Document No. 500-2-04 GLP, unpublished	Y	Mitsui Chemicals, Inc.
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A 3.3.1/01	Shimono S.	1999 a	Physical state of etofenprox (MTI-500) Mitsui Chemicals, Inc., LSL, Report No. not specified Landis Kane Consulting, Document No. 500-2-05 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.3.1/03	Mirbach M.	2006	Comments on the Physical State of Etofenprox Landis Kane Consulting, Report No. not specified Landis Kane Consulting, Document No. not specified Not GLP, unpublished	Y	Mistui Chemicals. Inc.
A 3.3.2/01	Shimono S.	1999 b	Color of etofenprox (MTI-500) Physical state of etofenprox (MTI-500) Mitsui Chemicals, Inc., Life Science Laboratory, Report No. not specified Landis Kane Consulting, Document No. 500-2-06 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.3.2/02	Shimono S.	2002 b	Color of manufactured etofenprox (MTI-500) Physical state of etofenprox (MTI-500) Mitsui Chemicals, Inc., Life Science Laboratory, Report No. not specified Landis Kane Consulting, Document No. 500-2-54 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.3.3/02	Shimono S.	2002 c	Odor of manufactured Etofenprox (MTI-500) Physical state of etofenprox (MTI-500) Mitsui Chemicals, Inc., Life Science Laboratory, Report No. not specified Landis Kane Consulting, Document No. 500-2-55 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.4/01	Tognucci A.	1998 c	Determination of the NMR-, IR-, UV/VIS absorption and mass spectra of etofenprox and amendment dated October 13, 1999 RCC Ltd, Report No. 692785 Landis Kane Consulting, Document No. 500-2-08 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.4/02	Matsumoto T.	2002 a	Measurement of UV-VIS absorption spectrum of 4'-OH Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82072 Landis Kane Consulting, Document No. 500-2-09 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.4/04	Tognucci A.	2003	Determination of the NMR-, IR, UV/VIS absorption and mass spectra of CEP RCC Ltd, Report No. 845212 Landis Kane Consulting, Document No. 500-2-56 GLP, unpublished	Y	Mitsui Chemicals, Inc.
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A 3.5/02	McCorquo-dale G.Y.	2002 a	Physico-chemical testing with [14C]-Alpha-CO: water solubility Inveresk Research, Report No: 21386 Landis Kane Consulting, Document No. 500-2-12 GLP, unpublished	Y	Mitsui Chemicals, Inc.
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A 5.3/01	Schumacher P., Fennert E.-M.	2003a	Determination of toxic values against *Reticulitermes santonensis* De Feytaud according to EN 117 (08/90) without accelerated ageing procedure – test material SPU-01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; Report No. 3.2/03/8417/01 Landis Kane Consulting, Document No. 500-6-62 Not GLP, not published	Y	Spiess-Urania Chemicals GmbH

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A 5.4	Nishimura K., Koba-yashi T., Fujita T.	1985	Symptomatic and neurophysiological activities of new synthetic non-ester pyrethroids, etofenprox, MTI-800, and related compounds Pesticide Biochemistry and Physiology Vol. 25, pp. 387 -395, 1986 Landis Kane Consulting, Document No. 500-3-01 Not GLP, published	N	Public in-formation
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A 6.1.1/03	Hashimoto K.	1982 a	Report on acute toxicity study of MTI-500 (ethofenprox) in rats Hatano Research Institute, Food and Drug Safety Center, Report No. A-82-27~34 Landis Kane Consulting, Document No. 500-5-08 Not GLP, not published	Y	Mitsui Chemicals, Inc.
