Committee for Risk Assessment

RAC

Annex 1

Background document

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

Etofenprox

EC Number: 407-980-2

CAS Number: 80844-07-1

CLH-O-0000003158-74-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

28 November 2012

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***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 ATP of CLP)	**Directive 67/548/EEC (Dangerous Substances Directive; 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 which in contact with water emit flammable gases	n.a.	n.a.	currently not classified	conclusive but not 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	n.a.	n.a.	currently not classified	data lacking

	metals				
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	n.a.	currently not classified	

		exposure if it is conclusively proven that no other routes of exposure cause the hazard>.			
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	SCL: N; R50-53: $C_n \geq 0.25\%$; N; R51-53: $0.025\% \leq C_n$	currently not classified	n.a.

	toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	< 0.25%; R52-53: 0.0025% ≤ C_n < 0.025%;		

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. (The factor of 2 is supported by literature indicating that up to 190 respective NOAEL ratios have a geometric mean between 1.5 to 2.3., depending on the analysis; Schneider et al 2006. Reg. Tox. Pharm. 44/2, 172-81 and Bokkers BG, Slob W. 2005 Toxicological Sciences 85, 1033-1040). The classification is based on the consideration that at the LOAEL "significant" adverse effects were observed, in the meaning of the CLH guidance. The same LOAELs were considered as significant for risk assessment.

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 (Annex VI, Article 3.2.8). 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

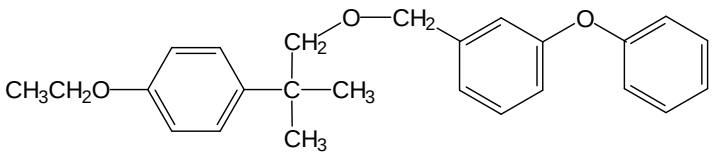
1 IDENTITY OF THE SUBSTANCE

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 Log Kow = 7.05	OECD 107 and 117; EEC A.8	Tognucci, 1998e Mirbach, 2004b Hansch, 1995[1]
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

[1] C.Hansch, A. Leo and D. Hoekman, Exploring QSAR: hydrophobic, electronic and steric constants, American Chemical Society, Washington (1995).

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

3.1.1 Summary and discussion of

No classification is proposed based on available data.

3.1.2 Comparison with criteria

No classification is proposed based on available data.

3.1.3 Conclusions on classification and labelling

No classification is proposed based on available data.

RAC evaluation of physical hazards
Summary of the Dossier submitter's proposal No classification is proposed based on available data. **Comments received during public consultation** No comments were received during public consultation. **Assessment and comparison with the classification criteria** RAC supported the non-classification for physico-chemical properties, as proposed by the dossier submitter. **Supplemental information - In depth analyses by RAC** -

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 11a). 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.

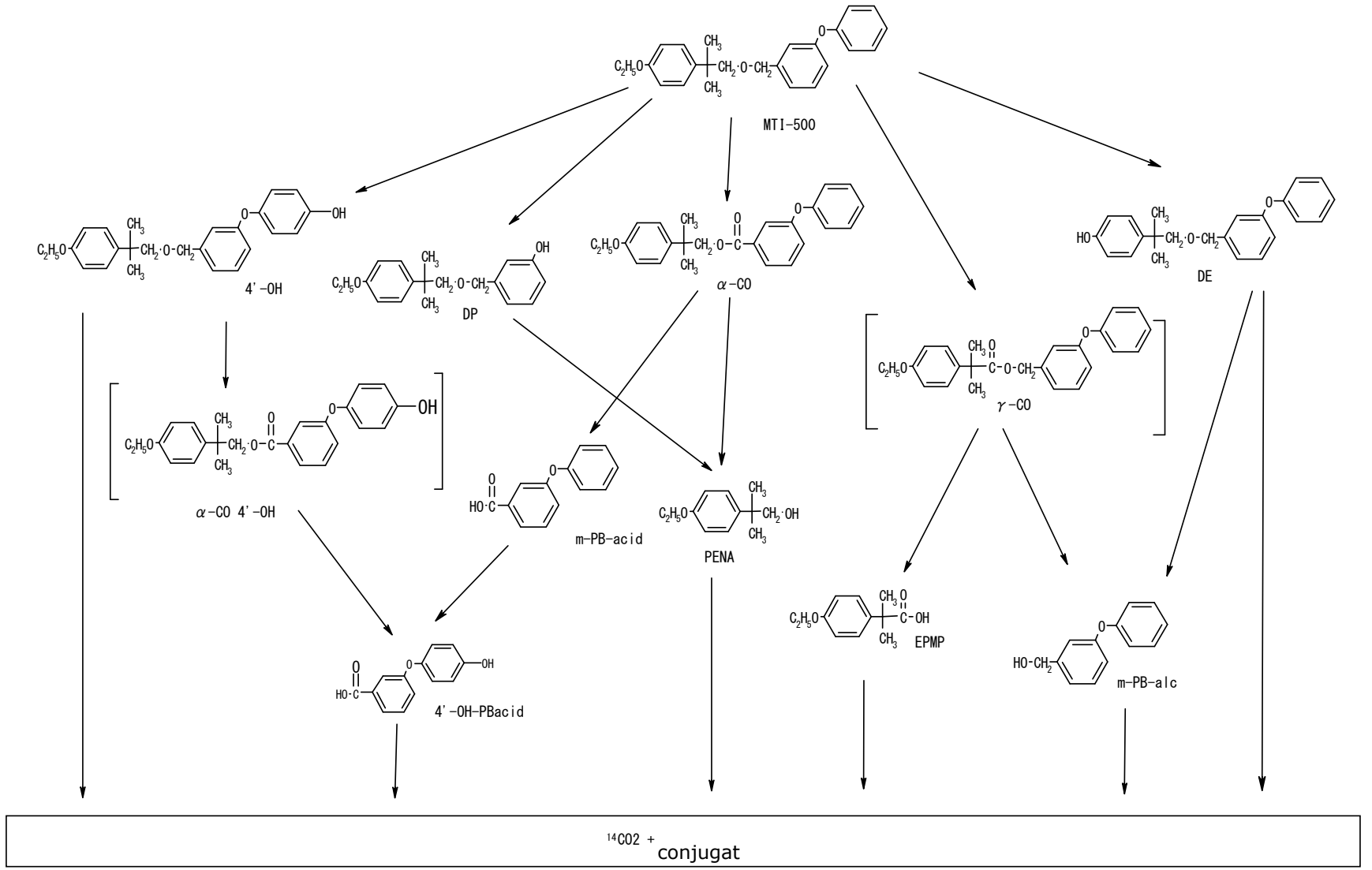
A proposed metabolic pathway in the rat is shown in Figure 3.1. (non key study: Burri et al. 2001)

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.

Figure 4.1. 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	LD_{50} > 42.88g/kg	
			14 days post-exposure		
Oral	Not applicable - no EU regulatory	Mouse, ICR , 10 males and 10 females /	50 and 100 mL/kg	LD_{50} > 107.2g/kg*	Hashimoto (1982b)
dermal			1 and 2 mL/kg	LD_{50} > 2.14g/kg*	

Subcutaneous	requirement	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.

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal Acute toxicity studies in rat and mouse are available by the oral, dermal, subcutaneous and intra-peritoneal route. In addition, one acute inhalation study in rat and one acute oral study in dog are available. The latest acute oral and dermal study in rat (Oda 2003a, b) and the inhalation study in rat (Jackson *et al.*, 1983) are considered to be the key studies by the dossier submitter. In these key studies, oral and dermal LD_{50}-values were both above 2000 mg/kg bw, and the inhalation 4-hour LC_{50} value was above 5.88 mg/l. All these values are above the acute toxicity estimates (ATE) that would lead to classification according to Regulation (EC) 1272/2008 (CLP) or Directive 67/548/EEC (DSD). Hence, no classification for acute toxicity is proposed. **Comments received during public consultation** One MSCA supported the proposal not to classify for acute toxicity. No comments opposing the proposal were received. **Assessment and comparison with the classification criteria** Following a comparison of the LD_{50} and LC_{50} values in the key studies with the criteria, RAC supported the conclusion of the dossier submitter that these values (as well as the LD_{50} values in the additional studies) are above the cut-off values for classification (2000 mg/kg bw for the oral and dermal route and 5 mg/l for inhalation of dust/mist/aerosol, under both CLP and DSD) and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for acute toxicity.

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

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

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)
Summary of the Dossier submitter's proposal No specific target organ toxicity after single exposure was identified in any of the relevant acute toxicity studies, and no classification is proposed. **Comments received during public consultation** No comments were received during public consultation. **Assessment and comparison with the classification criteria** According to the DAR (Public version of August 2007, volume 3, section B.6.2.1-3), no clinical signs were observed in the key acute oral and dermal studies at the limit dose level. In the key acute inhalation study, etofenprox treated animals showed abnormal body posture accompanied in some rats by partially or fully closed eyelids and abnormal respiratory movements, lethargy (approximately one hour post exposure) and oily appearance of the fur. Additionally, some female rats showed hair loss and transient hyperactivity. These signs are indicative of non-specific, general acute toxicity. Further to this, no functional or histopathological evidence of neurotoxicity was observed in an acute oral neurotoxicity study in rats (Smith, 2002). As there was no clear evidence of specific toxic effects on a target organ or tissue, and no signs of respiratory tract irritation or narcotic effects, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for specific target organ toxicity (single exposure) under CLP.

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

	30 minutes	24 hours	48 hours	72 hours	score*
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 does not require classification according to DSD criteria.

4.4.1.5 Conclusions on classification and labelling

No classification necessary.