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A 6.1.2/01	Oda S.	2003 b	Acute dermal toxicity study of etofenprox in rats Bozo Research Center Inc., Report No. B-5040 Landis Kane Consulting, Document No. 500-5-71 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.1.3	Jackson C.J., Hardy C.J., Clark G.C., Greg-son R.L., Lewis D.J., Gopinath C.	1983	MTI-500 Acute inhalation toxicity in rats 4 hour exposure Huntingdon Research Centre Ltd., Report No. MTC 60/821079 Landis Kane Consulting, Document No. 500-5-10 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.1.4.s	Kashima M., Ikeda H., Maru-yama Y., Ootsuka Y.	1985 a	MTI-500 Primary skin stimulation test in rabbits - Amendment No. 1 from October 28, 1991 Haruna Laboratory Nippon Experimental Medical Research Institute, Ltd., Report No. NEMRI-H-85-5 Landis Kane Consulting, Document No. 500-5-11 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.1.5	Kobayashi K.	1985	MTI-500 Skin sensitization test in guinea pigs - Correction to translation from October 21, 2003 Oizumi Laboratory Nippon Experimental Medical Research Institute, Ltd., Report No. not specified Landis Kane Consulting, Document No. 500-5-13 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.2/01	Hawkins D.R., Kirk-patrick D., Ewen B., Midgley I., Biggs S.R., Whitby B.R.	1985 a	The biokinetics and metabolism of ^{14}C-ethofenprox in the rat Huntingdon Research Centre Ltd., Report No. HRC/MTC 68/84610 Landis Kane Consulting, Document No. 500-5-02 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.2/03	Burri R.	2001 b	[14C]-alpha-CO: absorption, distribution, metabolism and excretion after single oral administration to male rats RCC Ltd., Report No. 819832 Landis Kane Consulting, Document No. 500-5-45 Not GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.2/04	Hawkins D.R., Kirk-patrick D., Ewen B., Midgley I., Biggs S.R.	1985 b	The metabolism of ^{14}C-ethofenprox in dogs Huntingdon Research Centre Ltd., Report No. HRC/MTC 69/84583 Landis Kane Consulting, Document No. 500-5-04 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.2/05	Tomoda K.	1986	Metabolism study of ethofenprox (MTI-500), metabolism in rat Mitsui Toatsu Chemicals, Inc., Report No. not specifed Landis Kane Consulting, Document No. 500-5-03 Not GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.2/06	Thalaker F.	1999	Dermal absorption of ^{14}C-etofenprox in male rats (preliminary and definitive phases) Covance Laboratories Inc., Report No. 6648-135 Landis Kane Consulting, Document No. 500-5-80 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.3.2	Killeen J.C.	2000	A 28-day repeated dose dermal toxicity study in rabbits with technical MTI-500 Ricerca, LLC Toxicology & Metabolism, Report No. 011077-1 Landis Kane Consulting, Document No. 500-5-18 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.4.1/01	Green O.P., Street A.E., Heywood R., Gopinath C., Almond R.H.	1983 a	Assessment of the toxicity of MTI-500 in rats during dietary administration for 13 weeks Re-issued amended pages on December 18, 1985 Huntingdon Research Centre Ltd., Report No. MTC 56/821067 Landis Kane Consulting, Document No. 500-5-14 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.4.1/02	Green O.P., Heywood R., Street A.E., Gopinath C., Almond R.H.	1983 b	Assessment of the toxicity of MTI-500 to mice by dietary administration for 13 weeks Re-issued amended pages on December 18, 1985 Huntingdon Research Centre Ltd., Report No. MTC 55/821112 Landis Kane Consulting, Document No. 500-5-15 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.4.3.1	Coombs D.W., Hardy C.J., Clark G.C., Street A.E., Gipson W.A., Gopinath C., Reed L.E.	1985	Ethofenprox (MTI-500) 90-day inhalation study in rats Huntingdon Research Centre Ltd., Report No. MTC 81/841257 Landis Kane Consulting, Document No. 500-5-17 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.5.1/01 and A 6.7/01	Green O.P., Heaps C.J., Heywood R., Street A.E., Gopinath C., Singh H., Gipson W.A.	1986 a	Ethofenprox (MTI-500) Potential tumorigenic and toxic effects in prolonged dietary administration to rats Huntingdon Research Centre Ltd., Report No. MTC 59/85581 Landis Kane Consulting, Document No. 500-5-24 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.5.1/02 and A 6.7/02	Green O.P., Heaps C.J., Heywood R., Street A.E., Go-pinath C., Imm S., Gipson W.A.	1986 b	Ethofenprox (MTI-500) Potential tumoregenic and toxic effects in prolonged dietary administration to mice Huntingdon Research Centre Ltd., Report No. MTC 