RAC evaluation of skin corrosion/irritation
Summary of the Dossier submitter's proposal One study in rabbits (Japanese White, 6 males, 4 hour exposure) is available, showing a mean skin irritation index score of 0.1 (24-72 hours). No individual score was greater than or equal to the scores that would justify classification (0 in 5/6 animals; 0.6 in 1/6

animals), and inflammation did not persist until the end of the observation period in more than one animal. The dossier submitter concluded that no classification for skin irritation or corrosion was justified according to CLP or DSD.

Comments received during public consultation

One MSCA supported the proposal not to classify for skin irritation. No comments opposing the proposal were received.

Additional key elements

According to the DAR (Public version of August 2007, volume 3, section B.6.2.4), the erythema in the one animal showing irritation resolved on day 8 (see below).

Assessment and comparison with the classification criteria

Five of the six test animals scored zero for both erythema and oedema throughout the observation period. The remaining test animal showed very slight erythema (grade 1) at the 48 and 72 hr observation points, and was examined for a further 11 days. The grade 1 erythema persisted up to day 7, after which no signs of skin irritation were apparent. Therefore, only slight, transient irritation was observed, with mean scores for erythema and oedema below the threshold value of 2.3 for Skin Irrit. 2 – H315 (CLP) or 2 for Xi; R38 (DSD) in all six animals, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for skin irritation.

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.

RAC evaluation of eye corrosion/irritation
Summary of the Dossier submitter's proposal One study in rabbits (Japanese White, 6 males) is available, showing no corneal opacity or iris lesions. Conjunctival oedema was only seen in one animal (score 1) after 1 hour, but not at the later observation times. Transient, minimal (score 1) conjunctival erythema was seen in 6/6 animals after 1 hour, 5/6 animals after 24 hours, 3/6 animals after 48 hours, and 0/6 animals after 72 hours; mean individual scores over 24-72 hours were 0–0.66, with an overall mean index score of 0.44. It was concluded that the irritation scores did not fulfil the criteria for classification according to the CLP or DSD and no classification was proposed. **Comments received during public consultation**

One MSCA supported the proposal not to classify for eye irritation. No comments opposing the proposal were received.

Assessment and comparison with the classification criteria
In the rabbit eye irritation study, only slight, transient effects on the conjunctivae were observed. The mean scores for conjuctival redness and chemosis were below the threshold values for classification (2 for Eye Irrit. 2 – H319 (CLP) or 2.5 (redness) and 2 (chemosis) for Xi; R36 (DSD)) in all six animals, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for eye irritation.

4.4.3 Respiratory tract irritation

No data available.

RAC evaluation of respiratory tract irritation

Summary of the Dossier submitter's proposal
No information is available and no classification was proposed.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
In the absence of data, no conclusion can be drawn on the classification for respiratory tract irritation.

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 3.4.2. (specified in table 3.4.3 for category 1A or 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.

RAC evaluation of skin sensitisation
Summary of the Dossier submitter's proposal A Guinea pig maximisation test is available, indicating no skin sensitising properties of etofenprox (0/20 animals scored positive), while all animals showed skin reactions in the positive control group. Hence, no classification for skin sensitisation was proposed. **Comments received during public consultation** No comments were received during public consultation. **Additional key elements** The tested concentration was 20% etofenprox, at intradermal and topical induction and at topical challenge. In the final addendum to the DAR (Public version of November 2008, addendum II to volume 3, section B.6.2.6) it was noted that the basis on which the induction concentration was selected was not specified in the report. Yet, since this maximisation test employed both intradermal induction (with adjuvant), and occluded topical application following skin treatment with 10% Na-lauryl sulphate, the administration conditions were considered particularly harsh and therefore, 20% etofenprox was considered to be a reasonable concentration at which to test. **Assessment and comparison with the classification criteria** A substance is classified as a skin sensitiser if, in a Guinea pig maximisation study, a positive response is observed in at least 30% of treated animals. As 0/20 animals gave a response following treatment with etofenprox, it can be concluded that it does not meet the criteria for classification in accordance with CLP or DSD, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for skin sensitisation.

4.6.2 Respiratory sensitisation

No information available.

RAC evaluation of respiratory sensitisation
Summary of the Dossier submitter's proposal No information is available and no classification was proposed. **Comments received during public consultation** No comments were received during public consultation. **Assessment and comparison with the classification criteria**

In the absence of data, no conclusion can be drawn on the classification for respiratory sensitisation.

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/L)**	**LOAEL[b] (mg/L)**	**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 4.7.4., 4.7.7 and 4.8.2.

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

See chapter 4.7.4. and 4.7.7. and 4.8.2.

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.

Please see also the summary and conclusion in chapter 4.8.2.

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. (The factor of 2 is supported by literature indicating that up to 190 respective NOAEL ratios have a geometric mean between 1.5 to 2.3., depending on the analysis; Schneider et al 2006. Reg. Tox. Pharm. 44/2, 172-81 and Bokkers BG, Slob W. 2005 Toxicological Sciences 85, 1033-1040). The classification is based on the consideration that at the LOAEL "significant" adverse effects were observed, in the meaning of the CLH guidance. The same LOAELs were considered as significant for risk assessment.

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.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)
Summary of the Dossier submitter's proposal Four short-term repeated dose studies are available; two 13-week oral studies (one in rat and one in mouse), one 13-week inhalation study in rat, and one 4-week dermal study in rabbit. Further, a 52-week study in dogs and two 2-year studies (one in rat and one in mouse), were considered relevant. The 4-week dermal study in rabbit was considered negative as only minor local skin irritation occurred (that appeared reversible), but no systemic toxicity was observed at doses up to and including 1000 mg/kg bw/d. In the 52-week dog study the liver was identified as the target organ (the LOAEL for minimal and reversible hepatic effects was 352/339 mg/kg bw/d), but at higher doses than in the rat. In the rat oral studies, the liver (e.g. hepatocyte enlargement and liver dysfunction) and thyroid gland (increase in thyroid microfollicles and reduced levels of thyroxine) were identified as target organs, with LOAELs of 120/142 and 25.5/34.3 mg/kg bw/day for the 13-week and 2-year study, respectively. In the 13-week rat inhalation study, effects on the adrenal glands were seen next to effects on liver and thyroid. The effects in the inhalation study were however considered minimal at the LOAEL of 0.21 mg/l, which is around the guidance value for classification (0.2 mg/l under CLP and 0.25 mg/l under DSD). In the mouse studies, the liver was also identified as a target organ, but at much higher doses than in the rat. Other target organs in the mouse were kidneys and (in 13-week study) haemolymphoreticular system. In the 13-week mouse study the effects were seen only at the highest dose (1975/2192 mg/kg bw/d) but in the 2-year study the LOAEL was determined to be 10.4/11.7 mg/kg bw/d. In deciding on the classification, the dossier submitter multiplied the LOAELs of the 2-year study by a factor of 2 to account for the longer exposure duration. The dossier submitter concluded that effects relevant for classification were not seen at doses below the guidance values (50 mg/kg bw/day) for classification according to DSD and hence no classification was proposed. Due to the large dosing step in the 13-week oral rat study (20 and 120 mg/kg bw/day), it was argued that the LOAEL could be below the guidance value of 100 mg/kg bw/day for STOT RE 2 according to CLP. Also the effects seen in the 2-year studies (with LOAELs of 25.5/34.3 and 10.4/11.7 mg/kg bw/d for rat and mouse, respectively) were considered relevant, even when multiplied by 2 to account for the longer study duration. Hence, classification with STOT RE 2 – H373 (liver, kidneys) was proposed.

Comments received during public consultation

During the public consultation several MSCAs and one industry representative commented on the classification proposal.

Three MSCAs and one IND representative disagreed with the dossier submitter's proposal for STOT RE 2. Arguments against classification included that effects seen were not severe enough for classification and that effects occurred above the guidance levels for classification. One MSCA commented that the dossier presented insufficient information to reach a decision on the proposed classification. This MSCA further noted that multiplying the LOAELs of the 2-year study by a factor of 2 to account for the longer exposure duration is not a correct application of Haber's rule. A correct way would be to divide the guidance values for a 90-day study by a factor of 8 to obtain guidance values for a 2-year study.

Two MSCAs agreed with STOT RE 2, although one raised doubts about the classification for liver effects.

Assessment and comparison with the classification criteria

Dermal: The 4-week dermal study in rabbit showed no systemic toxicity at doses up to and including 1000 mg/kg bw/d. Locally, only minor, reversible skin irritation occurred (from 400 mg/kg bw/d). No severe effects were observed at dose levels relevant for classification, neither under CLP (extrapolated guidance value 600 mg/kg bw/d) nor DSD (extrapolated guidance value 300 mg/kg bw/d).

Inhalation: In the 13-week rat inhalation study, effects observed at the LOAEC of 0.21 mg/l consisted of small increases in liver weight in females and in kidney weights in males and females, and minimally increased adrenal cortical width in 3/20 females. At the highest dose of 1.01 mg/l; weights of liver, kidney and thyroid were increased in males and females. Histopathologically, minimal hepatocyte enlargement (in 4/10 males and 4/10 females), increased number of thyroid microfollicles (in 4/10 males) and increased adrenal cortex thickness in 4/10 females were observed at 1.01 mg/l. RAC concludes that at dose levels relevant for classification (0.2 mg/l under CLP and 0.25 mg/l under DSD) the effects were not severe enough for classification.

Oral: In the available short- and longer term studies the liver (rat, mouse, dog), thyroid (rat), kidney (mouse) and haemolymphoreticular system (mouse) were identified as target organs. As to the liver effects, the rat was the most sensitive species. In the 13-week rat study, the high dose of 743/820 mg/kg bw/d (in males/females, respectively) caused clinical evidence of liver dysfunction in males (affecting fat metabolism and the synthesis of blood clotting factors) and minimal hepatocyte enlargement in 9/20 females. At the dose level of 120/142 mg/kg bw/d relative liver weight was slightly increased (9%) in females, 2/20 males had an enlarged liver but upon histopathology it was only 1/20 females that showed minimal hepatocyte enlargement. Considering the low

incidence and severity of the effects at 120/142 mg/kg bw/d, it is not expected that they will occur at a dose level at or just below the cut-off value for classification as STOT RE 2 (100 mg/kg bw/d). In the 13-week mouse study, the 52-week dog study and the 2-year rat and mouse studies, liver effects occurred only at dose levels (1975/2192, 352/339, 25.5/34.3 and 546.9/615.5 mg/kg bw/d, respectively) that are (far) above the (extrapolated) guidance values for classification (25 mg/kg bw/d for a 1-year study, 12.5 mg/kg bw/d for a 2-year study). Hence, the liver effects do not warrant classification under CLP or DSD, where the cut-off values for classification are even lower.

The thyroid effects observed in the 13-week rat study at the two highest doses (120/142 and 734/820 mg/kg bw/d) included a decrease in circulating thyroxine (T4) and an increase in relative thyroid weight in males only, as well as an increased incidence of minimal to moderate number of thyroid microfollicles in both sexes. In the 2-year study there was also an increase in benign neoplasms of the thyroid, follicular cell adenoma, at the highest dose (186.7/249.1 mg/kg bw/d) in both sexes (see section on Carcinogenicity). A mechanistic study is available providing some evidence that the thyroid effects could be secondary to microsomal enzyme induction in the liver (specifically UDPGT). If so, the thyroid effects would be of less relevance to humans, as it is known that humans are considerably less susceptible for thyroid effects mediated by UDPGT (see also section on Carcinogenicity). A definite conclusion on the exact mode of action is, however, not possible based on the available data. Nevertheless, the thyroid effects occurred at effect levels that are in fact above the (extrapolated) guidance values for classification under both CLP and DSD and thus do not warrant classification.

In mice, kidney effects were observed in the 13-week and the 2-year studies, but in the 13-week study only at a dose (1975/2192 mg/kg bw/d) far above the guidance values for classification (100 and 50 mg/kg bw/d under CLP and DSD, respectively). In the 2-year study, kidney effects were seen at 10.4/11.7 mg/kg bw/d and above. Given the extrapolated guidance values for a 2-year study (12.5 and 6.25 mg/kg bw/day under CLP and DSD, respectively) only the effects at 10.4/11.7 mg/kg bw/d may possibly be relevant for classification. At this dose, the incidences of dilated and basophilic tubules were slightly increased, sometimes accompanied by focal loss of tubules. Although the severity of the tubular lesions was also slightly increased, the majority was still grade 1 or 2, i.e. generally of minimal severity with few tubules affected. RAC considers these effects not severe enough for classification.

The effects on the haemolymphoreticular system in the 13-week mouse study are not relevant for classification, as they were observed at a dose (1975/2192 mg/kg bw/d) far above the guidance values for classification (100 and 50 mg/kg bw/d under CLP and DSD, respectively).

Overall, it can be concluded that in the available short- and longer term studies no biologically relevant effects warranting classification under CLP/DSD have been observed. Etofenprox further provided no functional or histopathological evidence of neurotoxicity in

a 13-week dietary neurotoxicity study in rats (Smith, 2003b). RAC therefore concludes that etofenprox should not be classified for toxicity upon repeated exposure. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.

Supplemental information - In depth analyses by RAC

The tables below present more detailed information from the DAR (Public version of August 2007, volume 3, sections B.6.3.2 and B.6.5.2) on effects in the oral 13-week rat and 2-year mouse studies that helped RAC in deciding on the possible need for classification.

13 week rat study (Green et al. 1983a)

	male			female		
Dose in ppm (in mg/kg bw/d)	0	1800 (120) **LOAEL**	10800 (734)	0	1800 (140) **LOAEL**	10800 (820)
Body weight gain			↓15.8%		↓8%	↓10.1%
Blood clotting			↑ TT, PT, APTT			
T4		↓17%	↓25%			
Cholesterol		↑19%	↑41%			↑49%
Enlarged liver		2/20	4/20			4/20
Relative liver weight			↑30%		↑9%	↑35%
Relative thyroid weight		↑23%	↑32%			
Relative adrenal weight			↑18%			↑16%
Minimal centrilobular hepatocyte enlargement				0/20	1/20	9/20
Minimal to moderate increased number of thyroid	10/19	19/20	18/20	0/20	2/20	9/20

microfollicles						

2-year mouse study (Green et al., 1986b)

	male (n=52)				female (n=52)			
Dose in ppm (in mg/kg bw/d)	0	100 (10.4) **LOAEL**	700 (75.2)	4900 (546.9)	0	100 (11.7) **LOAEL**	700 (80.9)	4900 (615.5)
Survival	46%	27%	35%	19%	54%	48%	44%	54%
Body weight gain				↓27.8%				↓13.7%
Kidney								
- mass(es)	0	0	1	4	1	2	0	1
- cortical scarring	12	9	10	23	7	4	6	19
- enlargement	1	3	4	7	0	4	1	0
- pale colour	7	12	15	23	6	12	10	13
Relative liver weight				↑10.1%				↑9.8%
Kidney								
- dilated/ basophilic tubules								
grade 1	7	6	9	5	3	5	6	7
grade 2	0	4	6	4	1	1	1	6
grade 3	0	1	1	11	0	0	2	6
grade 4	0	1	1	6	0	1	0	1
grade 5	0	0	0	4	0	0	0	0
- dilated/ cystic Bowman's capsule	1	3	10	14	3	4	6	11
- dilated medullary	1	2	7	18	1	1	1	6

tubules								
- focal loss of tubules	0	2	1	18	2	2	4	12
- cortical cyst(s)	11	9	10	21	4	5	12	15
↑= increased; ↓= decreased								

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

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.

RAC evaluation of germ cell mutagenicity
Summary of the Dossier submitter's proposal Etofenprox has been tested in three standard *in vitro* assays and one *in vivo* micronucleus assay which were all clearly negative. The dossier submitter concluded that these tests were enough to assess the mutagenic toxicity of etofenprox, and that no *in vivo* study in germ cells is needed. Based on the negative results it was concluded that no classification is justified. **Comments received during public consultation** One MSCA supported the no classification proposal for mutagenicity. No comments opposing the proposal were received. **Assessment and comparison with the classification criteria** Etofenprox tested negative in four *in vitro* assays (a bacterial mutation assay, a mammalian gene mutation assay, a cytogenicity test in human lymphocytes and an unscheduled DNA synthesis assay in cultured human cells) and in one *in vivo* micronucleus assay with mice, and RAC therefore supported the conclusion of the dossier submitter that etofenprox should not be classified for mutagenicity.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 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; Swiss mice (CD1 strain) 52 males and 52 females/group 0, 30, 100, 700, 4900 ppm	Carcinogenicity: **>547** (m) **>616** (f) All effects: **3.1** (m) [a] **3.6** (f)	Carcinogenicity: - - All effects: **10.4** **11.7**	Liver, Kidney: Histopathological alterations in kidneys At 4900ppm in addition: ↑ male mortality, ↓ weight gain, minor haematological effects, ↑ liver weight	**Green *et al.* (1986b)** → document IIIA 6.5.1/02
4-week dietary investigative study; Sprague-Dawley-derived rats (Crl:CD(SD)IGS) BR strain) 20 males and 20 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 turnover slower. This leads to a much more stable T4 concentration in humans and therefore T4 reduction will lead to a comparatively reduced positive feedback on TSH synthesis and hypertrophy of thyroid follicular cells.

For further details please see the attached study summaries.

4.10.1.2 Carcinogenicity: inhalation

No information available.

4.10.1.3 Carcinogenicity: dermal

No information available.

4.10.2 Human information

No information available.

4.10.3 Other relevant information

No other relevant information available.

4.10.4 Summary and discussion of carcinogenicity

See chapter 4.10.5.

4.10.5 Comparison with criteria

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

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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.

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.

4.10.6 Conclusions on classification and labelling

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

RAC evaluation of carcinogenicity
Summary of the Dossier submitter's proposal A 1-year study in dog and 2-year studies in rat and mouse, respectively, are available. No target organs that had not already been identified in short-term studies were identified in any of the species. Etofenprox did not induce any frank carcinogenic effects in either dog, rat or mouse. In rat there was an increase in benign neoplasms of the thyroid, follicular cell adenoma, at the highest dose (186.7 and 249.1 mg/kg bw/day in males and females, respectively). A mechanistic study is available investigating the aetiology of the follicular cell adenoma in the thyroid, and the results were consistent with the hypothesis that these effects are secondary to microsomal enzyme induction in the liver. This mode of action is considered to be an indirect, non-genotoxic mechanism, which is further considered of limited relevance to humans due to humans having different T4 plasma kinetics compared to rats. In the mouse study, three males at the highest dose (546.9 mg/kg bw/d) and one male at the next lower dose (75.2 mg/kg bw/d) showed a renal neoplasm. However, two of the neoplasms at the highest dose were benign and the increase was not statistically significant. It was concluded by the dossier submitter that there was insufficient evidence of carcinogenic effects in mice. Taking all data into consideration it was concluded by the dossier submitter that no classification for carcinogenicity was justified according to either CLP or DSD. **Comments received during public consultation** Two MSCAs supported the conclusion that no classification for carcinogenicity was warranted. No comments opposing the proposal were received. **Assessment and comparison with the classification criteria** In the 2-year rat study, an increase in follicular cell adenoma of the thyroid was observed in both males (not statistically significant) and females at the highest dose. A mechanistic study with etofenprox is available providing some evidence that the adenomas are not a primary effect of etofenprox, but could be the result of an increased hepatic microsomal enzyme induction (specifically UDPGT). This would reduce the relevance to humans, as it is known that humans are considerably less susceptible than rodents (especially rats) to the formation of follicular cell adenomas mediated by UDPGT induction, with consequent T4 reduction, TSH increase and finally increased thyroid stimulation (CLP guidance 3.6.2.3.2(k)). A definite conclusion on the exact mode of action is, however, not possible based on the available data. Given that the thyroid tumours induced were only benign in nature and only occurred at a high dose (at which the overall body weight gain was decreased by 24.2 and 34% in males and females, respectively), that the thyroid gland related carcinogenicity is of low potency (with a T25 > 100 mg/kg bw/d), and that etofenprox is not considered genotoxic, RAC concluded that the follicular cell adenomas present insufficient evidence for classification. In the 2-year mouse study, some renal cortical tumours were observed, three at the high dose (one of which was malignant) and one at the mid dose (malignant). These tumours