59/85582 Landis Kane Consulting, Document No. 500-5-25 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.5.2	Harling R.J., Burfort P., Street A.E., Heywood R., Majeed S.K., Gopinath C.	1985 b	Ethofenprox (MTI-500) Toxicity to dogs by repeated dietary administration for 52 weeks followed by a recovery period of 8 weeks Huntingdon Research Centre Ltd., Report No. MTC 71/85234 Landis Kane Consulting, Document No. 500-5-16 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.1	Edwards C., Forster R.	1985	Reverse mutation in *Salmonella typhimurium* Life Science Research, Roma Toxicology Centre, Report No. 162001-M-06185 Landis Kane Consulting, Document No. 500-5-19 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.6.2	Bootman J., Hodson-Walker G., Dance C.A.	1985 a	*In vitro* assessment of the clastogenic activity of MTI-500, ethofenprox, in cultured human peripheral lymphocytes Life Science Research Ltd., Report No. 85/MT0017/430 Landis Kane Consulting, Document No. 500-5-21 Not GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.3/01	Seeburg A.H., Forster R.	1985 a	Gene mutation in Chinese hamster V79 cells: test substance MTI-500 Life Science Research, Roma Toxicology Centre, report No. 162002-M-06985 Landis Kane Consulting, Document No. 500-5-20 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.3/02	Seeburg A.H., Forster R.	1985 b	Unscheduled DNA synthesis in human cells cell line: Hela S3 Life Science Research, Roma Toxicology Centre, Report No. 162003-M-05785 Landis Kane Consulting, Document No. 500-5-23 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.4	Bootman J., Hodson-Walker G., Dance C.A.	1985 c	MTI-500, ethofenprox: Assessment of clastogenic action on bone marrow erythrocytes in the micronucleus test Life Science Research, Report No. 85/MT0016/406 Landis Kane Consulting, Document No. 500-5-22 Not GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.6.7/01	Cummins H.A., Gardner J.R.	1985 a	MTI-500 α-CO: Acute oral toxicity in the rat Life Science Research Ltd, Report No. 85/MT0018/474 Landis Kane Consulting, Document No. 500-5-38 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.7/02	Cummins H.A., Gardner J.R.,	1985 b	MTI-500 α-CO: Acute percutaneous toxicity in the rat Life Science Research Ltd, Report No. 85/MT0019/473 Landis Kane Consulting, Document No. 500-5-39 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.7/03	Powell L.A.J., Coleman M., Hey-wood R., Gopinath C., Gibson W.A.	1987	MTI-500 α-CO Preliminary toxicity study in rats by dietary administration for 4 weeks Huntingdon Research Centre Ltd., Report No. MTC 140/87194 Landis Kane Consulting, Document No. 500-5-40 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.7/04	Powell L.A.J., Coleman M., Crock D., Gopi-nath C., Gibson W.A., Read R.M., An-derson A.	1988	MTI-500 α-CO Toxicity to rats by dietary administration for 13 weeks Huntingdon Research Centre Ltd., Report No. MTC 141/871458 Landis Kane Consulting, Document No. 500-5-41 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.6.7/06	Bootman J., May K.	1985 b	MTI-500 α-CO: Assessment of its ability to cause lethal DNA damage in strains of *Escherichia coli* Life Science Research Limited, report No. 85/MT0022/504 Landis Kane Consulting, Document No. 500-5-44 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.6.7/07	Bootman J., Hodson-Walker G., Dance C.A.	1985 b	*In vitro* assessment of the clastogenic activity of MTI-500 α-CO in cultured human peripheral lymphocytes Life Science Research Limited, Report No. 85/MT0021/711 Landis Kane Consulting, Document No. 500-5-43 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.8.1.1 /01	Cozens D.D., Hughes E.W., Clark R., Ander-son A.	1985 a	Effect of ethofenprox (MTI-500) on fertility and pregnancy of the rat Huntingdon Research Centre Ltd., Report No. MTC 66/84668 Landis Kane Consulting, Document No. 500-5-33 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.8.1.1 /02	Cozens D.D., Hughes E.W., An-derson A.	1985 b	Effect of ethofenprox (MTI-500) on pregnancy of the rat with rearing to maturation of the F1 generation Huntingdon Research Centre Ltd., Report No. MTC 64/85422 Landis Kane Consulting, Document No. 500-5-34 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.8.1.1 /03	Cozens D.D., Hughes E.W., Offer J., Anderson A.	1985 c	Effect of ethofenprox (MTI-500) on the peri and post natal period of the rat with rearing to maturation of the F1 offspring Huntingdon Research Centre Ltd., Report No. MTC 65/85423 Landis Kane Consulting, Document