were only observed in males, not in females, and were not observed rats. Besides, the incidences at the high and mid dose were not statistically significantly increased compared to controls, and etofenprox can be considered a non-genotoxic substance. Overall, the relevance of the observed one sex/one species renal tumours to humans is doubtful, and they present insufficient evidence for classification.
The study in dogs is considered less relevant for carcinogenicity due to the limited exposure and observation duration and the limited number of animals. Yet, no increase in tumours was observed.

Considering the above, RAC supports the conclusion of the dossier submitter that etofenprox should not be classified for carcinogenicity. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

4.11.1.1 Non-human information

See chapter 4.13.4

4.11.1.2 Human information

No information available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

See chapter 4.13.4

4.11.2.2 Human information

No information available.

4.11.3 Other relevant information

No other information available.

4.11.4 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; rat; 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 fetus 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; rat: P0 treatment from d6 to d17 of pregnancy; foetal analysis, follow up without treatment to F2 weaning 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 (4% lower than control, statistically not significant)	
Oral (gavage) peri / postnatal study, rat: 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: diets were fed continuously to the F0 generation for 25 weeks (from 6 weeks of age, 10 weeks premating, 20 days mating to weaning of the F1a, re-mating of F0 to weaning of F1b), like for F0 also from F1b the F2a and F2b generations were bred with continuous exposure till at least 13 weeks from weaning. 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; exposure from day 6 through day 18 of gestation, animals killed at day 28. 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; exposure from day 6 through day 28 of gestation. 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; F0 female exposure from day 6 of gestation to day 21 of lactation; F1 exposure via lactation and in late pre-weaning, but not after weaning at day 21; F1 CNS/PNS histopathology at 63 to 67 days of age. 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) [d] histopathology	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; overall pup mortality to weaning was comparable in all treated and control groups. Pre-weaning survival between days 14 and 21 was unaffected by treatment at 250 and 700ppm.). Because the increased pup mortality occurred in all studies only at relatively high doses above 238 mg/kg bw/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, some pups around nose) and at about 246 mg/kg bw/day (multigeneration study, 0/4/30/246 mg/kg bw: at necropsy sum of subcutaneous haemorrhage and ocular defects 0/1/3/4 in F1a and 0/1/0/3 in F2a; no such findings were observed in F1b or F2b) 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.

4.11.5 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.

4.11.6 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.)

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The reproductive toxicity of etofenprox has been investigated in several studies in rats and rabbits. In rabbits there were two developmental toxicity studies (via gavage). In rats, there was a fertility study (gavage), a dietary 2-generation, 2 litters/generation) study, a peri-/post-natal study (gavage) and a developmental toxicity study (gavage). In the latter study, part of the dams were allowed to litter normally and rear their young. Part of the F1 progeny in this study and in the peri-postnatal study were selected to produce the F2 generation. Further to these studies, there was a dietary developmental neurotoxicity study in rats.

Reference	**Test guideline**	**GLP**	**Short study description**	**Main effects / target organs**
Cozens *et al*, 1985a	no OECD TG	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 males: 9 weeks pre-mating until post-mating day 20 P0 females: 2 weeks pre-mating until GD 7 P0 animals sacrificed at GD 20.	*12.5-5000 mg/kg:* minor clinical signs (e.g. increased salivation and brown staining around the mouth) *5000 mg/kg:* Slightly higher pre-implantation loss and slightly lower litter size and weight (n.s.)
Cozens *et al*, 1985b	no OECD TG (in conformity with (88/302/EEC, Part B, with some deviations)	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 animals: GD 6-17 21-24 P0 females/ group sacrificed on GD 20; 11-14 P0 females/group kept to rear F1 pups until PND 21. F1 animals: treated only *in utero* and via lactation. Part of F1 animals mated to produce an F2 generation, kept until PND 21.	*12.5-5000 mg/kg:* minor clinical signs (e.g. increased salivation and red-brown staining around the mouth) *5000 mg/kg:* Slightly lower maternal gestation weight gain: P0 females: -3.6% bw at GD 20 F1 females: -7% bw at GD 20 (n.s.) F1 offspring: No treatment-related malformations,

				visceral anomalies or skeletal variations. No effects on physical, behavioural or sexual development in F1 offspring exposed *in utero*.
Cozens *et al*, 1985c	no OECD TG	Yes	**Rat**; 0, 12.5, 125, 250 & 5000 mg/kg bw/d (oral gavage) Exposure time: P0 females: GD 17 – PND 21; kept to rear pups until PND 21. F1 animals: treated only *in utero* and via lactation. Part of F1 animals mated to produce an F2 generation, kept until PND 21.	*250 mg/kg:* P0 animals: Increased salivation and brown staining around mouth. *5000 mg/kg:* P0 animals: Increased salivation and brown staining around mouth, yellow staining of fur in anogenital region, slight decrease in body weight gain during GD17-20 (13.4%). F1 weanlings: During (late) lactation: 3 total litter losses, increased pup mortality, reduced weight gain (6-9.4%), tremors, subcutaneous haemorrhage, general motor incoordination, increased kidney weights and histopathological alterations (cystic collecting ducts, focal fibrosis, cortical scarring, mineral deposits). F1 post-weaning: Increased water consumption, same kidney effects as weanlings. F2 offspring: Marginally reduced pup weight (n.s.) due to slightly larger litter size, 1 total

				litter loss.
Cozens *et al*, 1985d	no OECD TG (in conformity with (88/302/EEC, Part B, with some deviations)	Yes	**Rat**; 0, 100, 700, 4900 ppm (approx. 0, 4.3-14.3, 30-104, 225-753 mg/kg bw/d, depending on sex and age) <u>Exposure time:</u> P0 animals: continuously from 6 weeks of age through mating and gestation until weaning of F1 offspring F1b and F2a & F2b: continuous exposure until at least 13 weeks from weaning.	*30(-104) mg/kg:* <u>Parental animals:</u> 1 F1b pup (f) with cystic collecting ducts extending into renal cortex, increased kidney weight in F2b females. <u>Offspring:</u> 2 F1a pups with ocular defects (at late lactation/ weaning); 1 F1a pup with subcutaneous haemorrhage (PND12); increased liver weight in F1a (m&f), F1b (m), F2b (m&f) *225-753 mg/kg:* <u>Parental animals:</u> Slightly reduced body weight gain (F1b males at wk 14, F0 and F1b females at pre-mating, F1a and F2a females overall); increased water consumption in F1a/b and F2b; increased liver, kidney and thyroid weights; similar kidney lesions as in Cozens *et al.*, 1985c in F1b but not in F0; minimal hepatocyte enlargement in F1b; slightly increased height of columnar epithelium of thyroid in some F1b males. No effects on fertility or reproductive capacity. <u>Offspring:</u> During (late) lactation: 2 total litter losses, increased pup mortality (n.s.);

				reduced weight gain (5-14%); tremors, distended abdomen, abnormal gate; small number of pups with ocular defects and subcutaneous haemorrhage; increased liver, kidney and heart weights.
Bottomley, 1985	not stated	not stated	**Rabbit**; 0, 10, 50, 250 mg/kg bw/d (oral gavage) Exposure time: P0 animals: GD 6-18 Sacrificed on GD 28.	Not considered valid. Performed on groups of animals from different sources. *50 mg/kg:* Reduced weight gain in P0 animals *250 mg/kg:* Slight increase in post-implantation loss.
Fisher, 2000	OECD TG 414	Yes	**Rabbit**; 0, 30, 100, 300 mg/kg bw/d (oral gavage) Exposure time: Mated females: GD 6–28 Sacrificed on GD 29.	*300 mg/kg:* P0 animals: Increased post-implantation loss (10.1 vs 4.3% in controls) and reduced embryo-fetal weight gain. Abortion/unscheduled death in 4 dams (0, 1, 1 in 0, 20 and 100 mg/kg groups). Maternal toxicity seen at the same dose: -10% bw, -2.9% bw loss on GD 6-29; -18.9% reduced food consumption. F1 offspring: Fetal malformations considered not to be related to treatment. Skeletal variations at higher incidence than controls but not considered related to treatment.
Myers, 2003	no OECD TG (developme	Yes	**Rat**; 28.4, 79.2, 238 mg/kg bw/d (in diet)	*79 mg/kg:* P0 animals:

	ntal neurotoxicity study)		Exposure time: P0 females: GD 6 – PND 21. F1 animals exposed *in utero*, via lactation and late pre-weaning. Functional investigations at several time points post-natally. CNS/PNS histopathology of F1 animals at 63-67 days of age.	Slight, transient decrease in weight gain from GD 6-10. F1 offspring: Low incidence of ocular lesions. *238 mg/kg:* P0 animals: Slight, transient decrease in weight gain from GD6-10; increased rearing activity. F1 offspring: Increased pup mortality between PND 14 and 21 (5.7% vs. 0.6% in controls), low incidence of subcutaneous haemorrhage and ocular lesions. No effect on bw or bw gain until PND 63, and no effect on sexual development. Functional neurological effects possibly related to treatment: higher mean auditory startle response amplitudes, reduced habituation (females); clustering of differences in motor activity and latency to peak startle response (males). No selective developmental neurotoxicity at dose levels with slight maternal toxicity. Histo-morphological development of CNS and PNS nerve tissue not affected by treatment.

TG = test guideline
bw = body weight

n.s. = not significant
GD = gestation day
PND = post-natal day (= lactation day)

It was concluded that in rats, effects are seen in offspring exposed *in utero* and during lactation, and that these effects are not evident in adults who have not been exposed during this time period. The effects seen were increase in pup mortality, non-specific haemorrhagic lesions (subcutaneous and ocular), renal toxicity, liver/thyroid/renal histopathological changes as well as functional neurological effects. There are other effects seen in offspring but these are also seen in parental animals. It was concluded that the effects seen only in offspring could indicate a need for classification for developmental toxicity. However, since the effects were only evident 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 adult animals in other (non-reproductive) repeated dose studies the dossier submitter concluded that they did not justify classification for developmental toxicity.

It was instead argued that the effects were due to a naturally high ratio of milk uptake compared to bodyweight. Thisis also supported by toxicokinetic findings which indicate a potential for accumulation of etofenprox in fat and active secretion into milk, leading to a high concentration ratio between pup stomach content and maternal plasma content. Toxicokinetic studies show that etofenprox is transferred via the placenta to the fetus. Placental and fetal concentrations are however relatively low compared to plasma concentrations in the dams, and etofenprox is rapidly eliminated from these tissues. In general, etofenprox concentration decreases rapidly in all tissues except for fat. Toxicokinetic studies also show that unchanged etofenprox is actively secreted into maternal milk and is ingested by pups at a concentration ratio of over 20 (pup stomach content compared to maternal plasma). Transfer in milk decreases rapidly when dosing stops.

Based on these data, the dossier submitter concluded that classification for fertility or developmental toxicity is not justified, but classification for lactation effects (Lact. – H362 according to CLP) is proposed. The dossier submitter further argued that R64 according to DSD is not possible due to the fact that no other classification for health hazards is proposed according to this directive.

Comments received during public consultation
Several comments were received during public consultation.
Four MSCAs supported the proposed classification with Lact. - H362, three of which said that a corresponding classification with R64 according to DSD should be added to the proposal. They considered the reason given by the dossier submitter not to do this a misinterpretation of DSD as according to this directive, R64 can be added as additional labelling to any other classification, not only to classification in health hazard classes. Consequently, as environmental classification according to DSD has been proposed by the dossier submitter, R64 can be proposed as well. One MSCA also wanted to add labelling with R33 (Danger of cumulative effects) as the

substance seems to be accumulating in the body.
Classification for lactation effects was questioned by one MSCA and one IND representative. The IND representative argued that H362 was not justified e.g. since the haemorrhagic effects were of low incidence (and possibly secondary to other effects) and that some of the observations were not necessarily consistent with an effect on lactation. Aside from the low incidence of haemorrhagic effects, the MSCA also questioned whether the reduced body weight development in pups meets the classification criteria.

Assessment and comparison with the classification criteria

Fertility
No adverse effects on sexual function and fertility were observed in the fertility and 2-generation study in rats. Also rats that had only been exposed to etofenprox *in utero* or during lactation did not show these adverse effects when allowed to litter. RAC therefore supports the conclusion of the dossier submitter that etofenprox should not be classified for fertility effects. This conclusion was also drawn by EFSA in their peer review of etofenprox in 2008.
Development
No teratogenic effects were observed in either rats or rabbits. In the key study in rabbits (Fisher, 2000), some embryo- and foetotoxicity was observed (slightly increased post-implantation loss and reduced fetal weight) at the highest tested dose of 300 mg/kg bw/d, but this was considered secondary to the maternal toxicity induced at that dose, resulting in reduced food consumption and weight loss over the treatment period. They therefore do not warrant classification.
In rats, no treatment-related embryo- or foetotoxic effects were observed in the fertility study (with maternal dosing from 2 weeks prior to mating up to gestation day 7; Cozens *et al.*, 1985a) or in the developmental toxicity study (with maternal dosing from day 6-17 of gestation; Cozens *et al.*, 1985b). In the latter study, the physical, behavioural and sexual development of the F1 progeny exposed *in utero* was also not affected by treatment with etofenprox.
In contrast, in the rat peri-/post-natal study (with maternal dosing from day 17 of gestation to PND 21; Cozens *et al.*, 1985c), effects on the F1 progeny were observed at the highest tested dose of 5000 mg/kg bw/d, a dose at which no significant maternal toxicity occurred. The effects were not observed at the lower doses. The effects seen included reduced pup weight (up to 9.4%; from PND 8, but only statistically significant at PND 12 and 21), increased pup mortality during PND 12-21 (with cumulative loss of 26.1% at PND 21, compared to 2.7% for controls), pups showing subcutaneous haemorrhage, tremors and general motor incoordination during the 3rd week of lactation. All F1 weanlings, as well as F1 adults, further had increased kidney weights and histopathological renal alterations. The post-weaning physical, behavioural and sexual development of the F1 progeny was not affected.
In the rat 2-generation study (Cozens *et al.*, 1985d), at 4900 ppm (225-753 mg/kg bw/d) the same type of effects on the kidneys as in the peri-/post-natal study were observed in the progeny (but not in the F0 animals), and pups also showed tremors in late lactation, as well as distended abdomen and abnormal gait. Further at 4900 ppm (a dose level that for dams corresponded to an intake of approximately 300-350 mg/kg bw/d), pup weight was slightly decreased in all litters (up to 14%; from PND 4, but only statistically

significant at PND 8, 12 and 21), and pup mortality was slightly increased (not statistically significantly), mainly in the first matings due to one total litter loss in the 2nd half of lactation. A few pups also showed ocular lesions or subcutaneous haemorrhage when sacrificed at weaning or when dying during the second half of lactation. Next to the renal lesions also minimal hepatocyte enlargement was seen in the progeny, as well as some thyroid alterations (males only).
The rat developmental neurotoxicity study (Myers, 2003) showed no selective developmental neurotoxicity at dose levels with slight maternal toxicity, but impaired pre-weaning survival was observed in the 3rd week of lactation (5.7% vs 0.6% in controls) at 2100 ppm (238 mg/kg bw/d), as well as an increase in ocular lesions (enlarged/dark/opaque eyes, associated with intraocular haemorrhage) and subcutaneous haemorrhages at 700 ppm (79.2 mg/kg bw/d) and 2100 ppm, and some minor functional neurological effects at 2100 ppm.

The effects seen in rat offspring indicate a need for classification, but given their onset (mainly in the 3rd week of lactation or thereafter), classification for developmental toxicity seems not warranted. A classification for effects via lactation might be more appropriate. According to CLP, classification for effects via lactation can be assigned based on:

- human evidence indicating a hazard to babies during the lactation period; and/or
- results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
- absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk

Similarly, according to the DSD, R64 may also be applied to substances that are not toxic to reproduction but where

- toxicokinetic studies indicate the likelihood of toxic levels of the substance in breast milk and/or
- the results of one or two generation studies in animals indicate the presence of adverse effects on the offspring due to transfer in the milk and/or
- evidence in humans indicates a risk to babies during the lactational period.

The toxicokinetic study by Hawkins *et al.* (1985a) indicates a slight potential for accumulation in fat (half-life 5-8.5 days) and active secretion into milk, with a pup stomach/maternal plasma concentration ratio of 20. Etofenprox further has a log P_{ow} of 6.9. In the reproductive toxicity studies, several adverse effects were observed in the progeny during the lactation period, such as renal lesions and ocular defects and subcutaneous haemorrhage (for further details, see table above and background document). In addition, slightly decreased pup weight and increased pup mortality was observed during the lactation period. In the peri-/post-natal study (Cozens *et al.*, 1985c), pup weight was slightly decreased from PND 8 (significantly from PND 12) and pup mortality was increased from PND 12. As this is a gavage study, the effects seen must be due to lactation exposure. They are however only observed at a very high dose of 5000 mg/kg bw/d, not at doses of 250 mg/kg bw/d and below, and such a high dose (or in fact any other effective dose above 1000 mg/kg bw/d) is not considered relevant for classification. In the multi-generation study (Cozens *et al.*, 1985d), which is a diet study, pup weight

was slightly decreased from PND 4 (significantly from PND 8). Other adverse effects in this study (such as tremors, haemorrhages and kidney effects) were mainly observed from the 3rd week of lactation. Also in the dietary developmental neurotoxicity study by Myers (2003) increased pup mortality was seen in late lactation; subcutaneous haemorrhage and ocular lesions were also mainly observed in late lactation or pre-weaning, although some bruising was already seen in the first week of lactation. The time of onset of the effects in the latter two studies seems to indicate that the effects occur via lactation, although direct exposure via food intake of the pups cannot be completely ruled out (especially in the multi-generation study). Given, however, the similarity in effects with the gavage study, it seems more likely that they are caused via exposure through lactation. Moreover, the effect on body weight starts at a period during lactation (from PND 4) when pups are only exposed via lactation.