No. 500-5-35 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.8.1.2 /01	Bottomley A., Barton S.J., Masters R.E., Offer J., Parker C.A., Ander-son A., Dawe I.S.M.	1985	Effect of etofenprox (MTI-500) on pregnancy of the rabbit Re-issued amended pages on December 20, 1985 Huntingdon Research Centre Ltd., Report No. MTC 85(84)/85444 Landis Kane Consulting, Document No. 500-5-36 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.8.1.2 /02	Fisher B.J.	2000	Rabbit developmental toxicity study with etofenprox Covance Laboratories Inc., Report No. 6648-146 Landis Kane Consulting, Document No. 500-5-37 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.8.2/01	Cozens D.D., Barton S.J., Offer J.M., Parker C.A., Anderson A.	1985 d	Effect of ethofenprox (MTI-500) on multiple generations of the rat Re-issued amended pages on January 07, 1985 Huntingdon Research Centre Ltd., Report No. MTC 67/85706 Landis Kane Consulting, Document No. 500-5-32 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.9/01	Smith P.B.	2002	Acute oral gavage neurotoxicity study with MTI-500 in rats Covance Laboratories Inc., Report No. 6648-154 Landis Kane Consulting, Document No. 500-5-06 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.9/02	Smith P.B.	2003 a	13-week dietary neurotoxicity study with MTI-500 in rats Covance Laboratories Inc., Report No. 6648-153 Landis Kane Consulting, Document No. 500-5-47 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.9/03	Myers D.P.	2003	Etofenprox developmental neurotoxicity study in the rat by oral (dietary) administration Huntingdon Life Sciences, Report No. MTU 215/032731 Landis Kane Consulting, Document No. 500-5-48 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.9/04	Burton D.A.	2002	Etofenprox – Validation of an analytical method for the determination of Etofenprox in UAR VRF1 (VRF1) Diet Huntingdon Life Sciences Ltd., Report No. MTU/222/1023183 Landis Kane Consulting, Document No. 500-5-05 GLP, not published	Y	Mitsui Chemicals, Inc.
A 6.10	Smith P.B.	2003 b	4-week dietary investigative study on thyroid function and hepatic micriosomal enzyme induction with MTI-500 in rats Covance Laboratories Inc., Report No. 6648-156 Landis Kane Consulting, Document No. 500-5-83 GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.11/03	Kamiya J., Yoshiwara K., Saito S., Takahashi Y., Oseki K., Shimizu H., Kawa-zura H., Shiga Y., Yoshida M., Haya-kawa M.	1985	General pharmacology of MTI-500 Institute of Biological Sciences, Mitsui Pharmaceuticals Inc., Japanese Pharmacology & Therapeutics, Vol.13 (11), 229-244 (1985) Landis Kane Consulting, Document No. 500-5-46 Not GLP, published	N	Public in-formation
A 6.12.1	Yamazaki Y.	1992	Health report from the Industrial Hygiene Section, Ohmuta Factory Mitsui Toatsu Chemicals, Inc., Report No. not specified Landis Kane Consulting, Document No. 500-5-49 not GLP, not published	Y	Mitsui Chemicals, Inc.
A 7.1.1.1.1 /01	van der Gaauw A.	2001	^{14}C-etofenprox: hydrolysis at three different pH values RCC Ltd, Report No. 731158 Landis Kane Consulting, Document No. 500-2-20 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.1.1.1 /02	Clayton M.A., McCorquo-dale G.Y., Paterson K.	2003	Hydrolytic stability of [^{14}C]-alpha-CO in buffered aqueous solution Inveresk Research, Report No. 21993 Landis Kane Consulting, Document No. 500-7-09 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.1.1.1.2 /01	van der Gaauw A.	2003	Aqueous photolysis of [^{14}C]-etofenprox under laboratory conditions and determination of quantum yield RCC Ltd, Report No. 755526 Landis Kane Consulting, Document No. 500-2-21 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.1.1.2 /02	Clayton M.A., McCorquo-dale G.Y.	2003	Artificial sunlight photodegradation of [^{14}C]-alpha-CO in buffered aqueous solution Inveresk Research, Report No. 21971 Landis Kane Consulting, Document No. 500-7-10 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.1.2.1	Thus J.L.G., van der Laan-Straathof J.M.Th., Keetelaar-Jansen W.A.J.	1993	Biodegradation of ^{14}C-etofenprox in an adapted modified Sturm test Solvay Duphar B.V., Report No. C.DNL.62.002 Landis Kane Consulting, Document No. 500-7-12 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.1.2.1 /02	Thus J.L.G., van der Laan-Straathof J.M.Th	1992	Determination of the biodegradability of etofenprox in a closed bottle test Solvay Duphar B.V., Report No. C.DNL.62.001 Landis Kane Consulting, Document No. 500-7-11 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.1.2.2.2 /01	Lewis C.J.	2001	(^{14}C)-MTI-500: degradation and retention in water-sediment systems and amendment dated July 22, 2002 Covance Laboratories Ltd., Report No. CLE 719/6-D2142 Landis Kane Consulting, Document No. 500-7-13 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.2.2.2 /02	Lewis C.J.	2002	(^{14}C)-MTI-500: recovery of radioactivity, isolation and analysis of a degradation product from a water-sediment system Covance Laboratories Ltd., Report No. CLE 719/14-D2149 Landis Kane Consulting, Document No. 500-7-14 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.2.2.2 /03	Mirbach M.	2005	Etofenprox: estimation of the degradation in sediment Landis Kane Consulting, Report No. 05-alpha-31 Landis Kane Consulting, Document No. 500-7-44 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.1.3	Völkel W.	1999	Adsorption / desorption of MTI-500 (etofenprox) on three soils RCC Ltd, Report no: 663175 Landis Kane Consulting, Document No. 500-7-06 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.2.2.1	Völkl S.	2001	^{14}C-etofenprox: degradation and metabolism in four soils incubated under aerobic conditions - first amendment dated February 26, 2002 - second amendment dated June 03, 2003 RCC Ltd, Report No. 728987 Landis Kane Consulting, Document No. 500-7-01 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.2.2.4	Mamouni A	2002 b	Photolysis of ^{14}C-MTI-500 on soil surface under laboratory conditions RCC Ltd, Report No. 800616 Landis Kane Consulting, Report No. 500-7-04 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.2.3.2	Warncke U.	1998	Leaching behaviour of etofenprox after application of Trebon 30 EC Urania Agrochem GmbH, Chemical Laboratories, Report No. C96VSI03 Landis Kane Consulting, Document No. 500-7-07 GLP, unpublished	Y	Spiess-Urania Chemicals GmbH
A 7.3.1	Bates M.	2001 d	MTI-500: estimation of the photochemical oxidative degradation - Amended final report from January 31, 2001 Covance Laboratories Ltd., Report No. 719/12-D2141 Landis Kane Consulting, Document No. 500-2-27 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.4.1.1 /01	Machado M.W.	1995 a	Etofenprox technical - acute toxicity to Rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions Springborn Laboratories Inc., Report No. 94-12-5625 Landis Kane Consulting, Document No. 500-8-05 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.1 /02	Machado M.W.	1995 b	Etofenprox technical - acute toxicity to Bluegill sunfish (*Lepomis macrochirus*) under flow-through conditions Springborn Laboratories Inc., Report No. 95-1-5653 Landis Kane Consulting, Document No. 500-8-07 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.1 /03	Bätscher R.	2002 a	Acute toxicity of α-CO to Rainbow trout (*Oncorhynchus mykiss*) in a 96-hour flow-through test RCC Ltd., Report No. 841573 Landis Kane Consulting, Document No. 500-8-09 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.2 /01	Gries T.	2003	Etofenprox technical: static renewal acute toxicity test with Daphnids (*Daphnia magna*) Springborn Smithers Laboratories (Europe) AG, Report No. 1045.000.110 Landis Kane Consulting, Document No. 500-8-51 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.4.1.2 /02	Bätscher R.	2002 b	Acute toxicity of α-CO to *Daphnia magn*a in a 48-hour immobilization test RCC Ltd, Report No. 841575 Landis Kane Consulting, Document No. 500-8-10 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.3 /01	Gries T., Purghart V.	2003	Etofenprox technical: static toxicity test with the freshwater algae *Pseudokirchneriella subcapitata* Springborn Smithers Laboratories (Europe) AG, Report No. 1045.000.430 Landis Kane Consulting, Document No. 500-8-52 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.3 /02	Bätscher R.	2002 c	Toxicity of α-CO to *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in a 96-hour algal growth inhibition test RCC Ltd, Report No. 841577 Landis Kane Consulting, Document No. 500-8-11 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.1.4	Czech P.	2002	Toxicity of etofenprox to activated sludge in a respiration inhibition test RCC Ltd, Report No. 841615 Landis Kane Consulting, Document No. 500-8-50 GLP, unpublished	Y	Spiess-Urania Chemicals GmbH

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A 7.4.3.1	Wilhelmy H.	1997	Etofenprox technical: fish (rainbow trout), prolonged toxicity test, 21 days (semi-static) Dr. U. Noack-Laboratorium, Report No. 970304SP Landis Kane Consulting, Document No. 500-8-13 GLP, unpublished	Y	Spiess-Urania & Mitsui Chemicals, Inc.