In conclusion, there is high transfer of etofenprox into the milk, with clear effects on or via lactation at a dose level considered too high for classification (5000 mg/kg bw/d). There is still evidence, albeit weak, for effects on or via lactation at the next lower dose levels tested (up to approximately 350 mg/kg bw/d). Although no doses between 350 and 5000 mg/kg bw/d have been tested, RAC considered it not unlikely that more severe lactational effects could have occurred at dose levels higher than 350 mg/kg bw/d that are still relevant for classification (up to 1000 mg/kg bw/d). RAC therefore considers classification with **Lact. – H362** (CLP) and **R64** (DSD) justified. The labelling with R64 is applicable, as the required additional classification for etofenprox under DSD (Annex VI of DSD, 3.2.8) is present (namely for environmental effects). RAC noted that EFSA in their peer review of etofenprox in 2008 also proposed R64, but no classification for developmental toxicity.

Additional labelling with R33 - Danger of cumulative effects (next to R64) was not deemed necessary, as the fairly short half-life of etofenprox in fat does not seem to indicate a high accumulation potential.

Supplemental information - In depth analyses by RAC

Information from Cozens *et al.* (1985d; original study report) on ocular lesions/haemorrhages and their time of onset

Table A6_8_2-6. Incidence of selected clinical or necropsy findings in weanlings.

Generation	Observation	Incidence in:							
		1st litters (a) treated at (ppm):				2nd litters (b) treated at (ppm):			
		0	100	700	4900	0	100	700	4900
F1	No. examined	293	268	271	293	318	230	275	320
	Kidney lesions [a]	12	0	0	217	0	0	0	196
	Ocular lesions	0	0	2[c]	3[c]	0	0	0	0
	Haemorrhage	0	1[b]	1	1	0	0	0	0
F2	No. examined	250	250	234	253	205	229	240	234
	Kidney lesions	0	0	0	157	0	0	0	108
	Ocular lesions	0	1[c]	0	0	0	0	0	0
	Haemorrhage	0	0	0	3	0	0	0	0

[a] excludes renal pelvic dilatation; [b] associated with traumatic injury to cranium; [c] ocular lesions were small eye, lenticular opacity, dark eye or intraocular haemorrhage

Except for one pup at 4900 ppm that died at PND 6, all ocular defects were observed in second half of lactation or at weaning. The subcutaneous haemorrhages were observed between PND 12 and 18.

Information from Myers (2003; original study report) on ocular lesions/haemorrhages and their time of onset

Principal offspring clinical signs - group incidences (F1)

Group	:	3	4	1	2
Compound	:	Control	---------- Etofenprox ----------		
Dietary concentration (ppm)	:	0	250	700	2100

Clinical signs	Number of offspring (litters) affected in group			
	3	4	1	2
Initial eye abnormality				
One or both eyes large/prominent and dark	-	-	1 (1)	8 (6)
One or both eyes large/prominent	-	1 (1)PW	1 (1)PW	1 (1)
One eye large and opaque	1 (1)	1 (1)PW	-	-
One or both eyes opaque	-	-	3 (1)PW	1 (1)
One or both eyes dark	-	-	-	2 (2) 1(1)PW
Cut/bleeding on tail	-	-	-	2 (2)
Reddened/swollen/bruised area(s) on tail	1 (1)	-	3 (1)	4 (3)
Cut/bleeding on toes/paws	-	-	1 (1)	2 (2)
Swollen/bruised/reddened paw(s)	1 (1)	1 (1)	2 (2)	5 (4)

PW Eye changes first recorded post weaning

Two clinical signs were considered to be treatment-related. An increased incidence occurred at 2100 ppm of pups with ocular abnormalities comprising one or both eyes being enlarged / prominent / dark / opaque in various combinations. Thirteen pups in the 2100 ppm group displayed the abnormality compared with a single control pup with one eye large and opaque. The abnormalities first occurred most often between Days 16 - 21 of age, with the majority at 250 and 700 occuring after weaning. Overall, there was no difference in the distribution of the ocular abnormalities between the left and right eyes or between the sexes. Five pups at 700 ppm and 2 pups at 250 ppm also showed similar ocular abnormalities. Therefore, the incidences at 700 and 2100 ppm were considered to be elevated.

Further examination of the eyes of 6 pups at 2100 ppm and 1 at 700 ppm confirmed the presence of intraocular haemorrhage.

Eleven pups at 2100 ppm showed bleeding or reddened / swollen / bruised areas on the tail and/or toes and paws, compared with a control incidence of 2 pups. Five pups at 700 ppm and a single pup at 250 ppm showed similar lesions.

Most of these lesions occurred from the second half of lactation or thereafter, but bruising on hind paw was occasionally seen already on PND 1-2.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 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 (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**Target organs / main effects**	**Reference**
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**

4.12.1.2 Immunotoxicity

No information available.

4.12.1.3 Specific investigations: other studies

Not available.

4.12.1.4 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.

4.12.1.5 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) ϒ-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) ϒ-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)
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)

ID	Age / sex	Exposure period	Abnormal findings (and dates)
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

4.12.2 Summary and discussion

See chapter 4.12.

4.12.3 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

4.12.4 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 para-meter**	**Inoculum**			**Additi o-nal sub-strate**	**Test substan ce concent ra-tion**	**Degradation**		**Referenc e**
			Type	**Conce n-tratio n**	**Adap tatio n**			**Incub a-tion perio d**	**Degr ee [%]**	
OECD 301D (1982) EEC C.4-E (1984)	ready	oxygen consumption	Activa-ted 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	Activa-ted 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	

5.1.3 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 7.1.3
	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**	**Depuration 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} ≈ 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.

5.4 Aquatic toxicity

5.4.1 Fish

5.4.1.1 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	Duration	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 macrochirus*)	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/E ECC.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 7.4.1.1/03

5.4.1.2 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 (*Oncorhyn-chus 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 concentra-tions 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 deve-lopment and hatch-ing rate, hatching time, deve-lopment juv. fish, etc.)	Flow through	40 days	mortality of larvae and juvenile fish	**25**	**50**	5 concentra-tions tested, deaths in the highest dose group	**Peither (2005)** → Doc III A 7.4.3.2

* 90%mortality on day 21

5.4.2 Aquatic invertebrates

5.4.2.1 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	**Duration**	**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

5.4.2.2 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	**Duration**	**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

5.4.3 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	*Pseudo-kirchne-riella sub-capitata*	Growth and bio-mass in-hibition	static	72 hours	**56.25**	**56.25**	**> 56.25**	**> 56.25**	6 concentra-tions tested, no adverse effect on the biomass and the growth rate at the highest con-centration	**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	*Pseudo-kirchne-riella sub-capitata*	Growth and bio-mass in-hibition	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

5.4.4 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	**Duration**	**NOEC or EC10**	**EC_{50}**		
OECD 209	Activated sludge from predominant-ly domestic wastewater treating plant	Oxygen consumption /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/sediment system	10 days	**>20.9**[1]	**3.8**[2]	3 concentrations 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 concentrations tested, toxic effects observed at the two highest concentrations	**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 23h: 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/sediment 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

5.5 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} (fish) = 0.0027 mg/L**
- Doc. III A7.4.1.2/01: Gries T. (2003), OECD 202, Part1 (1984) EEC C.2 (1992) -> **EC_{50} (crustacean) = 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) >0.056 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 C6 -> **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**
- 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) =0.0027 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) >0.056 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) -> **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**

5.6 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.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The dossier submitter proposed classification according to the CLP criteria as Aquatic Acute 1 (H400) with an M-factor 100 and Aquatic Chronic 1 (H410) with an M-factor 1000. The proposal according to the DSD criteria is N; R50-53 with specific concentration limits of N; R50/53: C ≥ 0.25%; N, R51/53: 0.025% ≤C <0.25%; R52/53: 0.0025% ≤ C< 0.025%.

Rapid degradation

The rate of hydrolysis was tested according to OECD TG111 and was considered as an insignificant route of degradation.

Direct photo-transformation induced degradation of etofenprox with DT_{50} values of 4.7 and 7.9 days to two main metabolites comprising 75.6% and 52.2% of applied radioactivity in sterile buffer and natural water, respectively. Lack of toxicity data on photolytic metabolites and relatively low contribution to the removal justified conclusion that direct photolysis is an insignificant route of degradation (NB: due to problems with extrapolating the data to the aquatic environment, these data are normally difficult to use for concluding on the degradability of etofenprox (Guidance II.2.3.9)).

Two ready biodegradability tests were reported: a closed bottle oxygen consumption test conducted according to OECD TG 301D and a $^{14}CO_2$-evolution test conducted according OECD TG 301B. In the closed bottle test, 17% degradation in 28 days was reported. However, the test was performed at a concentration (i.e. 2 mg/l) which was above the water solubility limit of etofenprox (i.e. 0.012-0.0225 mg/l). The $^{14}CO_2$-evolution test was performed at a concentration (i.e. 0.0108 mg/l), which is within the water solubility limits and the resulting ultimate degradation of 32% was measured after 28 days incubation period. A limitation of this study is that no reference substance (positive control) was included. Using the former test as key study, the dossier submitter concluded etofenprox to be not readily biodegradable.

Simulation tests on etofenprox's degradation in soil and water/sediment systems were also reported. In the first water/sediment study, the reported primary degradation DT_{50} values for the whole system were 6.5 days for the pond system and 20.1 days for the lake system.

Mineralisation was 28 and 18% after 99 days for the pond and lake system, respectively. The second (repeat) study assessed the degradation of etofenprox in the pond system, resulting in a primary degradation DT_{50} value for the whole system of 6.5 days and a mineralization up to 35% within 100 days. Etofenprox was therefore not considered to undergo degradation to a level > 70% within a 28-day period, or to have fast primary degradation (DT_{50} in aquatic systems is not <16 days).

In the overall conclusion on rapid degradation, the DS used the closed bottle test, water/sediment simulation tests, hydrolytic stability and photolysis test as basis to conclude that etofenprox is not rapidly degradable.

Bioaccumulation

Octanol-water partition coefficient of etofenprox was reported to be 6.9. One experimental study on bioaccumulation on bluegill sunfish (*Lepomis macrochirus*) was reported (OECDTG 305) with a resulting BCF value of 2565 (whole body, lipid normalized).

Acute aquatic toxicity

Acute studies were reported for all key trophic levels (i.e. fish, crustacean, algae). Two acute studies according to US EPA Section 72-1 guideline on fish (*Oncorhynchus mykiss* and *L. macrochirus*) using technical etofenprox as the test substance gave 96-h LC_{50} values of 0.0027 and 0.013 mg/l both values based on mean measured concentrations, respectively. In an additional acute study (a limit test according to OECD TG 203) *O. mykiss* was exposed to etofenprox's metabolite α-CO but mortality was not observed at the used concentration (0.048 mg/l).

Acute toxicity of etofenprox and its metabolite α-CO were tested (both according to the OECD TG 202) in water flea (*Daphnia magna*). The EC_{50} (48-h) for etofenprox was 0.0012 mg/l based on mean measured concentrations. Metabolite α-CO did not cause any observed effect (i.e. immobilisation) at the applied concentration (i.e. 0.044 mg/l).

Two studies (OECD TG 201, biomass and growth) on acute toxicity of etofenprox and its metabolite to green algae (*Pseudokirchneriella subcapitata*) were reported. No acute toxicity was observed in the study in which the highest exposure concentration was 0.056 mg/l (NB: this is the average measured concentration; nominally 0.150 mg/l was applied, but the recovery was only 37.5% (geometric mean)). Similarly, acute toxicity of metabolite α-CO did not cause any effect at the applied concentration (i.e. 0.053 mg/l) of the limit test.

Chronic aquatic toxicity

Chronic studies were reported for all key trophic levels (i.e. fish, crustacean, algae). In fish a 40 days study (OECD TG 210) on zebra fish (*Brachydanio rerio*) was reported. In addition, the dossier submitter considered a 21 day study (OECD TG 204) on *O. mykiss* juveniles as a chronic study even though it is not normally considered as a chronic study. The NOEC value for mortality was 0.025 mg/l (mean measured concentration) in the *B. rerio* study and 0.0032 mg/l (nominal concentration) in the *O. mykiss* study. In the latter study, the mean measured concentration were 41-65% of the nominal concentration but still the DS applied nominal values in calculating the NOEC value.

One toxicity study in crustaceans (*D. magna OECD TG 211*) was reported. The measured NOEC for reproduction, i.e. the total number of living offspring produced per parent animal alive at the end of the test, was 0.000054 mg/l (mean measured concentration).

No inhibition of the growth by etofenprox or its metabolite α-CO was observed in the chronic test on algae (the same studies as described for acute toxicity) at the applied test concentrations.

Classification proposals

Aquatic acute classification according to CLP criteria:
The DS's conclusion on acute aquatic hazard, i.e. Aquatic Acute 1, was based on the lowest effective concentration of etofenprox that was observed in *D. magna* (0.0012 mg/l) that also lead to acute M-factor of 100.

Aquatic chronic classification according to CLP criteria:
The DS's conclusion on long-term aquatic hazard was based on the not rapid degradation of etofenprox and the NOEC value of 0.000054 mg/l in *D. magna* that justified classification as Aquatic Chronic 1 with an M-factor 1000.

Aquatic hazard classification according to DSD criteria:
The DS's conclusion on aquatic hazard was based on not ready degradation of etofenprox, a BCF value of 2565 and the lowest effective concentration of etofenprox that was observed in *D. magna* (0.0012 mg/l) that led to classification as N; R50-53 with the specific concentration limits of N; R50-53: C ≥ 0.25%; N, R51-53: 0.025% ≤ C <0.25%; R52-53: 0.0025% ≤ C < 0.025%.

Comments received during public consultation

Six MSCA's supported the proposed classification and no comments opposing the proposal were received.

Assessment and comparison with the classification criteria

The information provided on degradation shows that etofenprox is hydrolytically stable, is not ready biodegradable in screening studies, does not degrade to a level greater than 70% in 28 days and cannot be considered to have rapid primary degradation. Etofenprox is therefore considered not rapidly/readily degradable.

A BCF value of 2565 in whole fish (lipid normalised) was obtained in a bioaccumulation study. This value is higher than the threshold value of 500 (CLP) and 100 (DSD).

Aquatic acute and chronic toxicity studies are available for all trophic levels. The material tested in these studies is comparable to the specifications provided for etofenprox, so including the (confidential) impurities (none of which have a harmonised or self-classification for aquatic toxicity). For acute toxicity the lowest $L(E)C_{50}$ value obtained was 0.0012 mg/l in *Daphnia magna*. For chronic toxicity the lowest NOEC value obtained was 0.000054 mg/l in *Dapnia magna*.

Aquatic acute classification according to CLP criteria

The lowest L(E)C_{50} value is ≤1 mg/l. Etofenprox therefore fulfils the criteria for classification as **Aquatic Acute 1 (H400)**. As the lowest L(E)C_{50} value is between 0.001 and 0.01, this leads to an **M-factor 100**.

Aquatic chronic classification according to CLP criteria

Etofenprox is not rapidly degradable. Chronic data are available for all trophic levels. The lowest NOEC is ≤ 0.1 mg/l. Etofenprox therefore fulfils the criteria for classification as **Aquatic Chronic 1 (H410)**. As the lowest NOEC value is between 0.00001 and 0.0001, this leads to an **M-factor 1000**.

Aquatic hazard classification according to DSD criteria

Etofenprox is not readily degradable and has a BCF > 100. The lowest L(EC)$_{50}$ is ≤1 mg/l. Etofenprox therefore fulfils the criteria for classification as **N; R50-53**.

The lowest L(E)C_{50} value is 0.001 < L(E)C_{50} ≤ 0.01; this leads to the following **SCLs**:

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

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

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

RAC is thus in support of the environmental classification as proposed by the dossier submitter.

6 OTHER INFORMATION

No other informations

7 REFERENCES

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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.
A 3.3.3/01	Shimono S.	1999 c	Odor 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. 500-2-07 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
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.

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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.
A 3.4/03	Matsumoto T.	2002 b	Measurement of UV-VIS absorption spectrum of PENA Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82075 Landis Kane Consulting, Document No. 500-2-10 GLP, unpublished	Y	Mitsui Chemicals, Inc.
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.
A 3.4/05	Pouchert Ch.J., Behnke J.	1983	The Aldrich library of 13C and 1H FT NMR spectra Aldrich Chemical Company 1983 Landis Kane Consulting, Document No. 500-2-61 Not GLP, published	N	Public in-formation
A 3.4/06	Pouchert Ch.J.	1985	The Aldrich library of FT-IR spectra Aldrich Chemical Company 1985 Landis Kane Consulting, Document No. 500-2-62 Not GLP, published	N	Public in-formation
A 3.4/07	Heller S.R., Milne G.W.A.	1978	EPA / NIH mass spectral data base U.S. Department of Commerce, National Bureau of Standards 1978 Landis Kane Consulting, Document No. 500-2-63 Not GLP, published	N	Public in-formation

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A 3.5/01	Kunz C.	2000	Determination of the water solubility of ^{14}C-etofenprox at three pH values and amendment dated October 04, 2000 RCC Ltd, Report No. 755515 Landis Kane Consulting, Document No. 500-2-11 GLP, unpublished	Y	Mitsui Chemicals, Inc.
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.
A 3.5/03	Matsumoto T.	2002 c	Determination of water solubility for 4'-OH by column elution method Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82070 Landis Kane Consulting, Document No. 500-2-13 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.5/04	Matsumoto T.	2002 d	Determination of water solubility for PENA by flask method Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82073 Landis Kane Consulting, Document No. 500-2-14 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.5/05	Mirbach M.	2004 a	Etofenprox: estimation of the temperature dependence of the solubility in water and organic solvents and of the partition coefficient octanol/water. Landis Kane Consulting, Report No. 04-alpha-18 Landis Kane Consulting, Document No.500-2-67 Not GLP, not published	Y	Mistui Chemicals. Inc.