A 7.4.3.2	Peither A.	2005	Toxic effects of MTI-500 (Etofenprox) to zebra fish (*Brachydanio rerio*) in an early-life stage toxicity test ; RCC Ltd., Report no. 853517 Landis Kane Consulting, Document No. 500-8-66 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.3.3.1	van Dijk A.	2002	Bioconcentration: flow-through fish test with MTI-500 (Trebon) in Bluegill sunfish RCC Ltd, Report No. 762254 Landis Kane Consulting, Document No. 500-8-15 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.3.4	Groenefeld A.H.C., Berends A.G., van der Laan J.M.Th., van Dijk N.R.M.	1993	The chronic toxicity of ^{14}C-etofenprox to *Daphnia magna* Solvay Duphar B.V., Report No. C.DNL.51.007 Landis Kane Consulting, Document No. 500-8-18 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.4.3.5.1 /01	Memmert U.	2002 a	Effect of MTI-500 on larvae of *Chironomus riparius* in a 10-day toxicity test RCC Ltd, Report No. 803777 Landis Kane Consulting, Document No. 500-8-21 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.3.5.1 /02	Memmert U.	2002 b	Acute toxicity of 4'-OH to first - instar larvae of the midge *Chironomus riparius* RCC Ltd, Report No. 841579 Landis Kane Consulting, Document No. 500-8-12 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.4.3.5.1 /03	Memmert U.	2002 c	Effect of MTI-500 on the development of sediment-dwelling larvae of *Chironomus riparius* in a water-sediment system RCC Ltd, Report No. 803608 Landis Kane Consulting, Document No. 500-8-22 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.5.1.1	Kölzer U.	2003	Assessment of the side effects of etofenprox on the activity of the soil microflora Arbeitsgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Report No. 20031050/01-ABMF Landis Kane Consulting, Document No. 500-8-53 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.5.1.2	Roberts N.L., Hakin B.	1989	The subacute toxicity (LC50) of etofenprox (MTI-500) to the earthworm (*Eisenia foetida*) Huntingdon Research Centre Ltd., Report No. MTF 2/881276 Landis Kane Consulting, Document No. 500-8-25 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.5.1.3	Büche, C.	2004	Terrestrial (non-target) plant test with MTI-500 30%EC: seedling emergence and seedling growth & vegetative vigour test. RCC Ltd., Report No. 853515 Landis Kane Consulting, Document No. 500-8-64 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.5.3.1.1	Roberts N.L., Hakin B., Ander-son A.	1985	The acute toxicity (LD50) of MTI-500 (ethofenprox) to the Mallard duck Huntingdon Research Centre plc, Report No. MTC 77C/84793 Landis Kane Consulting, Document No. 500-8-01 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.5.3.1.2/ 01	Roberts N.L., Hakin B.	1984 a	The subacute dietary toxicity (LC50) of MTI-500 (etofenprox) to the Bobwhite quail - amended final report dated June 27, 1985 - signature pages added: August 21, 1985 Huntingdon Research Centre plc, Report No. MTC 77A/84795/2 Landis Kane Consulting, Document No. 500-8-02 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.5.3.1.2/ 02	Roberts N.L., Hakin B.	1984 b	The subacute dietary toxicity (LC50) of MTI-500 (etofenprox) to the Mallard duck - amended final report dated June 26, 1985 - signature pages added: August 21, 1985 Huntingdon Research Centre plc, Report No. MTC 77B/84795/2 Landis Kane Consulting, Document No. 500-8-03 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 7.5.3.1.3	Rodgers M.H.	1996	MTI-500 Effects on reproduction in Bobwhite quail after dietary administration Huntingdon Life Sciences Ltd., Report No. MTC 270/962282 Landis Kane Consulting, Document No. 500-8-04 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 7.5.6	Tanaka T.	2005	Insecticidal activity of the environmental metabolites of etofenprox. Mitsui Chemicals, Inc. Landis Kane Consulting, Document No. 500-8-67 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.

8 ANNEXES

Confidential Annex

Study Summaries