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A 3.6	Schmiedel U.	1998	Expert statement on the dissociation of MTI-500 (etofenprox) in water RCC Ltd, Report No. 692741 Landis Kane Consulting, Document No. 500-2-26 Not GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.7/01	Tognucci A.	1998 d	Determination of the solubility of etofenprox in organic solvents RCC Ltd, Report No. 692752 Landis Kane Consulting, Document No. 500-2-15 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.7/02 → A 3.5/05	Mirbach M.	2004 a	Etofenprox: estimation of the temperature dependence of the solubility in water and organic solvents and of the partition coefficient octanol/water. Landis Kane Consulting, Report No. 04-alpha-18 Landis Kane Consulting, Document No.500-2-67 Not GLP, not published	Y	Mistui Chemicals. Inc.
A 3.9/01	Tognucci A.	1998 e	Determination of the partition coefficient (N-octanol / water) of etofenprox and amendment dated October 13, 1999 RCC Ltd, Report No. 692763 Landis Kane Consulting, Document No. 500-2-16 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.9/02	McCorquo-dale G.Y.	2002 b	Physico-chemical testing with [14C]-Alpha-CO: partition coefficient Inveresk Research, Report No. 21024 Landis Kane Consulting, Document No. 500-2-17 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.9/03	Matsumoto T.	2002 e	1-Octanol/water partition coefficient test of 4'-OH (HPLC method) Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82071 Landis Kane Consulting, Document No. 500-2-18 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.9/04	Matsumoto T.	2002f	1-Octanol/water partition coefficient test of PENA (HPLC method) Kurume Laboratory, Chemicals Evaluation and Research Institute, Report No. 82074 Landis Kane Consulting, Document No. 500-2-19 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.9/05 → A 3.5/05	Mirbach M.	2004 a	Etofenprox: estimation of the temperature dependence of the solubility in water and organic solvents and of the partition coefficient octanol/water. Landis Kane Consulting, Report No. 04-alpha-18 Landis Kane Consulting, Document No.500-2-67 Not GLP, not published	Y	Mitsui Chemicals. Inc.
A 3.10	Tognucci A.	1998f	Screening of the thermal stability in air of etofenprox RCC Umweltchemie AG, Report No. 692774 Landis Kane Consulting, Document No. 500-2-37 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.11/01	Dublaski A.	1991 a	Determination of the flammability of etofenprox in accordance with EEC-Guideline A.10 Battelle Europe, Report No. BE-P-32-91-A10-02 Landis Kane Consulting, Document No. 500-2-29 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.11/02	Dublaski A.	1991 b	Determination of the auto-flammability of etofenprox in accordance with EEC-Guideline A.16 Battelle Europe, Report No. BE-P-32-91-A16-02 Landis Kane Consulting , Document No. 500-2-30 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.12	Bates M.	2001 a	MTI-500: determination of the flash point - Amended final report from January 31, 2001 Covance Laboratories Ltd., Report No. 719/8-D2141 Landis Kane Consulting, Document No. 500-2-31 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.13	Dublaski A.	1991 c	Determination of the surface tension of etofenprox in accordance with EEC-Guideline A.05 Battelle Europe., Report No. BE-P-32-91-A05-02 Landis Kane Consulting, Document No. 500-2-33 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.15	Bates M.	2001 b	MTI-500: evaluation of the explosive properties - Amended final report from January 31, 2001 Covance Laboratories Ltd., Report No. 719/9-D2141 Landis Kane Consulting. Document No. 500-2-32 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 3.16	Bates M.	2001 c	MTI-500: determination of the oxidizing properties - Amended final report from January 31, 2001 Covance Laboratories Ltd., Report No. 719/11-D2141 Landis Kane Consulting, Document No. 500-2-34 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 3.17	Ohnuma K.	2004	Statement concerning the stability of etofenprox technical during storage and shipment. Mistui Chemicals, Inc., Document No. not specified Landis Kane Consulting, Document No. 500-2-66 Not GLP, unpublished	N	Mitsui Chemicals, Inc.
A 4.1/01	Ramsay N.	2002 b	Etofenprox – Validation of analytical methods to support 5-batch analysis of Etofenprox to fulfil the requirements of OPPTS Guidelines 830.1700, 830.1750 and 830.1800 and EC Council Directive 94/37/EEC Article 1.9 to 1.11. Inveresk Research, Report No. 21164 Landis Kane Consulting, Document No. 500-4-01 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.1/02	Dobrat W., Martijn A.	1995	CIPAC Handbook Volume G - Analysis of technical and formulated pesticides method etofenprox 471 Collaborative Int. Pesticides Analytical Council Ltd. 1995 Landis Kane Consulting, Document No. 500-4-02 Not GLP, published	N	Public in-formation
A 4.2/01	Wolf S.	2003 a	Validation of the residue analytical method for MTI-500 and α-CO in soil RCC Ltd, Report No. 811607 Landis Kane Consulting, Document No. 500-4-12 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.2/02	Wolf S.	2003 b	Development and validation of the residue analytical method for MTI-500 and α-CO in air RCC Ltd, Report No. 811620 Landis Kane Consulting, Document No. 500-4-17 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 4.2/03	Wolf S.	2003 c	Validation of the residue analytical method for MTI-500 and α-CO in drinking, ground and surface water RCC Ltd, Report No. 811618 Landis Kane Consulting, Document No. 500-4-15 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.3/01	Wolf S.	2001	Validation of the residue analytical method for MTI-500 and α-CO in oil seed rape RCC Ltd, Report No. 789390 Landis Kane Consulting, Document No. 500-4-08 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.3/02	Wolf S.	2002	Validation of the residue analytical method for MTI-500 and α-CO in cabbage RCC Ltd, Report No. 814588 Landis Kane Consulting, Document No. 500-4-07 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.3/03	Wolf S.	2003 d	Validation of the residue analytical method for MTI-500 and α-CO in cucumber RCC Ltd, Report No. 789377 Landis Kane Consulting, Document No. 500-4-03 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.3/04	Class T.	2003 a	Etofenprox: independent laboratory validation of analytical methods used for the determination of residues of etofenprox in plant materials PTRL Europe GmbH, Report No. P 692 G Landis Kane Consulting, Document No. 500-4-40 GLP, unpublished	Y	Mitsui Chemicals, Inc.

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A 4.3/05	Wolf S.	2003 e	Development and validation of the residue analytical method for MTI-500 and α-CO in meat (ruminant and chicken), milk, fat (ruminant) and egg RCC Ltd, Report No. 791245 Landis Kane Consulting, Document No. 500-4-19 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 4.3/06	Class T.	2003 b	Etofenprox: independent laboratory validation of an analytical method used for the determination of residues of etofenprox in foodstuffs of animal origin PTRL Europe, Report No: P/B 701 G Landis Kane Consulting, Document No. 500-4-41 GLP, unpublished	Y	Mitsui Chemicals, Inc.
A 5.3/01	Schuma-cher P., Fennert E.-M.	2003 a	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
A 5.3/02	SchumacherP., Fennert E.-M.	2003 b	Determination of toxic values against *Reticulitermes santonensis* De Feytaud according to EN 117 (08/90) after leaching procedure according to EN 84 (05/97) – test material SPU-01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; Report No. 3.2/03/8417/02 Landis Kane Consulting, Document No. 500-6-63 Not GLP, not published	Y	Spiess-Urania Chemicals GmbH

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A 5.3/03	Schuma-cher P., Fennert E.-M.	2003 c	Determination of toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) without accelerated ageing procedure – test material SPU-01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; Report No. 3.2/03/8417/03 Landis Kane Consulting, Document No. 500-6-64 Not GLP, not published	Y	Spiess-Urania Chemicals GmbH
A 5.3/04	Schuma-cherP., Fennert E.-M.	2003 d	Determination of toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) after leaching procedure to EN 84 – test material SPU-01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; Report No. 3.2/03/8417/04 Landis Kane Consulting, Document No. 500-6-65 Not GLP, not published	Y	Spiess-Urania Chemicals GmbH
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
A 6.1.1/01	Oda S.	2003 a	Acute oral toxicity study of etofenprox in rats Bozo Research Center Inc., Report No. B-5039 Landis Kane Consulting, Document No. 500-5- 70, GLP, not published	Y	Mitsui Chemicals, Inc.

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A 6.1.1/02	Harling R.J., Burford P., Heywood R.	1985 a	Ethofenprox (MTI-500) acute limit test of toxicity to dogs following a single oral administration Huntingdon Research Centre Ltd., Report No. MTC 101/851185 Landis Kane Consulting, Document No. 500-5-07 GLP, not published	Y	Mitsui Chemicals, Inc.
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.
A 6.1.1/04	Hashimoto K.	1982 b	Report on Acute Toxicity Study of MTI-500 (ethofenprox) in Mice Hatano Research Institute, Food and Drug Safety Center, Report No. A-82-35~42 Landis Kane Consulting, Document No. 500-5-09 Not GLP, not published	Y	Mitsui Chemicals, Inc.
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.
A 6.1.2/02 → 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 6.1.2/03 → A 6.1.1/04	Hashimoto K.	1982 b	Report on acute toxicity study of MTI-500 (ethofenprox) in mice Hatano Research Institute, Food and Drug Safety Center, Report No. A-82-35~42 Landis Kane Consulting, Document No. 500-5-09 Not GLP, not published	Y	Mitsui Chemicals, Inc.
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.
A 6.1.4.e	Kashima M., Ikeda H., Maru-yama Y., Ootsuka Y.	1985 b	MTI-500 Primary ophthalmic stimulation test in rabbits - Amendment No. 1 from October 28, 1991 Haruna Laboratory Nippon Experimental Medical Research Institute, Ltd., Report No. NEMRI-H-85-55 Landis Kane Consulting, Document No. 500-5-12 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.
A 6.2/02	Burri R.	2001 a	[14C]-MTI-500: absorption, distribution, metabolism and excretion after single oral administration to male rats - amendment dated November 30,2001 RCC Ltd, Report No. 801382 Landis Kane Consulting, Document No. 500-5-01 Not GLP, not published	Y	Mitsui Chemicals, Inc.
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.

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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.
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.
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.

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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.
A 6.5.1/02 and A 6.7/02	Green O.P., Heaps C.J., Heywood R., Street A.E., Gopinath 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.

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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.
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.
A 6.8.1.1 /01	Cozens D.D., Hughes E.W., Clark R., Anderson 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., Anderson 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.

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A 6.8.1.1 /03	Cozens D.D., Hughes E.W., Offer J.M., 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.M., Barton S.J., Masters R.E., Offer J., Parker C.A., Anderson A., Dawe I.S.	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.
A 6.8.1.2 /02	Fisher B.R.	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.

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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.
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.
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.

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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.
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.

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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.
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

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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.
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
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.

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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.
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.

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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.
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., Anderson 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.
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